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High intraoperative blood product requirements in liver transplantation: risk factors and impact on the outcome

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Abstract. – OBJECTIVE: Liver transplantation (LT) is associated with a significant bleeding and the high transfusion requirements (HTR) negatively affect the outcome of LT patients. Our primary aim was to identify potential predictors of intraoperative transfusion requirements. Secondarily, we investigated, the effect of transfusion requirements on different clinical outcomes, including short-term morbidity and mortality.

PATIENTS AND METHODS: Data collected in 219 adult LT from a deceased donor, grouped according to HTR (defined as the need of 5 or more red blood cell units), were compared.

RESULTS: We found that previous portal vein thromboses (p=0.0156), hemoglobin (Hb) (p<0.0001), International Normalized Ratio (INR) (p=0.0010) at transplant and veno-venous bypass (p=0.0048) independently predicted HTR. HTR was always associated with poorer outcomes, including higher simplified acute physiology II score at Intensive Care Unit admission (p=0.0005), higher rates of pulmonary infections (p=0.0015) and early rejection (p=0.0176), longer requirement of mechanical ventilation, (p<0.0001), more frequent need for hemodialysis after transplantation (p=0.0036), overall survival (p=0.0010) and rate of day-90 survival (p=0.0016).

CONCLUSIONS: This study identified specific risk factors for HTR and confirmed the negative impact exerted by HTR on clinical outcomes, including recipient survival. Prospective investigations are worth to assess whether correcting pre-transplant Hb and INR levels may effectively reduce blood product need and improve prognosis.

Key Words:
Transfusion, Risk factors, Postoperative morbidity, Survival, Liver transplantation, Patient-centered care.

Introduction

Liver transplantation (LT) is the most effective treatment for patients with end-stage liver disease. In general, the impaired coagulation profile and the presence of portal hypertension greatly increase in LT candidates the risk for severe bleeding[1]. In particular, coagulopathy can develop or exacerbate during surgery in the anhepatic and/or neohepatic phases, when the metabolic graft liver function is still deficient, and hyperfibrinolysis and/or platelets sequestration in the graft occurs[2]. In addition, previous liver surgery seems to predispose to an increased bleeding[1]. Consequently, LT is associated with a considerable intraoperative blood loss resulting in variable needs of red blood cell (RBC), platelet (PLT) and fresh frozen plasma (FFP) units[3]. The high blood product re-

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quirement is associated with a poor outcome in several surgical settings, as well as in transplants other than LT[3-5]. Regarding LT, the transfusion burden predicts poor postoperative outcomes, including allograft failure, prolonged stay in Intensive Care Units (ICU) and in hospital, as well as increased mortality[6-8].

The rate of blood product utilization during LT depends on the multidisciplinary management of transfusion therapy and differs significantly among centers. In fact, blood product supply during LT varies according to transfusion thresholds or different RBC/PLT/FFP ratios[9]. In addition, the consumption of FFP units and PLT concentrates may be influenced by procedures adopted for the intraoperative coagulation monitoring, as well as by algorithms used for the administration of coagulation factor concentrates[9]. Despite a general trend toward a restrictive transfusion strategy, the imbalance between reduced supply and growing demand is nowadays a challenging issue[10]. In the LT setting this problem led to explore alternative approaches, such as donor-specific RBC transfusions[11,12].

At our hospital, a multidisciplinary LT team has been developing standardized procedures and decisional algorithms for surgical, anesthetic, and post-operative management of LT patients. These procedures have remained unchanged from 2014, so that patients transplanted from 2014 onward constitute a homogeneously treated population. In order to reduce transfusion requirements in LT patients and ameliorate the transfusion management in this setting, we revised blood consumption in LT performed at our hospital after 2014.

Our primary aim was to identify potential predictors of a high intraoperative blood product requirements. Secondarily, we investigated, the effect of transfusion requirements on different clinical outcomes, including short-term morbidity and patient survival.

Patients and Methods

Study Design

Using a prospectively maintained database, we performed a retrospective review of data collected in deceased donor liver transplants performed in adult patients at the Fondazione Policlinico Universitario A. Gemelli IRCCS of Rome between January 2014 and December 2020. All cases were considered eligible for the study, except for the combined transplant of liver and kidney, and early re-transplant (i.e., less than 90 days from the first LT). The study was approved by the Ethics Committee of the Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy (ID 4216). Transfusion requirements were evaluated considering all blood products transfused from the beginning of surgery until the admission to the ICU. Our primary aim was to assess clinical, laboratory, and surgical factors predicting a high intraoperative blood product requirements. Secondarily, we investigated, the effect of transfusion needs on clinical outcomes, including simplified acute physiology II (SAPS-II) score at ICU admission, rate of pneumonia, duration of mechanical ventilation, need for hemodialysis, length of stay (LoS) in ICU, graft rejection, and day-90 patient survival.

