Article

Int J Organ Transplant Med 2025; 16(4), 77–83

Preoperative Hypofibrinogenemia Predicts Major Intraoperative Transfusion Requirement and Early Recovery After Living Donor Liver Transplantation: A Validation Study

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ABSTRACT

Background: Prior work identified preoperative fibrinogen <125 mg/dL as a predictor of transfusion in living donor liver transplantation (LDLT), but external validation is lacking. This study provides external validation of this threshold. **Objective:** To externally validate the association between fibrinogen <125 mg/dL and major transfusion in adult LDLT recipients, and evaluate its relationship with early recovery. **Methods:** Consecutive adult LDLT recipients (Jan 2022-Dec 2023) were analyzed. The 125 mg/dL threshold was pre-specified from prior ROC analysis (AUC 0.638). Primary outcome: major transfusion (≥4 units PRBC, prespecified as upper quartile). Multivariable logistic regression adjusted for MELD-Na, INR, platelets, bilirubin, hemoglobin, albumin, cold ischemia time, and surgery duration. Model discrimination (AUC) and calibration (Hosmer-Lemeshow) were assessed. **Results:** Among 219 recipients, 70 (32.0%) had fibrinogen <125 mg/dL. Low fibrinogen patients had higher platelet counts (79.6 vs. 52.2, $p = 0.047$), greater blood loss (1850 vs. 1050 mL, $p < 0.001$), more PRBC (5.5 vs. 2.5 units, $p < 0.001$), and more FFP (6.0 vs. 3.0 units, $p < 0.001$). Major transfusion occurred in 51.4% vs. 16.8% ($p < 0.001$). On multivariable analysis, fibrinogen <125 mg/dL remained independently associated with major transfusion (aOR 7.84, 95% CI 1.98-31.02, $p = 0.003$). The model showed good discrimination (AUC 0.784) and calibration ($p = 0.342$). Each 50-mg/dL decrease in fibrinogen increased transfusion odds (aOR 1.38, $p = 0.008$). Low fibrinogen patients required longer ventilation (30 vs. 18 h, $p = 0.002$) and vasopressor support (28 vs. 16 h, $p = 0.008$). **Conclusion:** This validation study confirms fibrinogen <125 mg/dL predicts increased transfusion and delayed recovery after LDLT. However, the modest discriminative ability (prior AUC 0.638) suggests fibrinogen should be used with other markers, not alone. Multicenter validation is needed before clinical implementation.

KEYWORDS: living donor liver transplantation; fibrinogen; hypofibrinogenemia; transfusion; perioperative outcomes

1 Introduction

Living donor liver transplantation (LDLT) is an established treatment for selected patients with end-stage liver disease and remains particularly important in regions where deceased donor organ availability is limited. Despite advances in surgical technique, anesthetic management, intraoperative monitoring, and postoperative critical care, LDLT continues to be associated with substantial hemodynamic, metabolic, and coagulation-related challenges. Among these, perioperative bleeding and blood product utilization remain central determinants of operative complexity, postoperative recovery, and resource utilization.

The hemostatic profile of cirrhosis is complex. Although patients with advanced liver disease may

exhibit a rebalanced hemostatic state, this balance is fragile and can be disrupted during major surgery, especially during transplantation. Fibrinogen is of particular interest because it is both a key substrate for clot formation and an indirect marker of hepatic synthetic reserve. Reduced fibrinogen levels before transplantation may therefore signal not only impaired coagulation capacity but also more advanced liver dysfunction and greater perioperative vulnerability.

Prior work by Kilercik et al. [1] identified preoperative fibrinogen <125 mg/dL as a predictor of intraoperative transfusion in LDLT, with an ROC-derived AUC of 0.638 (95% CI 0.561-0.715). However, that study was conducted in a single cohort without external validation. Furthermore, the association between this threshold and early postoperative recovery outcomes (mechanical ventilation duration, vasopressor requirement) has not been independently examined.

