The Impact of Intraoperative Transfusion of Platelets and Red Blood Cells on Survival After Liver Transplantation

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BACKGROUND: Intraoperative transfusion of red blood cells (RBC) is associated with adverse outcome after orthotopic liver transplantation (OLT). Although experimental studies have shown that platelets contribute to reperfusion injury of the liver, the influence of allogeneic platelet transfusion on outcome has not been studied in detail. In this study, we evaluate the impact of various blood products on outcome after OLT.

METHODS: Twenty-nine variables, including blood product transfusions, were studied in relation to outcome in 433 adult patients undergoing a first OLT between 1989 and 2004. Data were analyzed using uni- and multivariate stepwise Cox's proportional hazards analyses, as well as propensity score-adjusted analyses for platelet transfusion to control for selection bias in the use of blood products.

RESULTS: The proportion of patients receiving transfusion of any blood component decreased from 100% in the period 1989–1996 to 74% in the period 1997–2004. In uni- and multivariate analyses, the indication for transplantation, transfusion of platelets and RBC were highly dominant in predicting 1-yr patient survival. These risk factors were independent from well-accepted indices of disease, such as the Model for End-Stage Liver Disease score and Karnofsky score. The effect on 1-yr survival was dose-related with a hazard ratio of 1.377 per unit of platelets ($P = 0.01$) and 1.057 per unit of RBC ($P = 0.001$). The negative impact of platelet transfusion on survival was confirmed by propensity-adjusted analysis.

CONCLUSION: This retrospective study indicates that, in addition to RBC, platelet transfusions are an independent risk factor for survival after OLT. These findings have important implications for transfusion practice in liver transplant recipients.

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Over the past decade, a variety of donor and recipient characteristics has been identified as risk factors influencing graft and patient survival after orthotopic liver transplantation (OLT). With knowledge and anticipation of these factors, graft and patient survival have improved substantially.[1] Important factors affecting patient and graft survival rates after OLT include primarily the indication for transplantation, pretransplant morbidity, renal function, the Model for End-Stage Liver Disease (MELD) score, Child-Turcotte-Pugh score (CTP), donor and recipient age, year of transplantation, primary dysfunction after transplantation, the warm and cold ischemia times, and type of immunosuppression.[2–13]

In addition to these recipient- and donor-related factors, several studies have shown that intraoperative blood loss and red blood cell (RBC) transfusion requirements have a negative impact on outcome after OLT.[14,15] The risk of allogeneic blood transfusion extends beyond viral transmission and includes allergic reactions, alloimmunization, bacterial sepsis, transfusion-related acute lung injury, renal failure, excessive intravascular volume, and immunosuppressive effects.[16] Most previous studies of OLT have focused on the impact of RBC transfusions only, ignoring the possible additional effect of other blood components, such as fresh frozen plasma (FFP) and platelet concentrates. In patients undergoing cardiac surgery, platelet transfusions have been identified as an independent risk factor for adverse postoperative outcome.[17] In addition, animal models of OLT have shown that platelets are critically involved in the pathogenesis of reperfusion injury of the liver.[18,19] Based on these experimental studies, it has been suggested that platelet transfusions should best be avoided in patients undergoing OLT. The influence of various blood components on outcome after clinical liver transplantation, however, has not been studied in detail. Moreover, blood transfusions may

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simply be a surrogate marker for sicker patients and more complex surgery and have no direct causal role in outcome.

The purpose of this study was to evaluate the effect of transfusion of individual blood products on outcome after OLT, as reflected by patient and graft survival rates. By including variables reflecting severity of disease and surgical risk factors for excessive blood loss (e.g., previous abdominal surgery), and by using propensity score-adjusted statistical analysis, we have attempted to limit the influence of possible confounding factors related to both blood transfusion and outcome.

METHODS

Patients

Seven hundred and forty-nine consecutive OLTs were performed in our center between January 1, 1989, and December 31, 2004. After excluding pediatric transplants (age <18 yr; $n = 236$), retransplantations ($n = 69$) and combined organ transplantations ($n = 11$), 433 adult patients undergoing a first OLT formed the basis of the current study. The end of follow-up was September 1, 2005. Characteristics of the patients, including donor and recipient variables, as well as surgical factors were obtained from a prospectively maintained computer database. When necessary, the original patient notes were reviewed for missing information. The maximum percentage of missing data per variable was 4%. National legislation and the ethical committee of our institution approved this retrospective study.

Surgical Technique

ABO blood group identical or compatible grafts from deceased brain-death donors and donation after cardiac death donors were used for all patients. Organ procurement was performed according to standard techniques.[20] Both the conventional technique for OLT and the cava-sparing piggyback technique were used for implantation.[21] The piggyback technique was first performed in our center in 1994 and it has become the preferred surgical technique in most patients since 1997.[22] Before 1997, venovenous bypass was used in most cases of conventional OLT, but in recent years, it is rarely used.

