Cost and outcome of liver transplantation

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Chapter 6

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

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ABSTRACT

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 univariate and multivariate stepwise Cox's proportional hazards analyses, as well as propensity score-adjusted analyses 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 univariate and multivariate analyses, the indication for transplantation, transfusion of platelets and RBC were dominant in predicting one-year 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 one-year 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 score-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.

1 INTRODUCTION

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, pre-transplant 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 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.

2 METHODS

2.1 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 year; 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.

2.2 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.

2.3 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.

2.4 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.

2.5 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 ≥ 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.

2.6 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 X^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).

3 RESULTS

3.1 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 months (range, 8 - 200 months). One-year and five-year patient survival rates were 84% and 76%, respectively. Graft survival rates at one and five years were 78% and 67%, respectively.

Table 1. Characteristics of the study population (1989 –2004).

	Study population (n = 433)	
Donor variables	**N**	**Range or %**
Age (years)	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		
donation after brain death	429	99%
donation after cardiac death	4	1%
Graft size		
full size	421	97%
Reduced-size or split	12	3%

Table 1. Characteristics of the study population (1989 –2004) (continued).

Recipient variables	N	Range or %
Age (years)	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
CTP class		
A	66	16%
B	165	38%
C	199	46%
Karnofsky score	60	10 – 100
Indication for transplantation		
biliary cirrhosis	131	30%
post necrotic cirrhosis	222	51%
acute liver failure	37	9%
metabolic disease	16	4%
miscellaneous	26	6%
MELD score	16	6 - 40
Serum creatinine before OLT (µmol/L)[a]	84	34 - 735
Serum total bilirubin before OLT (µmol/L)[b]	67	5 - 1343
INR before OLT	1.5	0.9 - 15.6
Platelet count before OLT ($x10^9$/L)[c]	89	2 - 651
Hemoglobin before OLT (mmol/L)[d]	6.8	3.1 - 9.9
Hematocrit before OLT[e]	0.32	0.14 - 0.50
Previous abdominal surgery		
no previous abdominal surgery	316	74%
previous surgery 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 (days)	4	0 - 155
Length of total hospital stay (days)	39	0 - 235

Table 1. Characteristics of the study population (1989 – 2004) (continued).

Transplantation variables	N	Range or %
Operating time (min)	540	280 - 1080
Venous anastomosis		
classic	252	58%
piggyback	181	42%
Cold ischemia time (min)	600	203 - 1440
Warm ischemia time (min)	55	20 - 129
RBC allogeneic transfusion (units)	7	0 - 105
RBC cell saver transfusion (units)	0	0 - 81
FFP transfusion (units)	9	0 - 51
Platelet transfusion (units)	0	0 - 4
Antifibrinolytic drugs used		
no	243	58%
aprotinin	160	38%
tranexamic acid	16	4%

Data represent numbers (percentages) for categorical variables, for continuous variables median (range). For some variables the total number of cases may be less than 433, reflecting missing data (overall < 4%). [a] *serum creatinine before OLT normal < 110 µmol/L, to convert the value to mg/dL, divide by 88.4.* [b] *serum total bilirubin before OLT normal = 0 - 17 µmol/L , to convert the value to mg/dL, divide by 17.1.* [c] *platelet count normal = 150 - 350 x10^9/L.* [d] *hemoglobin before OLT normal 8.7 - 10.2 mmol/L, to convert the value to g/dL, divide by 0.62.*[e] *hematocrit before OLT normal 0.33 - 0.40. Cold ischemia time: time from in situ flushing of the donor organ until the liver is removed from ice for implantation. Warm ischemia time: time from removal of liver from ice until reperfusion via portal vein, hepatic artery or both.* ***Abbreviations:*** *BMI = body mass index, CTP = Child Turcotte Pugh score, MELD = model for end-stage liver disease, OLT = orthotopic liver transplantation, INR = international normalized ratio, RBC = red blood cell, FFP = fresh frozen plasma.*

3.2 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).

Table 2. Blood product 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)**

Data represent numbers of units (range). ***Abbreviations:*** *RBC = red blood cell, FFP = fresh frozen plasma.*

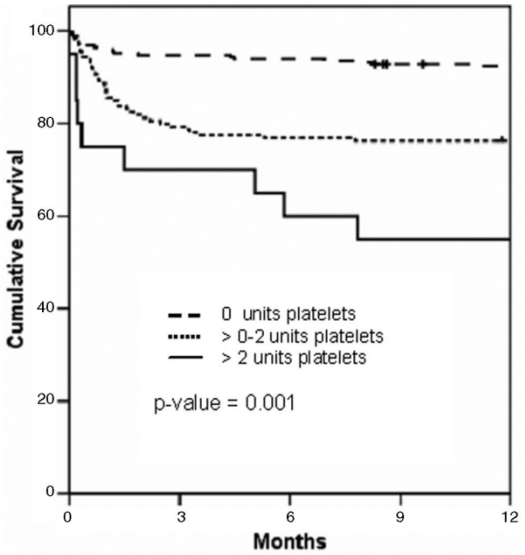
Table 3. Percentage of patients receiving blood transfusion per era.