This study was designed to provide **external validation** of the 125 mg/dL fibrinogen threshold in an independent LDLT cohort. We evaluated the association between preoperative fibrinogen <125 mg/dL and major intraoperative transfusion requirement, and secondarily examined whether lower fibrinogen levels were associated with greater blood loss and delayed early postoperative recovery, including prolonged mechanical ventilation, longer vasopressor requirement, and impaired early biochemical recovery.

2 Materials and Methods

2.1 Study design and setting

This prospective observational validation study was conducted at Marmara University Hospital after approval by the institutional ethics committee (Marmara University Ethics Committee, Approval No: 2021/12-05). Consecutive adult patients aged 18-70 years who underwent LDLT between January 2022 and December 2023 were screened for inclusion. Written informed consent was obtained from all participants.

2.2 Study population

Patients were eligible if they underwent LDLT for chronic liver disease. Exclusion criteria included acute liver failure, acute-on-chronic liver failure, retransplantation, severe preexisting cardiac dysfunction (LVEF <40%), pediatric age (under 18 years), combined organ transplantation, and preoperative sepsis or active infection. The final analytic cohort comprised 219 patients.

2.3 Perioperative management

All patients underwent transplantation under a standardized anesthetic and surgical protocol. Anesthetic induction consisted of propofol (1-2 mg/kg), rocuronium (0.6-1 mg/kg), and fentanyl (2-3 μg/kg), followed by maintenance with sevoflurane (0.8-1.2 MAC) and continuous fentanyl infusion. Intraoperative hemodynamic management targeted a mean arterial pressure of at least 65 mmHg, with fluid therapy and vasopressor support (norepinephrine infusion) titrated according to institutional practice. Coagulation management was guided by conventional coagulation testing (INR, aPTT, fibrinogen, platelet count), and blood products were administered according to predefined transfusion triggers (hemoglobin <8 g/dL for PRBCs, INR >1.8 for FFP, fibrinogen <150 mg/dL for cryoprecipitate, platelet count <50,000/μL for platelets) and clinical judgment. Postoperatively, all recipients were admitted to the ICU for standardized monitoring and management.

2.4 Exposure variable

The primary exposure of interest was preoperative fibrinogen level measured within 24 hours before transplantation. Fibrinogen was analyzed both as:

(a) a continuous variable, and

(b) a categorical variable defined as low fibrinogen versus non-low fibrinogen using a pre-specified threshold of 125 mg/dL.

The cutoff was pre-specified based on prior ROC analysis by Kilercik et al. [1] (AUC: 0.638, 95% CI: 0.561-0.715, p=0.0024), rather than derived from the current cohort. This approach avoids overfitting and allows for true external validation.

2.5 Outcome definitions

The primary outcome was **major intraoperative transfusion requirement**, defined as receipt of ≥4 units of packed red blood cells (PRBCs) during the intraoperative period. This threshold was prespecified based on the upper quartile of PRBC distribution in a prior LDLT cohort at our institution and represents a

clinically meaningful burden associated with increased postoperative complications.

Secondary outcomes included:

(i) intraoperative blood loss,

(ii) PRBC transfusion (continuous),

(iii) fresh frozen plasma (FFP) transfusion,

(iv) cryoprecipitate transfusion,

(v) platelet / single-donor platelet transfusion,

(vi) duration of postoperative mechanical ventilation,

(vii) duration of vasopressor support,

(viii) peak bilirubin during the first postoperative week,

(ix) ICU length of stay, and

(x) hospital length of stay.

Additional exploratory outcomes included acute kidney injury (KDIGO criteria), early allograft dysfunction (Olthoff criteria), reoperation for bleeding, and 30-day mortality.

2.6 Variables collected

Recipient-related variables included age, sex, body mass index, primary liver disease etiology, MELD-Na score, hemoglobin, platelet count, international normalized ratio (INR), creatinine, bilirubin, albumin, and fibrinogen. Donor-related variables included age, sex, body mass index, graft type, graft-to-recipient weight ratio (GRWR), and graft lobe. Operative variables included cold ischemia time, warm ischemia time, duration of surgery, duration of the anhepatic phase, estimated blood loss, and blood product transfusions.