Anesthetic Management and Blood Transfusion Policy

Anesthesia was maintained with a total IV technique using sufentanil, midazolam, and vecuronium, and volume-controlled ventilation. Aprotinin was administered in all patients, except patients with known thrombophilia or preexisting thrombotic conditions, or signs of hypercoagulability on thrombelastography at time of induction of anesthesia. Based on evolving scientific evidence concerning the efficacy of aprotinin, guidelines have been slightly adapted during the study period.[23]

The transfusion policy in our center is characterized by a restrictive use of blood products. Blood loss was counteracted by transfusion of allogeneic RBC, with the aim to maintain hematocrit between 0.25 and 0.30. In addition, the cell saver device (Hemonetics, Braintree, MA) was used in selected patients when excessive blood loss was anticipated. Administration of other blood products such as FFP and platelets was never solely dictated by laboratory values. These products were only given in the presence of excessive blood loss, which could not be controlled by standard surgical measures. FFP was then administered to correct prolonged prothrombin time, or prolonged *r*-value on thromboelastography. Fibrinogen concentrate or cryoprecipitate was given when fibrinogen levels decreased to <70 mg/dL, despite administration of FFP. Platelet concentrates were given in the above-mentioned situation if platelet count decreased to $<50 \times 10^9$/L. Until 1999, all patients received a lower body convective warming blanket (Warm Touch, Nellcor, Pleasanton, CA) and an esophagus heating device (Thermal Tube, TTA-2250, Maquet, Rastatt, Germany). After 1999, a lower body and upper body convective warming blanket was used.

Postoperative Management

Two types of immunosuppressive schemes were used. A triple immunosuppressive scheme, consisting of cyclosporine A, azathioprine, and small-dose prednisolone, was used for patients with autoimmune diseases such as autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis. All other patients received tacrolimus and small-dose prednisolone. In patients with compromised kidney function, calcineurin inhibitors were withheld until creatinine clearance was more than 50 mL/min and induction therapy with two doses of 20 mg/day basiliximab, with an interval of 4 days, was started.

Only biopsy-proven rejections were treated with a bolus of methylprednisolone on three consecutive days. Steroid-resistant rejections were treated either by conversion to tacrolimus in patients on cyclosporine A or by giving five doses of antithymocyte globulin 4 mg/kg IV on alternative days.

Risk Factors and Outcome Variables

Risk factors determined to be meaningful predictors of patient and graft survival were selected based on a review of the literature. The following recipient-related variables were included: age, sex, year of transplantation, body mass index, previous abdominal surgery, indication for transplantation, preoperative Karnofsky score, preoperative CTP score and MELD score, preoperative hemoglobin, hematocrit, platelet count, prothrombin time, serum total bilirubin level, serum creatinine level, postoperative immunosuppressive drug scheme (cyclosporine versus tacrolimus-based), acute rejection, and length of stay in the intensive care unit. Donor-related variables included age, sex, type of donor (deceased

brain-death versus donation after cardiac death), and graft type (full size versus partial grafts). In addition, the following surgical variables were studied: surgical technique (conventional versus piggyback), operating time, and cold and warm ischemia time. With respect to intraoperative blood component transfusion requirement, the following variables were analyzed: the number of units of allogeneic and autologous RBC (1 U contained 300 mL), units of FFP (1 U contained 250 mL), and units of platelets concentrates (1 U contained approximately 150 mL and was obtained from five donors).

Initial data analysis, as well as results obtained from the literature, allowed us to categorize continuous variables, such as age, MELD score, ischemia times, and units of blood products, into dichotomous or ordinal variables with discrete clinically meaningful cut-off points. For RBC transfusion, previous studies have shown that the requirement of $\geq$6 U is a clinically relevant cut-off value.[14]

Patient survival was defined as the time period between transplantation and the end of follow-up or patient death. Graft survival was defined as the time period between transplantation and the end of follow-up or graft loss by patient death or by graft failure requiring retransplantation.

Statistical Analysis

Continuous variables are presented as medians with ranges and categorical variables as numbers with percentages. Patient and graft survival rates were calculated according to the Kaplan–Meier method, and differences between groups were investigated using the log-rank test. Categorical variables were compared using the Pearson's χ^2 test or Fisher's exact test. Comparison of continuous variables was performed using the Mann–Whitney *U*-test. All variables tested in the univariate analysis with a $P \leq 0.10$ were included in a multivariate survival analysis, using stepwise Cox proportional hazard models with forward elimination. To determine the additional risk of each unit transfused, blood products were entered as continuous variables into the multivariate analysis. In addition, propensity score-based stratification in quintiles was used to study the impact of platelet transfusion on outcome (platelet transfusion versus no platelet transfusion). The propensity score is a single probability function in which confounding covariates are summarized and which can be used to control for all confounding covariates that could potentially affect treatment decision.[24] Propensity scores were calculated for each patient, based on a stepwise multiple logistic regression model consisting of the following covariates: preoperative platelet count, hematocrit, serum creatinine, MELD score, indication, era of transplantation, donor age and gender, operating time, type of graft and venous anastomosis, cold and warm ischemia time, and transfusion of RBC, FFP, and cell saver blood. The area under the receiver operating characteristic curve (*C*-index), for this model was 0.88, indicating good discrimination between patients receiving platelets transfusion or not. Statistical tests were assumed to have reached significance at the conventional level of 0.05. Statistical analysis was performed using the SPSS/PC Advanced Statistics Package, Version 12.0 (SPSS, Chicago, IL).

RESULTS

Patients Characteristics

Patient and donor characteristics as well as surgical variables for the entire group of 433 patients are summarized in Table 1. Median postoperative follow-up was 98 mo (range, 8–200 mo). One- and 5-yr patient survival rates were 84% and 76%, respectively. Graft survival rates at 1 and 5 yr were 78% and 67%, respectively.