Era	Allogeneic RBC transfusion %	Cell saver RBC transfusion %	Platelet transfusion %	FFP transfusion %	Any transfusion %
1989–1996	99 (192/194)	58 (112/194)	56 (109/194)	99 (192/194)	99 (193/194)
1997–2004	69 (163/236)	25 (60/237)	30 (71/236)	59 (140/236)	74 (175/236)
Total	**83 (355/430)**	**40 (172/431)**	**42 (180/430)**	**77 (332/430)**	**86 (368/430)**

Total number of cases may be less than 433, representing missing data (< 1%). ***Abbreviations:*** *RBC = red blood cell, FFP = fresh frozen plasma.*

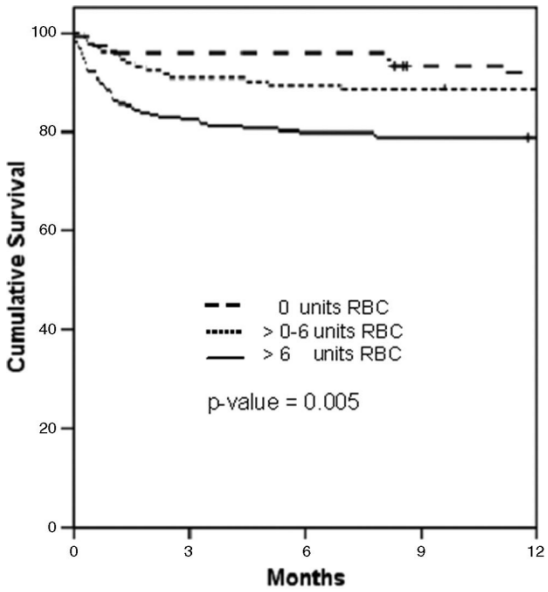
3.3 The impact of platelet and allogeneic RBC transfusion on survival

Patient survival after OLT was significantly associated with the number of allogeneic RBC or platelet concentrates transfused during surgery (Figures 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.



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

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

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

3.4 Univariate and multivariate analysis of patient survival

The results of univariate analysis of all potential risk factors for one-year and five-year patient survival are summarized in Table 4. Of the 26 variables studied, 11 were associated with one-year and five-year 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 one-year patient survival, whereas four variables were independent risk factors for five-year survival (Table 5). Platelet transfusions and RBC transfusions were highly dominant in predicting patient survival. Although indices of disease severity, such as the Karnofsky score and MELD score, were not associated with post transplant survival in multivariate analysis, patients receiving RBC or platelets may still be sicker than patients who do not need transfusion.

Table 4. Univariate analysis of patient survival.

	Survival:	One-year patient		Five-year patient	
Donor variables	**n**	**%**	***p*-value**	**%**	***p*-value**
Age			0.330		0.277
< 40 years	186	86		78	
> 40 years	247	83		75	
Gender			0.459		0.823
male	219	83		76	
female	202	86		77	
Donor-recipient gender match			0.875		0.681
male - male	124	84		76	
female - female	107	86		80	
male - female	95	82		76	
female – male	95	85		73	
Type donor liver			0.404		0.402
donation after brain death	429	84		76	
donation after cardiac death	4	100		100	
Graft size			0.009*		0.078*
full size	421	85		77	
split/ reduced-size	12	58		58	
Recipient variables					
Age			0.547		0.468
< 55 years	333	85		77	
> 55 years	100	82		74	
Gender			0.709		0.265
male	224	84		74	
female	209	85		78	
BMI			0.285		0.031*
< 20	56	86		84	
20 - 30	336	85		77	
30+	32	75		59	
Indication for transplantation			< 0.001*		0.006*
biliary cirrhosis	131	92		85	
postnecrotic cirrhosis	222	84		73	
acute liver failure	37	60		60	
metabolic disease	16	88		75	
miscellaneous	26	81		81	
Karnofsky score			< 0.001*		0.009*
0 - 40	145	72		68	
50 - 70	189	92		81	
80 - 100	99	87		79	

Table 4. Univariate analysis of patient survival (continued).