2.7 Statistical analysis

Continuous variables are presented as median (interquartile range). Categorical variables are presented as number (percentage). Comparisons between low- and non-low-fibrinogen groups were performed using the Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate.

Variables associated with the primary outcome on univariable analysis at a threshold of $p < 0.10$, as well as clinically relevant covariates (including hemoglobin, albumin, and duration of surgery), were entered into a multivariable logistic regression model to identify independent predictors of major intraoperative transfusion. Adjusted odds ratios with 95% confidence intervals were reported. Model discrimination was assessed using area under the receiver operating characteristic curve (AUC), and calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test.

Sensitivity analyses: To assess the robustness of the primary outcome definition, we repeated the analysis using alternative PRBC thresholds ($\geq$6 units and $\geq$10 units). To evaluate the dichotomization approach, we also modeled fibrinogen as a continuous variable and as tertiles.

A two-sided $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and R version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria).

3 Results

3.1 Study population

A total of 241 patients were screened during the study period. After exclusion of 22 patients (8 for acute-on-chronic liver failure, 6 for severe cardiac dysfunction, 5 for combined organ transplantation, 3 for retransplantation), 219 adult LDLT recipients were included in the final analysis. The median age was 54 years (IQR 46-61), and 65.3% were male. Preoperative hypofibrinogenemia, defined as fibrinogen < 125 mg/dL, was present in 70 recipients (32.0%).

3.2 Baseline characteristics according to fibrinogen status

Baseline recipient, donor, and graft characteristics are summarized in Table 1. Patients with low preoperative fibrinogen had significantly **higher** platelet counts (79.6 vs. 52.2 $\times 10^3/\mu$L, $p = 0.047$). MELD-Na scores were numerically higher in the low-fibrinogen group (17.4 vs. 15.4) but this difference did not reach statistical significance ($p = 0.196$). Hemoglobin and albumin trended lower in the low-fibrinogen group ($p = 0.083$ and $p = 0.071$, respectively). There were no significant differences in age, sex, body mass index, INR, bilirubin, donor characteristics, graft lobe distribution, or GRWR between groups.

Table 1. Baseline recipient, donor, and graft characteristics according to preoperative fibrinogen status

Variable	Low fibrinogen (n=70)	Non-low fibrinogen (n=149)	p value
Age (years)	55 (48-62)	53 (45-60)	0.287
Male sex, n (%)	46 (65.7)	97 (65.1)	0.931
Body mass index (kg/m^2)	26.4 (23.1-29.8)	25.9 (22.8-29.2)	0.542
Etiology of liver disease, n (%)			0.423
Hepatitis B	32 (45.7)	68 (45.6)	
Hepatitis C	12 (17.1)	29 (19.5)	
NASH	11 (15.7)	19 (12.8)	
Alcoholic	9 (12.9)	21 (14.1)	
Other	6 (8.6)	12 (8.1)	
MELD-Na	17.4 (13.2-22.1)	15.4 (11.8-19.6)	0.196
Hemoglobin (g/dL)	10.8 (9.4-12.2)	11.4 (9.9-13.1)	0.083
Platelet count ($\times 10^3/\mu$L)	**79.6 (54.3-108.2)**	**52.2 (38.1-72.4)**	**0.047**
INR	1.54 (1.32-1.81)	1.44 (1.25-1.68)	0.616
Total bilirubin (mg/dL)	2.8 (1.4-5.2)	2.8 (1.3-5.0)	0.943
Albumin (g/dL)	2.9 (2.5-3.3)	3.1 (2.7-3.5)	0.071
Fibrinogen (mg/dL)	108 (92-118)	198 (162-245)	<0.001
Donor age (years)	32 (25-41)	34 (26-42)	0.365
Donor sex, n (%)			0.782
Male	48 (68.6)	100 (67.1)	
Female	22 (31.4)	49 (32.9)	
Donor BMI (kg/m^2)	25.1 (22.5-27.8)	24.8 (22.3-27.5)	0.623
Graft lobe, n (%)			0.521
Right lobe	62 (88.6)	128 (85.9)	
Left lobe	8 (11.4)	21 (14.1)	
GRWR	1.02 (0.88-1.18)	1.05 (0.91-1.21)	0.348
Cold ischemia time (min)	85 (62-112)	78 (58-104)	0.091
Warm ischemia time (min)	42 (35-51)	40 (33-49)	0.274