Intraoperative Transfusion of Blood Products

The median (range) requirement of blood products for the entire study period was 7 U of RBC (0–105 U), 9 U of FFP (0–51 U), and 0 U of platelet concentrate (0–4 U) (Table 1). The use of blood products decreased during the study period (Table 2). The proportion of patients receiving transfusion of any blood component decreased from 100% in the period 1989–1996 to 74% in the most recent years (1997–2004) (Table 3).

The Impact of Platelet and Allogeneic RBC Transfusion on Survival

Patient survival after OLT was significantly associated with the number of allogeneic RBC or platelet concentrates transfused during surgery (Figs. 1 and 2). Although the observed step-wise relationship between the number of units transfused and survival is suggestive of a causal role, these observations could also mean that blood product transfusion is simply a surrogate marker for sicker patients. We, therefore, performed multivariate regression analysis including possible confounding factors, such as severity of disease, comorbidity, and previous abdominal surgery.

Uni- and Multivariate Analysis of Patient Survival

The results of univariate analysis of all potential risk factors for 1- and 5-yr patient survival are summarized in Table 4. Of the 26 variables studied, 11 were associated with 1- and 5-yr patient survival. Apart from the well-known variables associated with patient survival, such as the era of transplantation, significant factors affecting survival were indication for transplantation, severity of disease (e.g., Karnofsky score, CTP score and MELD score), graft type, and ischemia times, and all types of blood product transfusion (autologous and allogeneic RBC, FFP, and platelets). When entering all variables with a P value <0.10 into a multivariate Cox regression model, only three variables remained as independent predictors of 1-yr patient survival, whereas four variables were independent risk factors for 5-yr survival (Table 5). Platelet transfusions and RBC transfusions were highly dominant in predicting patient survival. Although indices of disease severity, such as

Table 1. Characteristics of the Study Population (1989–2004)

Variable	Study population (n = 433)
Recipient variables	
Age (yr)	45 (18–68)
Gender	
Male	224 (52%)
Female	209 (48%)
Era of transplantation	
1989–1996	195 (45%)
1997–2004	238 (55%)
BMI	24 (15–42)
Indication for transplantation	
Biliary cirrhosis	131 (30%)
Postnecrotic cirrhosis	222 (51%)
Acute liver failure	37 (9%)
Metabolic disease	16 (4%)
Miscellaneous	26 (6%)
Karnofsky score	60 (10–100)
CTP score	
CTP A	66 (16%)
CTP B	165 (38%)
CTP C	199 (46%)
MELD score	16 (6–40)
Serum creatinine before OLT (μmol/L; normal <110 μmol/L)[a]	84 (34–735)
Serum total bilirubin before OLT (μmol/L; normal 0–17 μmol/L)[a]	67 (5–1343)
INR before OLT	1.5 (0.9–15.6)
Platelet count before OLT ($\times 10^9$/L; normal, 150–350)	89 (2–651)
Hemoglobin before OLT (mmol/L; normal, 8.7–10.2)[a]	6.8 (3.1–9.9)
Hematocrit before OLT (normal, 0.33–0.40)	0.32 (0.14–0.50)
Previous abdominal surgery	
No previous surgery	316 (74%)
Previous surgery right upper abdomen	111 (26%)
Rejection	
No rejection	223 (52%)
Mild rejection, untreated	90 (21%)
Rejection treated	115 (27%)
Immunosuppression (initial postoperative period)	
Tacrolimus based	90 (21%)
Cyclosporin based	336 (79%)
Length of intensive care stay (d)	4 (0–155)
Length of total hospital stay (d)	39 (0–235)
Donor variables	
Age (yr)	42 (11–72)
Gender	
Male	219 (53%)
Female	202 (47%)
Donor-recipient gender match	
Male–male	124 (29%)
Female–female	107 (25%)
Male–female	95 (23%)
Female–male	95 (23%)
Type of donor liver	
Deceased donor (brain death)	429 (99%)
Donation after cardiac death (DCD)	4 (1%)
Graft size	
Full size	421 (97%)
Reduced size or split	12 (3%)
Transplantation variables	
Operating time (min)	540 (280–1080)
Venous anastomosis	
Classic	252 (58%)
Piggyback	181 (42%)
CIT[b] (min)	600 (203–1440)
WIT[c] (min)	55 (20–129)
RBC (units) (allogeneic)	7 (0–105)
FFP (units)	9 (0–51)
Platelets (units)	0 (0–4)
Cell saver RBC (units)	0 (0–81)
Antifibrinolytic drugs used	
No	243 (58%)
Aprotinin	160 (38%)
Tranexamic acid	16 (4%)

Data represent numbers (percentages) for categorical variables or median (range) for continuous variables.

For some variables the total number of cases may be less than 433, reflecting missing data (overall <4%).

BMI = Body Mass Index; CTP = Child Turcotte Pugh score; MELD = model of end-stage liver disease; CIT = cold ischemia time; WIT = warm ischemia time; RBC = red blood cell transfusion; FFP = fresh frozen plasma transfusion; DCD = donation after cardiac death; OLT = orthotopic liver transplantation; INR = International Normalized Ratio.

[a] To convert the value for creatinine to mg/dL, divide by 88.4. To convert the value for bilirubin to mg/dL, divide by 17.1. To convert the value for hemoglobin to g/dL, divide by 0.62.