Anesthetic Management

The detailed anesthetic management was carried out as previously reported[13]. Anesthesia was induced with propofol (2-3 mg/kg), fentanyl (2-3 μg/kg,) and rocuronium (1 mg/kg) and maintained with sevoflurane, remifentanil (0.05-0.4 μg/kg/min), and cisatracurium (1.0-1.5 μg/kg/min). Hemodynamic monitoring was performed using 2-lead electrocardiography, pulse oximeter, and arterial and pulmonary artery catheters. During the hepatectomy and anhepatic phase, a central venous pressure ≤5 mmHg was maintained in all patients by fluid restriction[14]. Vascular filling was performed with crystalloids and colloids (5% human albumin). Hypothermia was limited using forced air warmer blankets and intravenous fluids warmers with a target temperature of 36-37°C. Pre-operative standard coagulative tests (prothrombin time [PT], activated partial thromboplastin time [aPTT], international normalized ratio [INR], fibrinogen, and D-dimers), and hematological parameters were obtained in all patients. Coagulative management was carried out based on standard coagulative tests or thromboelastography (TEG, TEG® 5000, Haemonetics); clotting factors, FFP units, and PLT units were administered according to standardized algorithms[13]. PLT units included either pool platelet units or apheresis units. FFP consisted of pharmaceutical grade plasma (200 ml/unit). RBC transfusions were given to maintain a hemoglobin (Hb) level between 8 and 9 g/dL. During massive bleeding, transfusions were administered also depending on the hemodynamic state and the rate of bleeding. Cell saver technology was utilized in all patients without hepatocellular carcinoma (HCC). If microvascular oozing occurred in the post-reper-

fusion phase, protamine (50 mg) and tranexamic acid (10-1 mg/kg) were also administered. After surgery, patients were transferred to the ICU for postoperative care.

Surgical Procedures

The caval preservation technique with piggy-back venous anastomosis was used in most patients. Complex cases (previous abdominal surgery, severe portal hypertension) were managed by temporary porto-caval anastomosis (PCA) or conventional Starzl technique with veno-venous by-pass (VVBP). The grafts were perfused with University of Wisconsin or Histidine-Tryptophan-Ketoglutarate solution, as previously reported[13]. Cirrhotic patients and those with HCC were prioritized for transplantation depending on liver disease severity according to Model for End Stage Liver Disease (MELD) score[15]. Patients with HCC were equalized to cirrhotic ones as foreseen by the Italian allocation system, after a thorough assessment of the donor-recipient match[15,16].

Recorded Variables

Recipients' variables included demographics, body mass index (BMI, with low BMI defined as < 18.5 and high BMI defined as > 30), etiology of liver disease, MELD score and donor age per MELD (D-MELD) score at transplantation, previous trans-jugular intrahepatic portosystemic shunt, previous portal vein thrombosis (PVT), previous abdominal surgery due or not to HCC, concomitant hemodialysis, intubation, diabetes mellitus, anticoagulant or antiplatelet therapy at transplant, transfusions in the previous 5 years, preoperative Hb and platelet counts, preoperative standard coagulative tests (PT, aPTT, INR, fibrinogen, and D-dimers), ratio between platelet count and longitudinal diameter of the spleen (PLT/spleen ratio, i.e., a surrogate indicator of esophageal varices)[17], SAPS-II at ICU admission[18], duration of mechanical ventilation, length of stay (LoS) in ICU, post-transplant pulmonary infections, hemodialysis and date and status at last follow up. Donor variables included age, and graft type (standard and no-standard). Variables related to surgery were cold ischemia time (CIT), use of temporary PCA, and/or VVBP.