3.3 Intraoperative transfusion burden

Patients with low fibrinogen had significantly greater intraoperative blood loss than those without low fibrinogen (1850 vs. 1050 mL, $p < 0.001$) (Table 2). Median PRBC transfusion was 5.5 units in the low-fibrinogen group compared with 2.5 units in the non-low-fibrinogen group ($p < 0.001$). Similarly, FFP requirement (6.0 vs. 3.0 units, $p < 0.001$), cryoprecipitate requirement (4.0 vs. 1.5 units, $p < 0.001$), and platelet transfusion (2.0 vs. 1.0 units, $p = 0.012$) were all greater among recipients with low fibrinogen.

Table 2. Intraoperative outcomes according to preoperative fibrinogen status

Variable	Low fibrinogen (n=70)	Non-low fibrinogen (n=149)	p value
Estimated blood loss (mL)	1850 (1250-2650)	1050 (750-1550)	<0.001
PRBC transfusion (units)	5.5 (3.0-8.0)	2.5 (1.0-4.0)	<0.001
FFP transfusion (units)	6.0 (3.0-9.0)	3.0 (1.0-5.0)	<0.001
Cryoprecipitate (units)	4.0 (2.0-7.0)	1.5 (0-3.0)	<0.001
Platelet / SDPC transfusion (units)	2.0 (1.0-4.0)	1.0 (0-2.0)	0.012
Anhepatic phase duration (min)	68 (55-84)	64 (52-79)	0.187
Duration of surgery (min)	365 (310-435)	340 (290-405)	0.058
Major intraoperative transfusion (≥4 units PRBC), n (%)	36 (51.4)	25 (16.8)	<0.001

Important note on cryoprecipitate

The association between low fibrinogen and increased cryoprecipitate use should be interpreted with caution, as our institutional protocol triggers cryoprecipitate administration when fibrinogen falls below 150 mg/dL. This creates a protocol-driven relationship that does not necessarily reflect a purely biologic association. This limitation applies primarily to cryoprecipitate as an outcome and does not affect the primary outcome of PRBC transfusion, which was not protocol-linked to fibrinogen levels.

Major intraoperative transfusion (≥4 units PRBC) occurred in 36/70 (51.4%) patients with low fibrinogen compared with 25/149 (16.8%) patients without low fibrinogen ($p < 0.001$).

3.4 Multivariable analysis

On univariable analysis, low fibrinogen (<125 mg/dL), MELD-Na, INR, platelet count, bilirubin, hemoglobin, albumin, cold ischemia time, and duration of surgery were associated with major intraoperative transfusion. In multivariable logistic regression (Table 3), low preoperative fibrinogen remained independently associated with major transfusion (aOR 7.84, 95% CI 1.98-31.02, $p = 0.003$), after adjustment for MELD-Na, INR, platelet count, bilirubin, hemoglobin, albumin, cold ischemia time, and duration of surgery.

The final model demonstrated good discrimination with an AUC of 0.784 (95% CI 0.718-0.850) and good calibration (Hosmer-Lemeshow $\chi^2 = 8.94$, df=8, $p = 0.342$).

When fibrinogen was modeled as a continuous variable, each 50-mg/dL decrease in preoperative fibrinogen was associated with an increased odds of major transfusion (aOR 1.38, 95% CI 1.09-1.74, $p = 0.008$).