[b] Time from in situ flushing of the donor organ until the liver is removed from ice for implantation.

[c] Time from removal of liver from ice until reperfusion via portal vein, hepatic artery or both.

the Karnofsky score and MELD score, were not associated with posttransplant survival in multivariate analysis, patients receiving RBC or platelets may still be sicker than patients who do not need transfusion.

To exclude the effect of a possible interaction between transfusions and disease severity, we performed a second multivariate analysis including the interactions of RBC and platelets with the Karnofsky score and MELD score. The results of this second model were similar to the results of the first model with a hazard ratio (HR) of 1.359 per unit of platelets ($P = 0.014$) and 1.055 per unit of RBC ($P < 0.001$) for 1-yr survival and an HR of 1.429 per unit of platelets ($P = 0.001$) and 1.047 per unit of RBC ($P = 0.001$) for 5-yr survival.

To further eliminate the effect of selection bias for platelet transfusion, we performed a propensity score-adjusted analysis as described above. The propensity-adjusted HR for 1-yr survival in patients who received platelet transfusion was 2.613 (95% confidence interval, 1.315–5.192; $P = 0.012$).

Uni- and Multivariate Analysis of Graft Survival

The results of univariate analysis of all potential risk factors for 1- and 5-yr graft survival are summarized in Table 6. Of the 26 variables studied, 9 were identified to be associated with 1- and 5-yr graft survival. As for patient survival, all types of blood product transfusion (RBC, FFP, and platelets) were negatively associated with graft survival. Other significant factors were indication for OLT, acute rejection, graft type, era of OLT, and ischemia times. After

Table 2. Median Number (Interquartile Range) of Units Transfused per Era

Era	Allogeneic RBC transfusion	Cell saver RBC transfusion	Platelet transfusion	FFP transfusion
1989–1996	12 (8–18)	2 (0–6)	1 (0–1)	17 (11–22)
1997–2004	2.5 (0–6)	0 (0–1)	0 (0–1)	2 (0–7)
Total	7 (2–12)	0 (0–3)	0 (0–1)	9 (2–18)

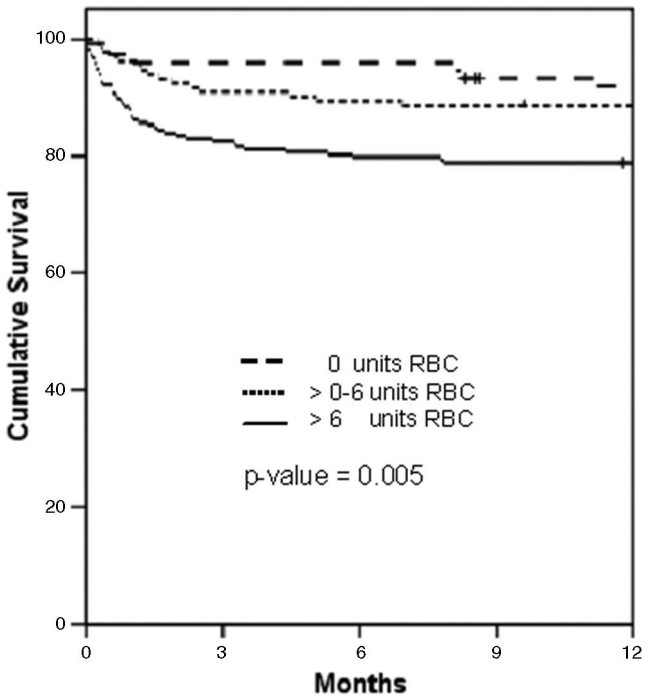
RBC = red blood cell; FFP = fresh frozen plasma.

Table 3. Percentage of Patients Receiving Blood Transfusion per Era

Era	Allogeneic RBC transfusion (%)	Cell saver RBC transfusion (%)	Platelet transfusion (%)	FFP transfusion (%)	Any transfusion (%)
1989–1996	100 (192/194)	58 (112/194)	56 (109/194)	100 (192/194)	100 (193/194)
1997–2004	69 (163/236)	25 (60/237)	30 (71/236)	59 (140/236)	74 (175/236)
Total	82 (355/430)	40 (172/431)	42 (180/430)	77 (332/430)	86 (368/430)

Total of cases may be less than 433, representing missing data (<1%).

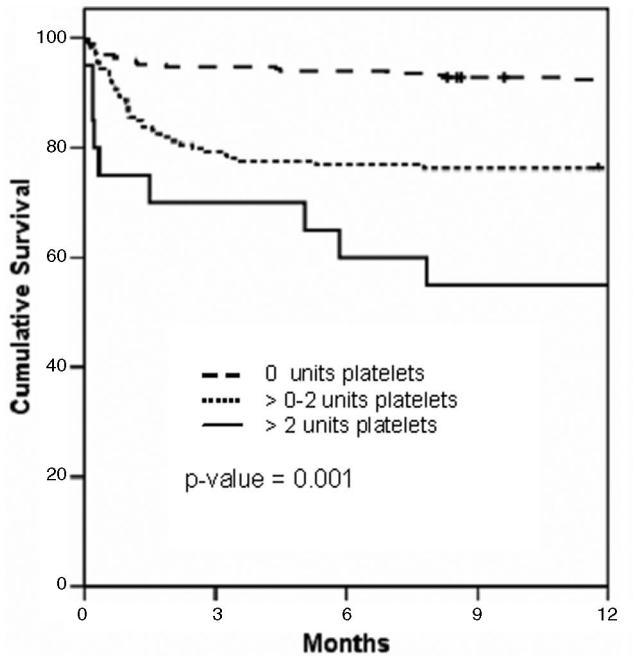
RBC = red blood cell; FFP = fresh frozen plasma.



