Original Article

Perioperative Single-Donor Platelet Apheresis and Red Blood Cell Transfusion Impact on 90-Day and Overall Survival in Living Donor Liver Transplantation

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Abstract

Background: Although many previous studies have confirmed that perioperative blood transfusion is associated with poor outcomes after liver transplantation (LT), few studies described the influence of single-donor platelet apheresis transfusion in living donor LT (LDLT). This study aimed to assess the effect of blood products on outcomes for LDLT recipients, focusing on apheresis platelets.

Methods: This retrospective study included 126 recipients who underwent their first adult-to-adult LDLT. Twenty-four variables including consumption of blood products of 126 LDLT recipients were assessed for their link to short-term outcomes and overall survival. Kaplan-Meier survival curve and the log-rank test were used for recipient survival analysis. A multivariate Cox proportional-hazard model and a propensity score analysis were applied to adjust confounders after potential risk factors were identified by a univariate Cox analysis.

Results: Patients who received apheresis platelet transfusion had a lower 90-day cumulative survival (78.9% vs. 94.2%, $P = 0.009$), but had no significant difference in overall survival in the Cox model, compared with those without apheresis platelet transfusion. Units of apheresis platelet transfusion (hazard ratio [*HR*] = 3.103, 95% confidence interval [*CI*]: 1.720–5.600, $P < 0.001$) and preoperative platelet count (*HR* = 0.170, 95% *CI*: 0.040–0.730, $P = 0.017$) impacted 90-day survival independently. Multivariate Cox regression analysis also found that units of red blood cell (RBC) transfusion (*HR* = 1.036, 95% *CI*: 1.006–1.067, $P = 0.018$), recipient's age (*HR* = 1.045, 95% *CI*: 1.005–1.086, $P = 0.025$), and ABO blood group comparison (*HR* = 2.990, 95% *CI*: 1.341–6.669, $P = 0.007$) were independent risk factors for overall survival after LDLT.

Conclusions: This study suggested that apheresis platelets were only associated with early mortality but had no impact on overall survival in LDLT. Units of RBC, recipient's age, and ABO group comparison were independent predictors of long-term outcomes.

Key words: Apheresis Platelets; Blood Transfusion; Living Donor Liver Transplantation; Outcome; Red Blood Cell

Introduction

Liver transplantation (LT) has been considered one of the most effective treatments for patients with end-stage liver disease. However, a remaining challenge for the transplantation community is a relative scarcity of deceased donor graft.[1,2] Therefore, in addition to deceased donor LT (DDLT), living donor LT (LDLT) has emerged as a solution to the lack of deceased donor organs and has effectively expanded the donor pool.[2] Although it is a complicated surgical procedure that deals with the right or left lobe and dramatic physiological changes resulting from liver regeneration,[3] a recent meta-analysis revealed that LDLT was associated with a higher rate of surgical complications but with no significant difference in perioperative mortality compared to DDLT.[4]

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Both DDLT and LDLT recipients often require blood transfusion during surgery or in the postoperative period because of coagulation defects or severe bleeding from the procedure itself.[4,5] Although the utilization of blood products such as red blood cells (RBCs), platelets, and plasma has decreased in recent decades, its detriment to recipients cannot be ignored. The potential hazards of

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allogeneic blood transfusion include viral or bacterial transmission, allergic reaction, disordered immunoreaction, transfusion-related lung injury, and kidney failure.[6] Many previous studies have demonstrated that RBC transfusion is associated with postoperative complications and that it is an independent risk factor for survival after DDLT[5-17] or LDLT.[18,19] Nevertheless, studies on platelet transfusion are rare and the results are controversial.[8,11,13,19-22] Moreover, platelets had already been supposed to stimulate hepatocyte mitosis and accelerate liver regeneration in healthy liver donors.[23] Considering that the previous research was mostly based on DDLT, we conducted this retrospective study to assess the relationship between blood transfusion and the outcomes of LDLT which include small-for-size syndrome and liver regeneration, focusing in particular on the influence of apheresis platelets.

Methods

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University, with a waiver of informed consent due to the retrospective study design.

Participants

A search of the electronic medical records in the First Affiliated Hospital, College of Medicine, Zhejiang University, ranging from December 1, 2006, to December 1, 2015, identified a total of 139 recipients undergoing LDLT. All donors were adults who were related to the recipients. All procedures surrounding LDLT were strictly supervised by the ethics community. No donors suffered severe complications or death. Pediatric transplantations (age <18 years; n = 6), retransplantations (n = 5), and combined organ transplantations (n = 1) were excluded from this study.[6] Recipient who died during surgery was also excluded (n = 1). Thus, 126 recipients who underwent their first adult-to-adult LDLT were included in the study, in which 94% of patients received LDLT before 2012 (the China Organ Transplant Response System was officially launched in 2011, since that time, liver donation after cardiac death surged). Follow-up was achieved by telephone call or searching of the medical records, which was ended on December 31, 2016.