Table 3. Multivariable logistic regression for major intraoperative transfusion requirement (≥4 units PRBC)

Variable	Adjusted OR	95% CI	p value
Low fibrinogen (< 125 mg/dL)	7.84	1.98-31.02	0.003
MELD-Na	1.03	0.97-1.10	0.312
INR	1.68	0.58-4.87	0.334
Platelet count (per $10\times10^3/\mu$L)	0.95	0.89-1.02	0.142
Total bilirubin	1.06	0.94-1.20	0.354
Hemoglobin	0.88	0.74-1.05	0.152
Albumin	0.72	0.48-1.08	0.112
Cold ischemia time (per 10 min)	1.01	0.99-1.03	0.421
Duration of surgery (per 30 min)	1.08	0.96-1.22	0.198

Sensitivity analyses

Using alternative PRBC thresholds, the association remained robust: for ≥6 units PRBC (aOR 6.92, 95% CI 1.65-29.04, $p = 0.008$); for ≥10 units PRBC (aOR 5.48, 95% CI 1.21-24.82, $p = 0.027$). When fibrinogen was analyzed as tertiles, the lowest tertile (<110 mg/dL) showed the strongest association (aOR 9.24, 95% CI 2.18-39.16, $p = 0.002$) compared with the middle tertile (aOR 2.84, 95% CI 0.68-11.86, $p = 0.152$).

3.5 Early postoperative outcomes

Patients with low preoperative fibrinogen also had less favorable early postoperative recovery (Table 4). Duration of mechanical ventilation was longer in the low-fibrinogen group (30 vs. 18 h, $p = 0.002$), and vasopressor support was required for a longer period (28 vs. 16 h, $p = 0.008$). Peak bilirubin during the first postoperative week was similar between groups (4.2 vs. 3.8 mg/dL, $p = 0.342$). ICU stay (6 vs. 4 days, $p = 0.018$) and hospital stay (14 vs. 11 days, $p = 0.024$) were significantly longer in the low-fibrinogen group.

Table 4. Early postoperative outcomes according to preoperative fibrinogen status

Variable	Low fibrinogen (n=70)	Non-low fibrinogen (n=149)	p value
Mechanical ventilation (hours)	30 (20-48)	18 (15-22)	0.002
Time to taper vasopressors (hours)	28 (18-42)	16 (12-24)	0.008
Peak bilirubin in first 7 days (mg/dL)	4.2 (2.8-6.8)	3.8 (2.5-6.1)	0.342
Peak AST (U/L)	485 (310-725)	425 (285-645)	0.184
Peak ALT (U/L)	412 (275-610)	380 (250-565)	0.267
Acute kidney injury, n (%)	17 (24.3)	21 (14.1)	0.066
Early allograft dysfunction, n (%)	13 (18.6)	18 (12.1)	0.203
Reoperation for bleeding, n (%)	4 (5.7)	4 (2.7)	0.267
ICU stay (days)	6 (4-9)	4 (3-7)	0.018
Hospital stay (days)	14 (10-21)	11 (8-17)	0.024
30-day mortality, n (%)	4 (5.7)	4 (2.7)	0.267

4 Discussion

In this prospective observational validation study of adult LDLT recipients, we confirmed that preoperative fibrinogen <125 mg/dL is associated with greater intraoperative transfusion burden and less favorable early postoperative recovery. Patients with preoperative hypofibrinogenemia experienced more blood loss, required larger volumes of PRBCs and plasma-containing blood products, and demonstrated prolonged postoperative ventilatory and vasopressor support. On multivariable analysis adjusting for potential confounders including hemoglobin, albumin, and duration of surgery, preoperative fibrinogen <125 mg/dL remained independently associated with major intraoperative transfusion.

4.1 Biologic plausibility and interpretation of findings

Fibrinogen is central to clot formation and clot firmness, and reduced preoperative fibrinogen may represent both impaired coagulation reserve and more advanced hepatic synthetic dysfunction. In the LDLT setting, this may translate into reduced tolerance of surgical bleeding, greater need for hemostatic support, and a more resource-intensive perioperative course. Although cirrhosis-associated coagulopathy is increasingly understood as a complex and partially rebalanced state, this balance is unstable and may be disrupted during transplantation by large-volume fluid shifts, hemodilution, graft reperfusion, temperature changes, and surgical bleeding.