Numbers at risk

RBC (U)	Months 0	3	6	9	12
0	75	72	72	67	66
>0-6	136	123	121	120	117
>6	219	181	175	173	171

Figure 1. Kaplan–Meier curves representing cumulative patient survival in relation to the number of intraoperative red blood cell (RBC) transfusion requirements.



Numbers at risk

Platelets (U)	Months 0	3	6	9	12
0	250	235	233	227	223
>0-2	160	127	123	122	121
>2	20	14	12	11	11

Figure 2. Kaplan–Meier curves representing cumulative patient survival in relation to the number of intraoperative platelet transfusions.

multivariate analysis, only the following three variables were identified as independent risk factors for 1-yr graft survival: RBC transfusions, indication for OLT, and graft type (Table 7). The following four variables were independent risk factors for 5-yr graft survival: RBC transfusion, indication for transplantation, graft size, and cold ischemia time.

DISCUSSION

Developing OLT as a therapy for patients with end-stage liver disease would not have been possible

Table 4. Univariate Analysis of Patient Survival

Variable	*n*	1-yr Percent	1-yr *P*	5-yr Percent	5-yr *P*
Recipient variables					
Age (yr)					
<55	333	85	0.547	77	0.468
>55	100	82		74	
Gender					
Male	224	84	0.709	74	0.265
Female	209	85		78	
BMI					
<20	56	86	0.285	84	0.031[a]
20–30	336	85		77	
30+	32	75		59	
Indication for transplantation					
Biliary cirrhosis	131	92	<0.001[a]	85	0.006[a]
Postnecrotic cirrhosis	222	84		73	
Acute liver failure	37	60		60	
Metabolic disease	16	88		75	
Miscellaneous	26	81		81	
Karnofsky score					
0–40	145	72	<0.001[a]	68	0.009[a]
50–70	189	92		81	
80–100	99	87		79	
CTP score					
A	66	88	0.015[a]	80	0.009[a]
B	165	89		82	
C	199	78		69	
Serum creatinine					
Normal (♀ <110 μmol/L, ♂ <120 μmol/L)	333	86	0.053[a]	78	0.095[a]
Abnormal (♀>110 μmol/L, ♂ >120 μmol/L)	100	78		70	
MELD-score			0.009[a]	Cont	0.023[a]
MELD category					
<11	81	89	0.018[b]	80	0.202
11–18	170	86		79	
19–24	73	89		77	
>25	91	74		69	
Platelet count before OLT ($\times 10^9$/L)			0.158		0.143
Hemoglobin before OLT (mmol/L)			0.214		0.314
Hematocrit before OLT			0.243		0.282
Previous abdominal operations					
Yes	111	88	0.689	78	0.712
No	316	85		77	
Rejection					
No	223	83	0.201	75	0.520
Mild, untreated	90	90		80	
Yes, treated	115	86		77	
Immunosuppression					
Tacrolimus	90	90	0.150	83	0.126
Cyclosporin	336	84		76	
Donor variables					
Age (yr)					
<40	186	86	0.330	78	0.277
>40	247	83		75	
Gender					
Male	219	83	0.459	76	0.823
Female	202	86		77	
Donor-recipient gender match					
Male–male	124	84	0.875	76	0.681
Female–female	107	86		80	
Male–female	95	82		76	
Female–male	95	85		73	
Type donor liver					
Deceased (brain death)	429	84	0.404	76	0.402
DCD	4	100		100	

Table 4. Continued

Variable	*n*	1-yr Percent	1-yr *P*	5-yr Percent	5-yr *P*
Graft size					
Full size	421	85	0.009[a]	77	0.078[a]
Split/reduced size	12	58		58	
Transplantation variables					
Year of transplantation					
1989–1996	195	81	0.120	71	0.067[a]
1996–2004	238	87		80	
Operating time (cont)			0.781		0.862
Venous anastomosis					
Classic	252	82	0.298	73	0.192
Piggy back	181	86		80	
CIT					
<12 h	286	87	0.022[a]	82	0.001[a]
>12 h	143	78		64	
WIT					
<60 min	266	86	0.095[a]	80	0.016[a]
>60 min	163	80		69	
RBC units (allogeneic)			<0.001[a]		<0.001[a]
RBC units					
0	75	92	0.007[b]	87	0.004[b]
0–6	136	88		82	
>6	219	79		69	
FFP units			<0.001[a]		<0.001[a]
FFP units					
0	98	94	<0.001[b]	89	0.001[b]
0–4	50	94		86	
>4	281	79		70	
Platelets units			<0.001[a]		<0.001[a]
Platelets units					
0	250	92	<0.001[b]	84	<0.001[b]
>0–2	160	76		68	
>2	20	55		40	
Cell saver RBC units			0.075[a]		0.013[a]
Cell saver RBC					
0	258	86	0.092[b]	80	0.082[b]
0–6	106	86		75	
>6	66	76		65	
Antifibrinolytic use					
No	243	86	0.235	79	0.033[a]
Yes	176	81		71	

Cont = continuous variables; BMI = Body Mass Index; CTP = Child Turcotte Pugh score; MELD = model of end-stage liver disease; RBC = red blood cell transfusion; FFP = fresh frozen plasma transfusion; CIT = cold ischemia time; WIT = warm ischemia time; DCD = donation after cardiac death; OLT = orthotopic liver transplantation.