Surgical technique and anesthetic management

The routine LDLT procedures were performed using a right-lobe graft by the same surgical team; only three recipients underwent left lobe graft transplantation. The donor operation began with cholecystectomy, followed by dissociation of the right lobe. All recipients underwent duct-to-duct biliary anastomosis.

Induction of anesthesia was achieved by a total intravenous injection with propofol, midazolam, and fentanyl. Rocuronium or vecuronium was used to facilitate intubation. Anesthesia was maintained with propofol and remifentanil. Neuromuscular blockade, by cisatracurium or vecuronium, was maintained throughout surgery. Invasive arterial pressure and central venous pressure were routinely monitored. Other intraoperative monitoring included constant end-tidal CO_2 partial pressure, 5-lead electrocardiogram, and pulse oximetry.

Blood products and transfusion protocol

Because the supply of blood products is insufficient compared to the massive consumption in China, our center adopted a strict blood transfusion protocol. Allogeneic packed RBCs (PRBCs) were transfused for hemoglobin <70 g/L or hematocrit <0.20, with a goal of maintaining hematocrit between 0.25 and 0.30. The utilization of other blood products such as fresh frozen plasma (FFP) and platelets was decided based on both laboratory values (international normalized ratio [INR] >2.0 and platelet count $<20 \times 10^9$/L) and clinical criteria such as wound hemorrhage or blood loss not corrected by surgical management.

Only five recent recipients received irradiated PRBCs, while the others were transfused with nonirradiated blood products. All platelets used in our center were apheresis platelets, in which 1 unit was concentrated from a single donor (1 unit contains 2.5×10^{11} platelets). Although we most often used FFP for plasma transfusion, FP was also occasionally transfused (1 unit = 100 ml). All RBCs used were PRBCs, in which 1 unit was concentrated from 200 ml of whole blood.

Postoperative treatment

Recipients were admitted to an Intensive Care Unit (ICU) specialized for LT immediately after the surgery. Blood tests including blood cell counts, coagulation, liver biochemistry, and renal function were implemented daily for 3 weeks after LDLT. Doppler ultrasonography was used to monitor the vascular flow in the graft. All recipients received immunosuppression regimens based on tacrolimus and mycophenolate mofetil with or without corticosteroid. When they were stable, recipients were transferred to the clinical ward for further therapy. During the postoperative period, the need for blood products was determined by the surgeons based on, but not limited to, laboratory findings such as blood cell counts and coagulation studies.

Data collection

All data involving recipients and donors, from demographic baseline to surgical factors, were acquired by scrutinizing the recipients' electronic medical records. When necessary, the original recipient paper records were reviewed. A total of 24 risk factors associated with short- or long-term outcomes were selected by reviewing the literature.

Thus, the recipient-related valuables, for example, age, gender, diagnosis, previous abdominal surgery, body weight, graft-to-recipient weight ratio (GRWR, %), Child-Pugh classification, and model for end-stage liver disease (MELD) score calculated with the most recent blood test results available before LDLT, were all included.[1,2,6,24-29] MELD score = 9.6 × Ln creatinine (mg/dl) + 3.8 × Ln bilirubin (mg/dl) + 11.2 × Ln (INR) + 6.4 × etiology (biliary or

alcoholic cirrhosis was 0, otherwise 1).[30] Donor-related variables such as donor age, gender, and graft weight were also collected.[24,31] Meanwhile, the following risk factors during the surgery were noted: cold ischemic time (min), warm ischemic time (min), operating time (min), and intraoperative blood loss (L).[20,25,31] The consumption of blood products during the operation and for 48 h postoperatively was also recorded (blood transfusions were mostly performed during this period in our center). ABO blood group comparison and the most recent preoperative laboratory values of serum alanine transaminase, serum total bilirubin level, creatinine level, hemoglobin, platelet count, and INR were also documented.[6,22]

The short-term outcomes were accessed by 90-day cumulative survival, and the long-term outcomes were evaluated by overall survival. Patient survival was defined as the time period between transplantation and the end of follow-up or patient death. In this study, missing data per variable was <3%. No patient was lost to follow-up.