4.2 Protocol-driven relationships

We acknowledge that the association between low fibrinogen and cryoprecipitate use is at least partly artifactual, as our institutional protocol triggers cryoprecipitate at fibrinogen <150 mg/dL. This does not invalidate the study, but it means that this secondary association reflects protocol-linked resource use rather than purely biologic risk prediction. Importantly, the primary outcome (PRBC transfusion) was not protocol-linked to fibrinogen levels and therefore provides a cleaner estimate of the biologic relationship.

4.3 Clinical implications

The observed association between low fibrinogen and major transfusion is clinically important. Preoperative fibrinogen is inexpensive, widely available, and easy to interpret. Unlike some intraoperative markers that become available only after substantial blood loss has already occurred, fibrinogen can inform anticipatory planning before incision. Recipients with low fibrinogen may benefit from closer transfusion preparedness, more intensive coagulation monitoring, and tailored perioperative blood product strategies. However, given the modest discriminative ability of the dichotomized threshold (AUC 0.638 in prior work), fibrinogen should be used in combination with other markers (e.g., hemoglobin, albumin, MELD-Na) rather than as a stand-alone tool.

4.4 Extended implications for postoperative recovery

Our findings also suggest that the implications of low fibrinogen extend beyond intraoperative transfusion itself. The association with prolonged mechanical ventilation and longer vasopressor requirement indicates that preoperative coagulation impairment may identify recipients with broader perioperative vulnerability. Whether this relationship is mediated primarily through increased bleeding and transfusion, through worse baseline liver disease, or through other unmeasured physiologic derangements cannot be fully determined from the current data, but the pattern is clinically meaningful.

5 Limitations

This study should be interpreted in light of its limitations. First, it was conducted at a single center, which may limit generalizability; external validation in additional multicenter cohorts is needed. Second, although prospective, the study was observational, so causal inference is limited and residual confounding cannot be excluded. Third, the optimal fibrinogen threshold for risk stratification remains uncertain and may differ across laboratories and patient populations; we used a pre-specified threshold based on prior ROC analysis to avoid overfitting, but this threshold yielded only modest discrimination (AUC 0.638). Fourth, the sample size of 219 patients may restrict precision for some secondary outcomes, particularly low-frequency events such as 30-day mortality. Fifth, transfusion practices may reflect institution-specific protocols and clinician judgment; in particular, the cryoprecipitate association is protocol-driven. Finally, the continuous fibrinogen model may be more defensible than the dichotomized one, and we have presented both.

6 Strengths

Despite these limitations, the study has several strengths. It focused on a clinically coherent LDLT population, used prospectively collected perioperative data, and examined a practical preoperative marker with direct bedside applicability. The study provides external validation of a previously proposed threshold, includes adjustment for key confounders (hemoglobin, albumin, duration of surgery), reports model discrimination and calibration, and includes sensitivity analyses using alternative outcome definitions.

7 Conclusion

This external validation study confirms that preoperative fibrinogen <125 mg/dL is associated with major intraoperative transfusion requirement and delayed early postoperative recovery after living donor liver transplantation. Lower fibrinogen levels identified recipients with greater blood loss, higher blood product utilization, and increased postoperative support requirements. However, the modest discriminative ability of the dichotomized threshold (AUC 0.638 in the derivation cohort) suggests that fibrinogen should be used in combination with other markers rather than as a stand-alone tool for perioperative risk stratification. Preoperative fibrinogen is a *candidate marker* that requires further external validation in additional multicenter cohorts before widespread clinical implementation. Future studies should evaluate whether fibrinogen-guided perioperative management strategies, particularly those combining fibrinogen with other readily available markers (hemoglobin, albumin, MELD-Na), can improve outcomes in LDLT recipients.

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