	Survival:	One-year patient		Five-year patient	
Recipient variables (continued)	**n**	**%**	***p*-value**	**%**	***p*-value**
CTP class			0.015*		0.009*
A	66	88		80	
B	165	89		82	
C	199	78		69	
Serum creatinine[a]			0.053*		0.095*
normal	333	86		78	
abnormal	100	78		70	
MELD score	cont	cont	0.009*	cont	0.023*
MELD category			0.018**		0.202
< 11	81	89		80	
11 - 18	170	86		79	
19 - 24	73	89		77	
> 25	91	74		69	
Platelet count before OLT ($x10^9$/L)	cont	cont	0.158	cont	0.143
Hemoglobin before OLT (mmol/L)	cont	cont	0.214	cont	0.314
Hematocrit before OLT	cont	cont	0.243	cont	0.282
Previous abdominal operations			0.689		0.712
yes	111	88		78	
no	316	85		77	
Rejection			0.201		0.520
no	223	83		75	
mild, untreated	90	90		80	
yes, treated	115	86		77	
Immunosuppression			0.150		0.126
tacrolimus	90	90		83	
cyclosporin	336	84		76	
Transplantation variables					
Year of transplantation			0.120		0.067*
1989 - 1996	195	81		71	
1996 - 2004	238	87		80	
Operating time (min)	cont	cont	0.781	cont	0.862
Venous anastomosis			0.298		0.192
classic	252	82		73	
piggyback	181	86		80	
Cold ischemia time			0.022*		0.001*
< 12 h	286	87		82	
> 12 h	143	78		64	
Warm ischemia time			0.095*		0.016*
< 60 min	266	86		80	
> 60 min	163	80		69	
RBC units (allogeneic)	cont	cont	< 0.001*	cont	< 0.001*

Table 4. Univariate analysis of patient survival (continued).

	Survival:	One-year patient		Five-year patient	
Transplantation variables	**n**	**%**	***p*-value**	**%**	***p*-value**
RBC category			0.007**		0.004**
0	75	92		87	
0 - 6	136	88		82	
> 6	219	79		69	
FFP units	cont	cont	< 0.001*	cont	< 0.001*
FFP category			< 0.001**		0.001**
0	98	94		89	
0 - 4	50	94		86	
> 4	281	79		70	
Platelets units	cont	cont	< 0.001*	cont	< 0.001*
Platelets category			< 0.001**		< 0.001**
0	250	92		84	
> 0 - 2	160	76		68	
> 2	20	55		40	
Cell saver RBC units	cont	cont	0.075*	cont	0.013*
Cell saver RBC category			0.092**		0.082**
0	258	86		80	
0 - 6	106	86		75	
> 6	66	76		65	
Antifibrinolytic use			0.235		0.033*
no	243	86		79	
yes	176	81		71	

*For some variables the total number of cases may be less than 433, representing missing data (overall < 4%). [a] Serum creatinine normal = ♀ < 110 µmol/L, ♂ < 120 µmol/L; abnormal = ♀ > 110 µmol/L, ♂ > 120 µmol/L. * Included in multivariate analyses. ** Continuous variables were used for multivariate analysis instead of categories.* ***Abbreviations:*** *BMI = body mass index, CTP = Child Turcotte Pugh score, MELD = model for end-stage liver disease, cont = continuous variables, OLT = orthotopic liver transplantation, RBC = red blood cell, FFP = fresh frozen plasma.*

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 one-year 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 five-year 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 one-year survival in patients who received platelet transfusion was 2.613 (95% confidence interval, 1.315 – 5.192; $p = 0.012$).

Table 5. Multivariate Cox regression analysis of patient survival.

	One-year patient survival		Five-year patient survival	
Variable	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**
Indication	0.020		*	*
biliary cirrhosis		*reference category*		
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)
Cold ischemia time	*	*	0.002	0.494 (0.315 - 0.776)
Era of transplantation	*	*	0.008	0.515 (0.315 - 0.843)

** Not statistically significant after multivariate analysis.* ***Abbreviations:*** *HR = hazard ratio, CI = confidence interval, RBC = red blood cell.*

3.5 Univariate and multivariate analysis of graft survival

The results of univariate analysis of all potential risk factors for one-year and five-year graft survival are summarized in Table 6. Of the 26 variables studied, 9 were identified to be associated with one-year and five-year 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.

Table 6. Univariate analysis of graft survival.

	Survival:	One-year graft		Five-year graft	
Donor variables	**n**	**%**	***p*-value**	**%**	***p*-value**
Age			0.361		0.208
< 40 years	186	80		70	
> 40 years	247	76		66	
Gender			0.703		0.987
male	219	77		68	
female	202	79		68	
Donor-recipient gender match			0.456		0.870
male - male	124	80		68	
female - female	107	76		65	
male - female	95	74		67	
female - male	95	82		71	
Type donor liver			0.332		0.332
donation after brain death	429	77		67	
donation after cardiac death	4	100		100	
Graft size			< 0.001*		< 0.001*
full size	421	79		69	
split/reduced-size	12	25		25	

Table 6. Univariate analysis of graft survival (continued).