For some variables the total number of cases may be less than 433, representing missing data (overall <4%).

[a] Included in multivariate analyses.

[b] Continuous variables were used for multivariate analysis.

without therapeutic approaches for bleeding, including blood products. Advances in the surgical and anesthetic management of patients undergoing OLT, as well as better understanding of risk factors for massive blood loss, have resulted in a steady decrease in intraoperative blood loss and transfusion requirements.[14,25–27] Currently, several centers report the complete avoidance of RBC transfusions in up to 40% of their OLT recipients.[14,25,26,28] Despite these major achievements, most OLT recipients require blood product transfusions. However, there is increasing evidence that transfusion of blood products is associated with side effects.[16,29] Our study confirms previous reports suggesting that intraoperative RBC transfusions are an independent risk factor for patient survival after OLT.[14,15] More importantly, this study identified the transfusion of platelet concentrates as an important prognostic factor for survival after OLT in addition to RBC transfusions. This negative effect of platelets is in agreement with a study by Spiess et al.[17] reported in patients undergoing cardiac surgery.

The risk of allogeneic blood transfusion extends beyond viral transmission and includes allergic reactions, alloimmunization, bacterial sepsis, transfusion-related acute lung injury, graft-versus-host-disease, renal failure, and immunosuppressive effects.[16,29] Of all blood components, most previous studies have focused on the adverse effects of RBC transfusions. In OLT recipients, clinical studies have shown that even

Table 5. Multivariate Cox Regression Analysis of Patient Survival

	1-yr patient survival		5-yr patient survival	
Variable	*P*	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)
Indication				
Biliary cirrhosis	0.020	†	*	*
Acute liver failure		4.206 (1.653–10.070)		
Postnecrotic cirrhosis		1.500 (0.729–3.086)		
Metabolic disease		3.548 (0.764–16.475)		
Miscellaneous		1.232 (0.385–3.946)		
RBC units (allogeneic)	<0.001	1.055 (1.036–1.076)	0.001	1.047 (1.028–1.067)
Platelets units	0.014	1.359 (1.064–1.736)	0.001	1.429 (1.166–1.751)
CIT	*	*	0.002	0.494 (0.315–0.776)
Era of transplantation	*	*	0.008	0.515 (0.315–0.843)

CIT = cold ischemia time; RBC = red blood cell transfusion.

* Not statistically significant after multivariate analysis.

† Biliary cirrhosis was used as the reference category for indication.

a moderate number of RBC transfusions is associated with longer hospital stay, and transfusion of more than six RBC transfusions has been associated with diminished survival[14,15,28] Even today, centers with median RBC transfusion requirements of 2–3 U in adult patients still report a significant correlation between intraoperative blood transfusion requirement and postoperative infection rate and morbidity.[14,15,28–32] The impact of RBC transfusion has been shown to be independent of other well-known predictors of surgical blood loss and posttransplant survival, such as previous abdominal surgery, renal failure, other comorbidities, and the severity of liver disease. Although the exact mechanisms underlying the adverse effects of RBC transfusions are not fully elucidated, residual amounts of donor leukocytes present in RBC transfusions, as well as preservation-related changes in erythrocytes, are assumed to be involved.[33–36] Currently, leukoreduction technologies are increasingly used according to local and national regulations.[37] Whether these technologies will lead to a decrease of transfusion-related complications will need to be validated.[37] Other studies have suggested that duration of storage of transfused RBC is an important factor for transfusion-associated complications.[38] Unfortunately, we did not have access to the storage time of RBC or other blood products used in our patients.

There are few data on the negative effect of platelet transfusion on patient survival after OLT, as suggested in the current study. A negative effect of platelet transfusion on graft survival has been described previously.[39] In this study, patients were arbitrarily divided in two groups based on the transfusion of more than 20 U of platelets. This study of platelet transfusions is less relevant to current practice, because fewer platelet transfusions are administered.

Many cirrhotic patients undergoing OLT have a low platelet count due to hypersplenism, increased platelet consumption, bone marrow depression, and reduced thrombopoietin levels.[40–42] Platelet concentrates are frequently administered during OLT for the prevention or treatment of bleeding. Although the "Practice Guidelines for Perioperative Blood Transfusion" of the American Society of Anesthesiologists do not recommend prophylactic administration of platelets in patients undergoing surgery,[43] a recent survey indicated that most centers would use prophylactic platelet administration in cirrhotic patients undergoing invasive procedures.[44] However, there is no consensus regarding the appropriate threshold for platelet transfusion. Platelet transfusion-related complications are among the leading causes of fatalities associated with blood product transfusions in the United States.[17] In a study of 1720 patients undergoing coronary artery bypass graft surgery, Spiess et al.[17] identified platelet transfusion as an important risk factor for serious adverse events such as infection, vasopressor use, respiratory medication use, stroke, multiorgan failure, and death. Using multivariate logistic regression analysis with propensity score adjustments for confounding variables, a five times higher death rate was identified in patients who received platelet transfusion.[17]