Statistical analysis

The continuous and categorical variables were expressed as median (Q1–Q3) and number (%), respectively. When necessary, continuous variables were cut off by clinical threshold or receiver-operating characteristics (ROCs) curve. Categorical variables were compared by Pearson's Chi-square test or Fisher's exact test. Continuous variables were compared by the Mann-Whitney *U*-test. Kaplan-Meier survival curve and the log-rank test were used for recipient survival analysis. A univariate Cox analysis was performed to determine risk factors associated with recipient survival. Factors with $P < 0.10$ were selected as potential risk factors and were further analyzed in a multivariate Cox proportional-hazard mode with forward stepwise selection. The hazard ratio (*HR*) and 95% confidence interval (*CI*) were calculated for each variable. Logistic regression analysis was used to determine the risk factors associated with platelet transfusion. For the purpose of mitigating impact from confounding factors, propensity score analysis was also utilized. The propensity score is the probability of treatment distribution conditional on observed baseline characteristics. Patients who shared a similar value of the propensity score had a similar distribution of baseline covariates to adjust for potential confounders.[30] Two-sided level of significance was set at $P < 0.05$. Statistical analysis was performed using the software SPSS Statistics version 23.0 (IBM Corp., New York, USA).

Results

Patient characteristics

A total of 126 recipients who underwent adult-to-adult LDLT between December 1, 2006, and December 1, 2015, were included in this retrospective study. Recipient and donor characteristics and demographics, including preoperative laboratory values and potential surgical-related risk factors, are summarized in Table 1. Recipients with or without apheresis platelet transfusion were compared. Compared to recipients without apheresis platelet transfusion, the MELD score, Child-Pugh classification, blood loss, total bilirubin level, and INR were significantly higher and hemoglobin and platelet counts were lower in those with apheresis platelet transfusion. Not surprisingly, recipients with apheresis platelet transfusion also received more PRBCs and FFP. When analyzing the length of hospital stay, those recipients who died during the hospitalization were excluded ($n = 17$). Recipients who received platelets had longer hospital stays (39 [32–58] days vs. 32 [24–42] days, $P = 0.001$). The donors' age (23 [22–27] years vs. 25 [22–27] years, $P = 0.122$) and gender (male/female: 62/7 vs. 54/3, $P = 0.313$) were comparable between recipients with and without apheresis platelet transfusion.

Blood transfusion of recipients

All 126 recipients were transfused with FFP, 119 (94.4%) recipients received PRBCs, and 57 (45.2%) patients received apheresis platelets. The median consumption of blood products during surgery and 48 h postoperatively was 23 (19–33) U of FFP, 11 (6–19) U of PRBCs, and 0 (0–1) U of apheresis platelets, as shown in Table 1. No whole blood was administered and only two recipients required cell salvage technology.

Prediction of platelet transfusion in living donor liver recipients

To determine the variables associated with perioperative platelet transfusion, those with $P < 0.05$, such as the MELD score, Child-Pugh classification, PRBCs, FFP, blood loss, total bilirubin level, INR, hemoglobin, and platelet counts were assessed by multivariate logistic regression analysis, which revealed that only lower preoperative platelet count (odds ratio *OR* = 0.969, 95% *CI*: 0.956–0.983, $P < 0.001$), higher MELD score, (*OR* = 1.083, 95% *CI*: 1.024–1.146, $P = 0.005$), and more PRBCs transfusion (*OR* = 1.129, 95% *CI*: 1.058–1.204, $P < 0.001$) were independent predictors of perioperative platelet transfusion. No collinearity was recognized after collinearity determination among these three factors.

Univariate and multivariate analyses of overall survival

The average survival time of this population was 91 months and the median survival time was longer than 120 months. The 1-, 3-, and 5-year cumulative survival rates were 89.9%, 78.1%, and 76.6%, respectively, in recipients who did not receive platelets. Among recipients transfused with platelets, the 1-, 3-, and 5-year survival rates were 75.4%, 71.8%, and 70.1%, respectively. The log-rank test was performed and no significant differences were found between two groups ($P = 0.229$; Figure 1).

Therefore, the Cox proportional-hazards model was applied for adjusting confounders. The results of the univariate analysis of the potential risk factors for overall survival are summarized in Table 2. In the multivariate analysis, while the *P* value of the serum creatinine level was <0.05, it was still replaced by the MELD score, which was calculated using the creatinine level. Obviously, the MELD score was a