Statistical Analysis

Continuous variables were expressed as median with relative interquartile range (IQR) and categorical variables as n (%). Univariate analysis of continuous variables was performed by the Mann-Whitney U test or the Wilcoxon matched-pairs rank test, as appropriate. For categorical variables, Fisher's exact test or the χ^2 test were used, as appropriate. The relationship between continuous variables was evaluated by linear regression analysis and expressed as Spearman's Rank correlation. The multivariate logistic regression analysis was performed by backward stepwise method incorporating all variables with a significant effect on the outcome at univariate analysis ($p<0.05$). The results were expressed as odds ratio (OR) with the relative 95% CI. All tests were two-sided, and a p-value <0.05 was considered statistically significant. Probabilities of overall survival (OS) were calculated using the Kaplan-Meier estimate and expressed as hazard ratio (HR), with relative 95% confidence intervals (95% CI). Analyses were performed using the IBM SPSS Statistics 27.0 and GraphPad v6 (La Jolla, CA, USA). The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

In total, data relative to 222 consecutive LTs performed at Fondazione Policlinico Gemelli IRCCS from January 2014 to December 2020 were examined. Three cases were excluded, one for combined kidney-liver transplant and two due to early re-transplant. A total of 219 LTs were finally included in the analysis. Epidemiologic, clinical, and laboratory characteristics of recipients and data relative to donors are shown in Table I. Most frequent underlying diagnoses were HCC, HBV-, HCV-, and alcohol-related cirrhosis (68.5% of cases). Cholestatic liver disease were present in 9.1% of patients and acute liver failure in 7.8%. Remaining diagnoses included Budd Chiari syndrome, autoimmune, metabolic and cryptogenetic liver diseases (Table I). The median number of transfused RBC units was 5 (IQR 2-9). Overall, 29 out of 219 patients (13.2%) received no blood product, whilst 190 patients were given at least 1 RBC transfusion, with the majority of them (125 patients, 65.7%) receiving 5 or more RBC units (Figure 1). Accordingly, we divided our series of patients in two groups: those needing ≥ 5 RBC units (the high transfusion requirement, HTR group, including 125 patients) and those needing <5 RBC units (non-HTR group, including 94 patients). The ensuing analysis was performed comparing patients in the HTR and non-HTR groups.

Table I. Baseline characteristics of 219 investigated liver transplants.

Recipients	Median (IQR) / n (%)	Number of missing data
Age, years	57 (49-62)	0
Female sex	37 (16.9)	0
Body Mass Index, Kg/m^2	25.6 (23.4-28.3)	0
Primary Indication for LT		
Hepatocellular carcinoma	96 (43.8)	0
Hepatitis B/C virus cirrhosis	101 (46.1)	0
Alcoholic cirrhosis	97 (44.7)	0
Cholestatic liver disease	20 (9.1)	0
Acute Liver Failure	17 (7.8)	0
Budd-Chiari	2 (0.9)	0
*Others**	32 (14.6)	0
Portal vein thrombosis	23 (10.9)	8
Portal vein thrombosis Yerdel II-III	16 (7.6)	8
Previous abdominal surgery	42 (19.3)	1
Previous liver surgery	24 (10.9)	0
Previous transfusions	126 (57.5)	0
Previous RBC transfusions	72 (32.9)	0
TIPS	19 (8.9)	6
Pre-LT intubation	10 (4.6)	0
Pre-LT hemodialysis	10 (4.6)	0
Antiplatelet therapy	10 (4.6)	4
Anticoagulant therapy	9 (4.2)	4
Diabetes mellitus	60 (27.4)	0
MELD	19 (13-25)	0
MELD-Na	21 (15-28)	0
D-MELD	1058 (662-1503)	0
PLT/spleen diameter>909	48 (21.9)	4
Hemoglobin, g/dL	11.2 (9.3-13.0)	0
Platelets, 10^3/µL	73 (50-113)	0
INR	1.5 (1.3-2.1)	0
Fibrinogen, mg/dL	224 (170-288)	0
aPTT, seconds	44.3 (37.6-53.0)	0
Creatinine, mg/dL	0.84 (0.65-1.15)	0
Donors		
Age, years	60 (44-71)	0
No-standard	91 (42.1)	0
Surgical procedures		
TEG assisted	85 (38.8)	10
Cold ischemia time, minutes	465 (400-510)	0
Porto-caval anastomosis	49 (23.2)	8
Veno-venous by-pass	42 (19.9)	8
Blood product support		
RBC units	5 (2-9)	0
FFP units	5 (0-10)	0
PLT units	0 (0-1)	0

IQR: Interquartile range; LT: Liver Transplantation; TIPS: Trans-jugular Intrahepatic Porto-systemic Shunt; MELD: Model for End-stage Liver Disease; D-MELD: Donor Model for End-stage Liver Disease; PLT: platelet, INR: International Normalized Ratio; aPTT: activated Partial Thromboplastin Time; TEG: thromboelastography; RBC: red blood cell; FFP: fresh frozen plasma; *Other indications include polycystic, autoimmune and metabolic diseases.