In experimental liver transplantation, several studies have demonstrated that platelets are involved in the pathogenesis of reperfusion injury of the liver graft by inducing endothelial cell apoptosis.[18,19] This effect is independent of ischemia-related endothelial cell injury and cannot simply be explained by activation of the coagulation system and aggregation of platelets at the site of endothelial cell injury.[18,19,45,46] There is compelling evidence that the role of platelets is not limited to their well-known involvement in hemostasis. Platelets contain many cytokines and vasoactive and inflammatory mediators, which are rapidly released on activation by various stimuli after reperfusion. In addition, during procurement and preparation of platelet concentrates for transfusion, additional changes may occur. Platelets

Table 6. Univariate Analysis of Graft Survival

Variable	*n*	1-yr %	1-yr *P*	5-yr %	5-yr *P*
Recipient variables					
Age (yr)					
<55	333	78	0.896	67	0.929
>55	100	78		69	
Gender					
Male	224	80	0.224	68	0.590
Female	209	75		67	
BMI					
<20	56	77	0.695	75	0.137
20–30	336	79		68	
30+	32	72		53	
Indication for transplantation					
Biliary cirrhosis	131	83	<0.001*	76	0.013*
Postnecrotic cirrhosis	222	80		66	
Acute liver failure	37	54		51	
Metabolic disease	16	75		63	
Miscellaneous	26	65		62	
Karnofsky score					
0–40	145	68	0.003*	63	0.265
50–70	189	84		70	
80–100	99	79		69	
CTP score					
A	66	79	0.356	70	0.244
B	165	81		72	
C	199	74		63	
Serum creatinine					
Normal (♀ <110 μmol/L, ♂ <120 μmol/L)	333	79	0.308	68	0.667
Abnormal (♀ >110 μmol/L, ♂ >120 μmol/L)	100	74		66	
MELD-score			0.189		0.487
MELD category					
<11	81	80	0.085†	68	0.586
11–18	170	79		71	
19–24	73	85		70	
>25	91	69		64	
Platelet count before OLT ($\times 10^9$/L)			0.411		0.158
Hemoglobin before OLT (mmol/L)			0.735		0.397
Hematocrit before OLT			0.803		0.429
Previous abdominal operations					
Yes	111	81	0.520	71	0.484
No	316	78		67	
Rejection					
No	223	74	0.018*	63	0.018*
Mild, untreated	90	88		78	
Yes, treated	115	80		70	
Immunosuppression					
Tacrolimus based	90	86	0.065*	76	0.105
Cyclosporin based	336	77		67	
Donor variables					
Age (yr)					
<40	186	80	0.361	70	0.208
>40	247	76		66	
Gender					
Male	219	77	0.703	68	0.987
Female	202	79		68	
Donor-recipient gender match					
Male–male	124	80	0.456	68	0.870
Female–female	107	76		65	
Male–female	95	74		67	
Female–male	95	82		71	
Type donor liver					
Deceased (brain death)	429	77	0.332	67	0.332
DCD	4	100		100	
Graft size					
Full size	421	79	<0.001*	69	<0.001*
Split/reduced size	12	25		25	

Table 6. Continued

Variable	*n*	1-yr %	1-yr *P*	5-yr %	5-yr *P*
Transplantation variables					
Year of transplantation					
1989–1996	195	74	0.167	62	0.094*
1996–2004	238	80		72	
Operating time			0.736		0.866
Venous anastomosis					
Classic	252	77	0.600	64	0.242
Piggyback	181	79		72	
CIT					
<12 h	286	81	0.018*	74	<0.001*
>12 h	143	71		54	
WIT					
<60 min	266	80	0.153	73	0.020*
>60 min	163	74		60	
RBC units (allogeneic)			<0.001*		<0.001*
RBC units					
0	75	91	0.002†	85	0.002†
0–6	136	80		69	
>6	219	72		60	
FFP units			<0.001*		<0.001*
FFP units					
0	98	88	0.001†	83	0.003†
0–4	50	90		74	
>4	281	72		61	
Platelets units			<0.001*		<0.001*
Platelets					
0	250	84	<0.001†	74	<0.001†
>0–2	160	71		61	
>2	20	55		35	
Cell saver blood units			0.081*		0.025*
Cell saver blood units					
0	258	80	0.102†	72	0.236
0–6	106	79		64	
>6	66	68		59	
Antifibrinolytic use					
No	243	77	0.933	69	0.283
Yes	176	77		66	

For some variables the total of cases may be less than 433, representing missing data (overall <4%).

Cont = continuous variables; BMI = body mass index; CTP = Child Turcotte Pugh score; MELD = model of end-stage liver disease; RBC = red blood cell transfusion; FFP = fresh frozen plasma transfusion; CIT = cold ischemia time; WIT = warm ischemia time; DCD = donation after cardiac death; OLT = orthotopic liver transplantation.

* Included in multivariate analysis.

† Continuous variables were used for multivariate analysis.