Table 1: Recipients characteristics and demographics in this study

Variables	All recipients (n = 126)	Recipients without PLTs (n = 69)	Recipients with PLTs (n = 57)	Statistical values	P
Age (years)	46 (40–53)	47 (39–56)	45 (41–52)	−0.319*	0.750
Male/female	105/21	60/9	45/12	1.442	0.230
Diagnosis				4.344	0.361
HBV cirrhosis	61 (48.4)	28 (40.6)	33 (57.9)		
Non-HBV cirrhosis	11 (8.7)	7 (10.1)	4 (7.0)		
Hepatocellular carcinoma	39 (31.0)	24 (34.8)	15 (26.3)		
Acute hepatic failure	14 (11.1)	9 (13)	5 (8.8)		
Metabolic disease	1 (0.8)	1 (1.4)	0 (0.0)		
Body weight (kg)	64 (56–70)	66 (58–71)	63 (55–70)	−1.204*	0.228
Previous abdominal surgery	39 (31.0)	25 (36.2)	14 (24.6)	1.989	0.158
GRWR (%)	1.0 (0.9–1.2)	1.0 (0.9–1.1)	1.0 (0.9–1.3)	−1.415*	0.157
Child-Pugh classification				15.053	0.001
A	18 (14.3)	17 (24.6)	1 (1.8)		
B	33 (26.5)	19 (27.5)	14 (24.6)		
C	75 (59.5)	33 (47.8)	42 (73.7)		
MELD score	18 (9–26)	13 (7–22)	22 (13–30)	−3.595*	<0.001
Graft weight (g)	656 (599–701)	640 (593–695)	668 (600–704)	−0.811*	0.417
Transplantation					
ABO group comparison (identical/compatible)	111/15	63/6	48/9	1.498	0.221
Cold ischemic time (min)	60 (50–77)	60 (50–79)	63 (48–77)	−0.378*	0.705
Warm ischemic time (min)	1 (1–1)	1 (1–1)	1 (1–1)	−1.398*	0.162
Operating time (min)	530 (470–610)	510 (455–600)	540 (485–630)	−1.754*	0.080
Blood loss (L)	2.0 (1.0–3.5)	1.8 (0.8–3.0)	2.6 (1.5–4.4)	−3.046*	0.002
PRBC (U)	11 (6–19)	8 (4–13)	16 (10–23)	−5.244*	<0.001
Apheresis PLT (U)	0 (0–1)	0 (0–0)	1 (1–2)	−10.716*	<0.001
FFP (U)	23 (19–33)	21 (17–29)	29 (22–36)	−3.568*	<0.001
Preoperative laboratory values					
ALT (U/L)	49 (32–104)	51 (32–109)	45 (32–101)	−0.694*	0.488
Total bilirubin (μmmol/L)	189 (34–445)	88 (21–399)	296 (65–543)	−3.046*	0.002
INR	1.53 (1.31–2.16)	1.43 (1.20–1.80)	1.92 (1.43–2.53)	−4.034*	<0.001
Creatinine (μmmol/L)	69 (53–90)	69 (56–86)	67 (52–111)	−0.321*	0.748
Hemoglobin (g/L)	99 (86–121)	109 (91–130)	92 (81–108)	−3.123*	0.002
PLT count ($\times 10^9$/L)	65 (35–106)	89 (62–122)	35 (28–54)	−6.133*	<0.001
Hospital stay (days)	36 (27–48)	32 (24–42)	39 (32–58)	−3.260*	0.001

Data are presented as median (Q1–Q3), n or n (%). *Z values, otherwise Chi-square values. HBV: Hepatitis B virus; GRWR: Graft-to-recipient weight ratio; MELD: Model for end-stage liver disease; ALT: Alanine transaminase; INR: International normalized ratio; PRBC: Packed red blood cell; FFP: Fresh frozen plasma; PLTs: Platelets.

better indicator of preoperative disease severity. Transfusion requirements have also been considered to be surrogates for sicker patients and introducing the MELD score into the multivariate analysis can diminish confounders. Thus, recipients' age, ABO blood group comparison, MELD score, blood loss, operating time, units of PRBCs, FFP, platelets, as well as preoperative platelet count were entered into the multivariate Cox model using forward selection. The results still suggested that platelet transfusion had no effect on overall survival. Nevertheless, recipients' age (HR = 1.045, 95% CI: 1.005–1.086, P = 0.025), ABO blood group comparison (HR = 2.990, 95% CI: 1.341–6.669, P = 0.007), and units of PRBCs (HR = 1.036, 95% CI: 1.006–1.067, P = 0.018) were independent risk factors [Table 3]. A ROCs curve analysis and Youden's index were used to define the ideal cutoff points; 10 U of PRBCs (area under the curve = 0.655, P = 0.008) was decided as the appropriate cutoff value that offered the best prediction for survival (sensitivity = 0.794, specificity = 0.500).

The Schoenfeld residuals test was performed and proved this Cox model to be satisfied with the proportional hazards assumption. To further verify the conclusion, the propensity score was calculated by performing a propensity score matching program in SPSS software, which made the baseline covariates listed in Table 1 balanced (except for hospital stay). We then made covariate adjustment using the propensity score as described by Austin and Mamdani.[32] The estimated score was introduced into the multivariate Cox analysis as an independent covariate; other variables such as the recipient's age, ABO group comparison, and units of PRBCs were still considered as independent risk factors. The final propensity score-adjustment HR was 1.041 (1.002–1.081) for recipient's age, 3.080 (1.380–6.876) for ABO group comparison, and 1.058 (1.015–1.103) for units of PRBCs.