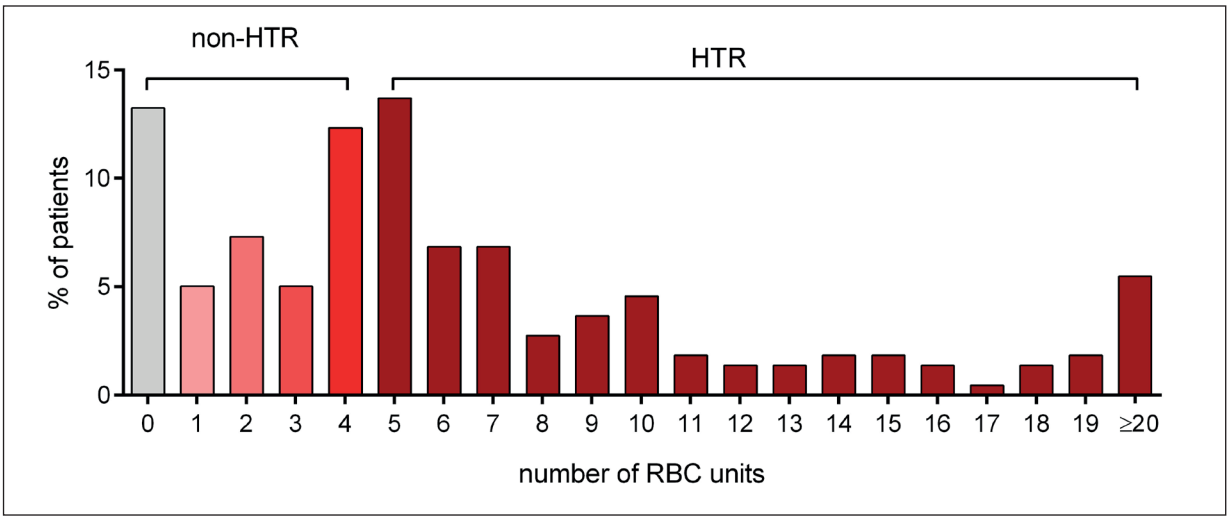

Figure 1. Distribution of 219 cases of liver transplantation according to the number of RBC units transfused intraoperatively. In total, 125 patients (65.7%) received 5 or more RBC units.

There was a close correlation between the number of RBC units and that of either FFP units (Spearman's Rank correlation 0.7654, $p<0.0001$) or PLT units (Spearman's Rank correlation 0.6391, $p<0.0001$) (Figure 2). This finding supports our assumption to define the transfusion burden according to the number of RBC, showing that predicting a higher RBC consumption also predicts a higher consumption of other blood products.

Variables Associated with High Transfusion Requirements

Table II shows the univariate analysis of characteristics of patients grouped according to the RBC unit supply. The rate of patients with HTR was independent from the transplant period ($p = 0.5250$ at Pearson's Chi-Square test for the transplant year, data not shown). HTR was independent from the age or type (standard or no-standard) of donors. Patients requiring a higher transfusion support displayed poorer hematological and coagulative profiles, were more frequently under hemodialysis, and showed higher MELD and D-MELD scores at transplant. Accordingly, a lower proportion of patients in the HTR group had HCC as primary LT indication. Moreover, patients in the HTR group more frequently had previous PVT, or were intubated at the time of LT. Finally, we observed that patients who received transfusions in the five years preceding LT (either RBC or other blood products), more frequently displayed HTR at transplant. We then included in a multivariate model the covariates related to recipient, donor or graft that were significantly associated to HTR at univariate analysis.