Table 7. Multivariate Cox Regression Analysis of Graft Survival

Variable	1-yr graft survival *P*	1-yr graft survival Hazard ratio (95% CI)	5-yr graft survival *P*	5-yr graft survival Hazard ratio (95% CI)
Indication				
Biliary cirrhosis	0.006	*	0.005	*
Acute liver failure		3.215 (1.607–6.432)		2.982 (1.615–5.506)
Postnecrotic cirrhosis		1.051 (0.627–1.760)		1.334 (0.873–2.039)
Metabolic disease		2.238 (0.844–7.584)		2.682 (1.098–6.549)
Miscellaneous		1.370 (0.549–3.420)		1.365 (0.622–2.993)
Graft size (full/split)	0.001	0.181 (0.086–0.382)	<0.001	0.269 (0.130–0.558)
RBC unit	0.001	1.050 (1.029–1.071)	0.001	1.032 (1.013–1.051)
CIT	†	†	0.001	0.592 (0.414–0.846)

CIT = cold ischemia time; RBC = red blood cell transfusion.

* Biliary cirrhosis was used as the reference category for indication.

† Not statistically significant after multivariate analysis.

become conjugated with leukocytes and undergo activation and expression of various cellular ligands.[17] Cytokine levels can increase as much as 1000-fold with processing, making platelet transfusions proinflammatory.[45] These substances may potentially be involved in posttransplantation inflammatory reactions, but

have not been specifically studied. Despite this experimental evidence, we have not been able to identify platelet transfusion as an independent risk factor for graft survival. Platelet transfusion was significantly associated with lower graft survival in the univariate analysis, but not in the multivariate analysis. This topic is the subject of further research in our group.

Two types of platelet products currently used worldwide are pooled random donor platelets, manufactured from whole blood donations and single donor platelets, collected by pheresis.[46,47] Pheresis from single donors is most often used in the United States, whereas many European blood banks use the less expensive method of buffy coat whole blood-derived platelet concentrates. In the current study, patients received platelet concentrates derived from five pooled random donors, resulting in a total volume of approximately 150 mL. The results of our study may not be directly extrapolated to patients who received pheresis-derived platelets from single donors because these products may not be the same. Although whole blood-derived platelets are less expensive and a more efficient use of limited donor resources, pheresis-derived platelets have been associated with a lower risk of alloimmunization and infectious complications.[46] In addition, some data suggest that different manufacturing methods of whole blood-derived platelets (platelet-rich plasma or buffy coat intermediate steps) result in differing degrees of platelet activation, which may impact the quality of stored concentrates.[47] The impact of these differences on outcome after OLT requires further investigation.

Although the current multivariate analysis provides strong support for a detrimental impact of RBC and platelet transfusions on outcome after OLT, it is difficult to prove causality in a retrospective analysis. RBC and platelet transfusions may be a surrogate marker for sicker patients and more complex surgery and have no causal role in the outcome observed. However, we have attempted to minimize the influence of these potential confounders by studying the interaction of RBC and platelets with Karnofsky and MELD scores in the second multivariate model. This did not change the results of our first multivariate analysis, indicating the negative impact of RBC and platelet transfusion is not simply related to a higher transfusion need in sicker patients. Moreover, we confirmed the negative impact of platelet transfusions on survival in a propensity score-adjusted analysis, which is currently considered to be one of the most robust statistical methods to control for selection bias for the use of specific treatment.[24] Nevertheless, in this study, we could not completely distinguish if the worse outcome in platelet-transfused patients was that they were thrombocytopenic and bleeding (the only condition under which platelets were administered) or that they received platelets. This distinction could not even be fully addressed by using propensity scores, because comparative patients who did not receive platelets (despite similar propensity scores) were either not thrombocytopenic and/or not bleeding. Definite proof could only come from prospective, randomized, controlled studies in which different transfusion thresholds are compared. Although a prospective study comparing different triggers for RBC transfusion has been performed in patients admitted to a critical care unit,[48] to our knowledge, such studies have never been performed in OLT recipients. Ethical considerations as well as the large variations in thrombocytopenia and platelet function in patients undergoing OLT make it difficult to perform such a trial. Despite the lack of randomized studies, our findings are in agreement with previous clinical studies and are reinforced by the serious detrimental effects of platelets found in experimental models of OLT.[14,15,18,19,49,50] These combined observations, both within and outside the field of liver transplantation, provide substantial support for the hypothesis of detrimental effects of RBC and platelet transfusions on outcome, independent from other risk factors.

The current results should be considered when determining the risk–benefit ratio of blood product transfusions in OLT patients. Apart from general measures to reduce blood loss, patients undergoing OLT could possibly benefit from a more restrictive blood transfusion policy.[51,52] Although we currently have no alternatives for RBC and platelet transfusions in critical situations, there is wide variability in using blood products among different centers[51,53] as well among anesthesiologists within centers.[51] Therefore, improvements in the care for liver transplant patients should not be limited to surgical and anesthetic measures to minimize intraoperative blood loss, but also include a conservative and more targeted use of blood products, weighing in each individual patient the short-term benefits versus increased postoperative risk for adverse events. As well as meticulous surgical technique, the use of prohemostatic drugs, such as aprotinin, lysine analogs, or recombinant factor VIIa, may contribute to a reduction or transfusion requirements in selected cases.[23,54,55]

In conclusion, this retrospective study confirms the negative impact of RBC transfusion on outcome after OLT. In addition, we have shown that intraoperative platelet transfusions are a strong independent risk factor for patient survival after OLT. The negative impact of platelet transfusions is independent from other well-known risk factors and in accordance with the biological adverse effects of platelets identified in patients undergoing cardiac surgery and in experimental models of OLT. Our findings have clinical implications for the use of blood products in OLT recipients, and support previous reports regarding outcomes associated with both RBC and platelet transfusions.

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