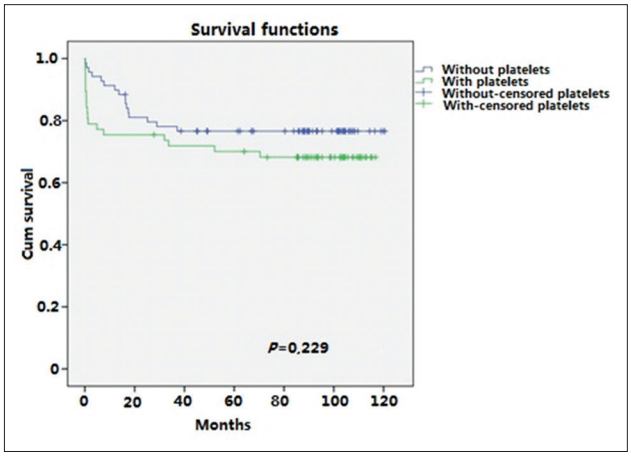

Figure 1: Overall survival between recipients with and without intraoperative platelet transfusion using Kaplan-Meier curves and log-rank test.

Effect of blood products on short-term outcomes

Although platelet transfusion was not regarded as a risk factor for overall survival, we found that it was associated with 90-day cumulative survival via K-M curve and log-rank test, as shown in Figure 2. Similar procedures were processed as described above. The results of the univariate analysis are shown in Table 2. The GRWR was selected instead of graft weight and recipient body weight and INR was replaced by MELD score. Blood loss and preoperative platelet count were added to adjust confounders. Thus, GRWR, blood loss, platelet count, MELD score, ABO group comparison, units of PRBCs, FFP, and platelets were entered into the multivariate Cox model [Table 3]. The results suggested that unit of platelets (*HR* = 3.103, 95% *CI*: 1.720–5.600, $P < 0.001$) was an independent risk factor and high preoperative platelet count (>50 × 10^9/L) was an independent protective

Table 2: Univariate analysis of survival for recipients receiving living donor liver transplantation in this study

Variables	90-day survival		Overall survival	
	HR (95% *CI*)	*P*	*HR* (95% *CI*)	*P*
Recipient				
Age	1.044 (0.991–1.100)	0.106	1.044 (1.007–1.082)	0.019
Gender (male/female)	1.170 (0.333–4.107)	0.806	0.876 (0.339–2.263)	0.785
Diagnosis		0.841		0.256
HBV cirrhosis (reference)				
Non-HBV cirrhosis versus HBV cirrhosis	1.164 (0.251–5.387)	0.846	0.919 (0.206–4.104)	0.911
Hepatocellular carcinoma versus HBV cirrhosis	0.481 (0.130–1.775)	0.272	2.229 (1.063–4.672)	0.034
Acute hepatic failure versus HBV cirrhosis	0.957 (0.207–4.431)	0.955	1.146 (0.323–4.063)	0.833
Body weight	0.958 (0.913–1.006)	0.083	0.995 (0.963–1.028)	0.775
Previous abdominal surgery (yes vs. no)	0.978 (0.340–2.814)	0.967	1.415 (0.708–2.827)	0.326
GRWR (<0.8% vs. >0.8%)	1.601 (0.364–7.045)	0.534	1.060 (0.324–3.468)	0.923
Child-pugh classification		0.577		0.110
A (reference)				
B vs. A	2.240 (0.250–20.045)	0.471	0.441 (0.170–1.147)	0.093
C vs. A	2.874 (0.371–22.264)	0.312	0.440 (0.196–0.989)	0.047
MELD score	1.034 (0.990–1.087)	0.127	0.993 (0.959–1.028)	0.695
Donor				
Age	1.027 (0.960–1.099)	0.443	0.997 (0.944–1.053)	0.919
Gender (male/female)	1.709 (0.388–7.521)	0.479	0.761 (0.182–3.179)	0.708
Graft weight	0.993 (0.998–0.999)	0.012	0.997 (0.994–1.001)	0.134
Transplantation				
ABO group (identical/compatible)	2.643 (0.851–8.205)	0.093	2.951 (1.330–6.546)	0.008
Cold ischemic time	0.985 (0.960–1.010)	0.234	0.993 (0.978–1.009)	0.398
Warm ischemic time	1.586 (0.599–4.200)	0.354	0.818 (0.311–2.151)	0.684
Operating time	1.002 (0.998–1.005)	0.388	1.002 (1.000–1.005)	0.098
Blood loss	1.056 (0.863–1.293)	0.597	1.124 (0.992–1.274)	0.066
PRBC units	1.044 (1.002–1.087)	0.041	1.037 (1.007–1.067)	0.015
Apheresis PLT units	1.869 (1.214–2.878)	0.004	1.202 (0.837–1.727)	0.319
FFP units	1.040 (1.009–1.072)	0.011	1.025 (1.001–1.050)	0.040
Preoperative laboratory values				
ALT	1.001 (0.999–1.002)	0.193	1.000 (0.999–1.002)	0.795
Total bilirubin	1.000 (0.999–1.002)	0.618	0.999 (0.997–1.000)	0.171
INR	1.262 (0.972–1.639)	0.081	0.985 (0.707–1.373)	0.930
Creatinine	1.002 (0.997–1.006)	0.466	1.003 (1.000–1.006)	0.049
Hemoglobin	0.999 (0.978–1.021)	0.951	1.009 (0.995–1.024)	0.208
PLT count	0.702 (0.244–2.021)	0.512	0.912 (0.456–1.821)	0.793