	Survival:	One-year graft		Five-year graft	
Recipient variables	**n**	**%**	***p*-value**	**%**	***p*-value**
Age			0.896		0.929
< 55 years	333	78		67	
> 55 years	100	78		69	
Gender			0.224		0.590
male	224	80		68	
female	209	75		67	
BMI			0.695		0.137
< 20	56	77		75	
20 - 30	336	79		68	
30+	32	72		53	
Indication for transplantation			< 0.001*		0.013*
biliary cirrhosis	131	83		76	
post necrotic cirrhosis	222	80		66	
acute liver failure	37	54		51	
metabolic disease	16	75		63	
miscellaneous	26	65		62	
Karnofsky score			0.003*		0.265
0 - 40	145	68		63	
50 - 70	189	84		70	
80 - 100	99	79		69	
CTP score			0.356		0.244
A	66	79		70	
B	165	81		72	
C	199	74		63	
Serum creatinine			0.308		0.667
normal	333	79		68	
abnormal	100	74		66	
MELD score	cont	cont	0.189	cont	0.487
MELD category			0.085*		0.586
< 11	81	80		68	
11 - 18	170	79		71	
19 - 24	73	85		70	
> 25	91	69		64	
Platelet count before OLT (x 109/L)	cont	cont	0.411	cont	0.158
Hemoglobin before OLT (mmol/L)	cont	cont	0.735	cont	0.397
Hematocrit before OLT	cont	cont	0.803	cont	0.429
Previous abdominal operations			0.520		0.484
yes	111	81		71	
no	316	78		67	

Table 6. Univariate analysis of graft survival (continued).

	Survival:	One-year graft		Five-year graft	
Recipient variables	**n**	**%**	***p*-value**	**%**	***p*-value**
Immunosuppression			0.065*		0.105
tacrolimus based	90	86		76	
cyclosporin based	336	77		67	
Rejection			0.018*		0.018*
no	223	74		63	
mild, untreated	90	88		78	
yes, treated	115	80		70	
Transplantation variables					
Year of transplantation			0.167		0.094*
1989 - 1996	195	74		62	
1996 - 2004	238	80		72	
Operating time	cont	cont	0.736	cont	0.866
Venous anastomosis			0.600		0.242
classic	252	77		64	
piggyback	181	79		72	
Cold ischemia time			0.018*		< 0.001*
< 12 h	286	81		74	
> 12 h	143	71		54	
Warm ischemia time			0.153		0.020*
< 60 min	266	80		73	
> 60 min	163	74		60	
RBC units (allogeneic)	cont	cont	< 0.001*	cont	< 0.001*
RBC units category			0.002**		0.002**
0	75	91		85	
0 - 6	136	80		69	
> 6	219	72		60	
FFP units	cont	cont	< 0.001*	cont	< 0.001*
FFP units category			0.001**		0.003**
0	98	88		83	
0 - 4	50	90		74	
> 4	281	72		61	
Platelets units	cont	cont	< 0.001*	cont	< 0.001*
Platelets units category			< 0.001**		< 0.001**
0	250	84		74	
> 0 - 2	160	71		61	
> 2	20	55		35	
Cell saver blood units	cont	cont	0.081*	cont	0.025*
Cell saver blood units category			0.102**		0.236
0	258	80		72	
0 - 6	106	79		64	
> 6	66	68		59	

Table 6. Univariate analysis of graft survival (continued).

	Survival:	One-year graft		Five-year graft	
Transplantation variables	**n**	**%**	***p*-value**	**%**	***p*-value**
Antifibrinolytic use			0.933		0.283
no	243	77		69	
yes	176	77		66	

*For some variables the total of cases may be less than 433, representing missing data (overall < 4%). [a] Serum creatinine normal = ♀ < 110 µmol/L, ♂ < 120 µmol/L; abnormal = ♀ > 110 µmol/L, ♂ > 120 µmol/L. * Included in multivariate analysis. ** Continuous variables were used for multivariate analysis. **Abbreviations**: BMI = body mass index, CTP = Child Turcotte Pugh score, MELD = model of end-stage liver disease, cont = continuous variables, OLT = orthotopic liver transplantation, RBC = red blood cell, FFP = fresh frozen plasma.*

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

Table 7. Multivariate Cox regression analysis of graft survival.

	One-year graft survival		Five-year graft survival	
Variable	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**
Indication	0.006		0.005	
biliary cirrhosis		*reference category*		*reference category*
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)
Cold ischemia time	*	*	0.001	0.592 (0.414 - 0.846)

** Not statistically significant after multivariate analysis. **Abbreviations**: HR = hazard ratio, CI = confidence interval, RBC = red blood cell transfusion.*

4 DISCUSSION

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