HBV: Hepatitis B virus; GRWR: Graft-to-recipient weight ratio; MELD: Model for end-stage liver disease; ALT: Alanine transaminase; INR: International normalized ratio; *HR*: Hazard ratio; *CI*: Confidence interval; FFP: Fresh frozen plasma; PLTs: Platelets; PRBC: Packed red blood cell.

Table 3: Multivariate Cox proportional-hazards model for survival

Variables	90-day survival		Overall survival	
	HR (95% *CI*)	*P*	*HR* (95% *CI*)	*P*
Age			1.045 (1.005–1.086)	0.025
MELD score		0.681		0.402
GRWR		0.448		
ABO group (identical/compatible)		0.166	2.990 (1.341–6.669)	0.007
Operating time				0.332
Blood loss		0.666		0.927
PLT count (≤50×10^9/L vs. >50×10^9/L)	0.170 (0.040–0.730)	0.017		0.338
PRBC units		0.619	1.036 (1.006–1.067)	0.018
Apheresis PLT units	3.103 (1.720–5.600)	<0.001		0.661
FFP units		0.155		0.625

GRWR: Graft-to-recipient weight ratio; MELD: Model for end-stage liver disease; *HR*: Hazard ratio; *CI*: Confidence interval; PRBC: Packed red blood cell; FFP: Fresh frozen plasma; PLTs: Platelets.

factor (*HR* = 0.170, 95% *CI*: 0.040–0.730, *P* = 0.017) for 90-day survival. One unit of platelets (area under the curve = 0.687, *P* = 0.016) was decided as the appropriate cutoff value that offered sensitivity with 0.750 and specificity with 0.591 to the best prediction for survival by ROC curve analysis. When propensity score-adjustment analysis was performed, the adjusted *HR* was 3.705 (1.784–7.094) for units of platelets and 0.184 (0.040–0.845) for platelet count.

Discussion

Adult-to-adult LDLT, evolved from pediatric LT, has been regarded as a practical cure for end-stage liver diseases in recent decades, particularly in Asian countries where cultural or religious values impact access to cadavers. Although blood loss and perioperative blood transfusion (PBT) during LT have been significantly decreased with enhanced surgical techniques and anesthetic management, the impact of blood products on recipient outcomes should still be considered carefully. Previous studies have demonstrated that PBT was linked with worse outcomes in noncardiac surgery[33] and in solid malignancy resection such as gastric operations.[34]

However, little information about PBT in LDLT is known. Therefore, we studied LDLT recipients and confirmed that single-donor apheresis platelets played a negative role in 90-day survival as did pooled random donor platelets.[22] Pooled platelet concentrates are isolated from donated whole blood with the plasma method or buffy coat (BC) method. The former method prepares platelet-rich plasma by centrifuging whole blood softly at first and then spinning the plasma hard to sediment and separate platelets. Multiple units (generally 5–10) are pooled to create an adult dose shortly before transfusion. With the BC method, whole blood is centrifuged hard directly to form the BC layer, which contains PRBCs, leukocytes, and platelets. When pools of 4 or 5 BCs are prepared, the platelet-rich supernatant is made through soft-spin centrifugation.[35] Single-donor platelets (SDPs) can be obtained by apheresis, which collects platelet concentrates from a single donor using a cell separator and the remainder of blood cells are simultaneously returned to the donor via the device. Apparently, whole-blood-derived platelet (WBDP) has higher donor exposure and is associated with a higher incidence of viral transmission and allergic transfusion reaction as expected.[36,37] Various cytokines and chemokines, histamine, for instance, accumulating during the storage of plasma play important roles in allergic reactions.[36]

We therefore hypothesized that low survival rates associated with platelet transfusion described in previous research may contribute to WBDP. Nevertheless, this retrospective study revealed that SDP is an independent risk factor on 90-day survival. Pereboom *et al*.[22] retrospectively analyzed their clinical data and attributed this platelet-associated mortality in DDLT recipients to acute lung injury (ALI). Furthermore, perioperative platelet transfusion was also identified as a risk factor in lung transplantation and coronary artery bypass graft surgery.[38,39] Platelets are plasma-rich blood products, passive transfer of antileukocyte antibodies via plasma and the accumulation of inflammatory mediators during storage may contribute to lung endothelial injury.[22] Meanwhile, platelets facilitated the formation of postoperative thrombosis and ischemia/reperfusion (I/R) injury by induction of sinusoidal endothelial cell apoptosis.[23,40] However, focused on LDLT, Han *et al*.[20] found liver regeneration to increase in relation to the amount of platelet transfusion and platelet count postreperfusion. To our knowledge, platelets influence tissue regeneration by secreting various cytokines, chemokines, and growth factors; controlling of apoptosis; and interactions with progenitor cells.[41] Platelet-derived serotonin or 5-hydroxytryptamine was thought to stimulate hepatocyte mitosis *in vitro* and was responsible for liver regeneration in healthy liver donors.[23] We speculated that the adverse effect of platelets in enhancing ALI was superior to its impact on liver regeneration in the early period, so that low 90-day survival was observed. This indicated that we should not broaden the criteria for platelet transfusion only because platelets can facilitate liver regeneration. However, it is interesting to us that SDP had no impact on overall survival in this study. That may be the result of inflammation, I/R injury, or thrombosis formation associated with platelets that were only predominant for a short period. Whether

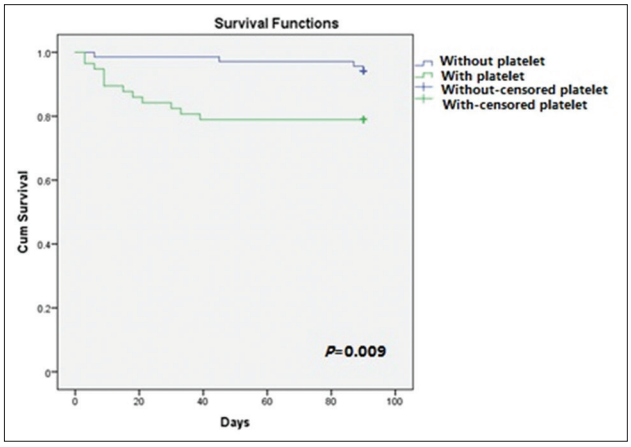

Figure 2: The 90-day survival between recipients with and without intraoperative platelet transfusion using Kaplan-Meier curves and log-rank test.

platelets play an important role in long-term follow-up will require additional research.

Regarding PRBC transfusion, previous results indicated that it was decreased 1-, 2-, and 5-year and the overall survival rate in recipients with LT.[6-8,12,15-17] We confirmed that perioperative PRBCs utilization, especially more than 10 units for LDLT, was indeed an independent risk factor for overall survival in the multivariate Cox proportional-hazards model, but we also noticed that there was no effect on 90-day survival. Because a tiny minority of patients did not receive PRBCs, we are not convinced that PRBCs have no effect on short-term outcomes. Moreover, Benson *et al*.[13] had already reported that PRBCs increased the risk of postoperative infection in a dose-dependent manner. They also implied that plasma-enriched products promoted the development of transfusion-related ALI. In addition, a large PRBCs transfusion may lead to iron overload, which may give rise to free radicals that eventually damage the cells and impair organ function. Residual donor leukocytes in PRBCs, human leukocyte antigen peptides, bioactive lipids, and preservation lesion were responsible for poor outcomes after PRBCs transfusion. Massive PRBCs transfusion will also lead to immunologic adverse effects and metabolic derangements and may facilitate the formation of hepatic artery thrombosis after LT.[42] Thus, we should avoid large PRBCs transfusions and use leukocyte reduction techniques to improve outcomes.

FFP was transfused more often in recipients with LT; however, few studies focused on it. Massicotte *et al*.[16] observed that any amount of intraoperative plasma were decreased 1-year survival in DDLT. Nacoti *et al*.[11] also found that FFP was an independent risk factor for pediatric LT. However, other research as well as ours regarding FFP mostly inferred that it was not associated with poor survival.

In this study, we affirmed that recipients' age and ABO blood group comparisons were independent risk factors for LDLT recipients in terms of overall survival and high preoperative platelet count was a protective factor for 90-day survival. As far as we know, antibody-mediated rejection (AMR) can be induced by anti-donor ABO antibodies. Methods of desensitization to alleviate AMR such as plasmapheresis, splenectomy, aggressive immunosuppression, and intravenous immunoglobulin may result in unsatisfactory outcomes.[43] Although no ABO-incomparable transplantation was performed in this population, the result showed that long-term outcomes of ABO-identical transplantation were still better than ABO-compatible ones. As the majority of the previous research only focused on the discrepancy between ABO-compatible and ABO-incompatible LT, whether ABO-identical LT was really superior to ABO-compatible LT remains unknown. We supposed that it may share a similar mechanism as the ABO-incompatible LT, leading to worse outcomes such as high occurrence of rejection, severe infection, and biliary duct and vascular complications. As for advanced age, worse outcomes are reported earlier, especially for Child-Pugh class C patients. Elderly recipients may had a worse response to anti-infection therapy once they were admitted to ICU after LT and may suffer an increased incidence of malignancies.[44,45] GRWR and MELD score were not identified as risk factors in univariate and multivariate analyses possibly because of the small sample size.

Several limitations existed in the present study. First, this study was conducted by retrospectively reviewing previous clinical data, so we could not prove causality between blood transfusion and patient's survival, the statistical associations of perioperative SDP (apheresis) and RBC transfusion with early- and late-term postoperative mortality after LDLT might not be causal relationship. Although we had estimated sample size by mimicking a prospective cohort study focusing on platelet transfusion before data collection, the 66 patients necessary in the exposure and control groups were not satisfied in this study. Only 57 recipients had a perioperative platelet transfusion experience. The small total sample size, a relatively large proportion of censored data, and risk factors such as intraoperative adverse cardiovascular events, use of inotropic agents, and surgical complications were not taken into consideration may have led to the weakness of the multivariate Cox model. Therefore, a large sample, multicenter, prospective study is necessary. Another criticism was that we did not take preoperative blood transfusions and other postoperative related risk factors into consideration. Finally, graft survival might be as important as patient survival and it should be considered as an outcome criterion. Unfortunately, this information was missed in medical records for numerous patients during that time.

In conclusion, this study found that perioperative apheresis platelet transfusion was associated with lower 90-day survival and high preoperative platelet count was a protective factor for LDLT recipients. However, platelets had no effect on overall survival. We also recognized that lower preoperative platelet count, higher MELD score and more PRBCs transfusions were independent predictors for perioperative platelet transfusion. Meanwhile, we confirmed the relationship between PRBC transfusion and poor overall

survival in Cox analysis. Apart from PRBCs, the recipient's age and ABO-blood group comparison were identified as independent risks factors for overall survival in LDLT recipients. Furthermore, we did not find that FFP transfusion influenced a patient's short- or long-term outcomes. Although we could not reach a direct causal conclusion, we still considered that the results of this study are beneficial to anesthesiologists and surgeons when they decide whether to use blood products in LDLT.

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Conflicts of interest

There are no conflicts of interest.

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活体肝移植围术期单采血小板与红细胞输注影响患者生存

摘要

背景：尽管已有研究证实围术期输血与肝移植术后不良预后相关，但关于单采血小板对活体肝移植预后影响的研究仍缺乏。本研究旨在评估血制品输注对活体肝移植预后的影响，尤其是来自单采血小板的作用。

方法：这是一项基于126例活体肝移植受者临床资料的回顾性研究，本研究评估了包括血制品输注情况在内的24个变量与短期及总体生存情况的关系。生存分析采用Kaplan-Meier曲线及log-rank检验，单因素Cox分析确定潜在危险因素后再使用多因素Cox分析及倾向性评分法调整混杂因素。

结果：输注单采血小板的受者较未输注者90天累积生存率更低 (78.9% vs. 94.2%, P=0.009)，但在总体生存率方面却无差别。单采血小板输注单位量 (HR=3.103, 95% CI: 1.720–5.600, P<0.001)及术前血小板计数（HR=0.170, 95% CI: 0.040–0.730, P=0.017）对90天累计生存率有着独立影响。多因素Cox回归分析后还发现，红细胞输注单位量 (HR=1.036, 95% CI: 1.006–1.067, P=0.018), 受者年龄（HR=1.045, 95% CI: 1.005–1.086, P=0.025）及供受者ABO血型相符情况 （HR=2.990, 95% CI: 1.341–6.669, P=0.007）是活体肝移植后影响总体生存的独立危险因素。

结论：本回顾性研究提示单采血小板输注仅与早期死亡率相关而对总体生存情况未产生影响，红细胞输注量、受者年龄与供受者ABO血型相符情况为活体肝移植术后长期生存的独立预测因素。