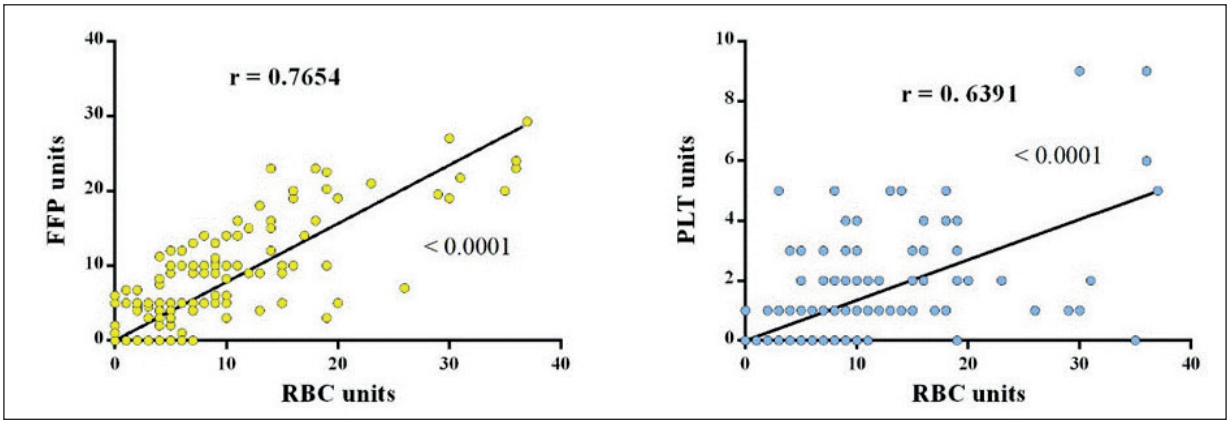

Figure 2. Correlation between the numbers of RBC and platelet or FFP units transfused intraoperatively in 219 adult patients submitted to liver transplantation from deceased donors. The Spearman's rank correlation coefficient is shown.

Table II. Univariate analysis of clinical, laboratory and surgical variables in liver transplants with or without high transfusion requirements (HTR). Data are given as median values (IQR) or number (%).

	No HTR (n = 94)	HTR (n = 125)	p-value
Recipients			
Age, years	57 (54-58)	57 (54-59)	0.8175
Female sex	16 (17.0)	21 (18.8)	1.0000
Body Mass Index, Kg/m^2	25.6 (24.8-26.2)	25.7 (24.8-26.2)	0.6909
Body Mass Index <18.5 or >30	16 (17.0)	22 (17.6)	1.0000
Hepatocellular carcinoma	50 (53.2)	46 (36.8)	**0.0193**
Hepatitis B/C virus cirrhosis	44 (46.8)	57 (45.6)	0.8916
Alcoholic cirrhosis	38 (40.4)	59 (47.9)	0.2681
Cholestatic liver disease	13 (13.8)	7 (5.6)	0.0558
Acute Liver Failure	4 (4.3)	13 (10.4)	0.1259
Budd-Chiari syndrome	1 (1.1)	1 (0.8)	1.0000
Other diseases	16 (17.0)	16 (13.6)	0.2258
Diabetes mellitus	30 (31.9)	30 (24.0)	0.2218
Antiplatelet therapy	2 (2.2)	8 (6.5)	0.1357
Anticoagulant therapy	3 (3.2)	6 (4.8)	0.5579
MELD score	16 (13-18)	22 (19-23)	**0.0000**
D-MELD score	809 (715- 949)	1215 (1100-1330)	**0.0000**
Previous RBC transfusions	16 (17.1)	56 (44.8)	**0.0000**
Previous transfusions (any blood product)	35 (37.2)	91 (72.8)	**0.0000**
Previous PVT	5 (5.5)	18 (15.0)	**0.0282**
Previous abdominal surgery	20 (21.3)	22 (17.8)	0.5122
Previous HCC liver surgery	12 (12.8)	12 (9.6)	0.5153
pre-LT hemodialysis	1 (1.1)	9 (7.2)	**0.0461**
pre-LT TIPS	7 (7.7)	12 (9.8)	0.5871
pre-LT intubation	1 (1.1)	9 (7.2)	**0.0461**
Platelets/spleen ratio < 909	26 (27.6)	22 (17.6)	0.0984
Hemoglobin, g/dL	12.2 ± 2.1	10.3 ± 2.2	**0.0000**
Platelets, $10^3/\mu L$	97.8 ± 55.6	82.7 ± 55.6	**0.0094**
INR	1.5 ± 0.6	1.9 ± 0.7	**0.0000**
aPTT, seconds	43.6 ± 13.0	51.7 ± 17.5	**0.0000**
Fibrinogen, mg/dL	266 ± 91	210 ± 93	**0.0000**
Creatinine, mg/dL	0.88 ± 0.4	1.15 ± 0.8	**0.0037**
Donors			
Age, years	59 (55-65)	60 (55-63)	0.8270
Non-standard	38 (41.3)	53 (42.7)	0.8324
Surgical procedures			
Thromboelastography assisted	41 (43.6)	44 (35.2)	0.4487
Veno-venous by-pass	8 (8.8)	34 (28.3)	**0.0004**
Porto-cavas anastomosis	21 (23.1)	28 (23.3)	0.9561
Blood product and fluid support			
RBC units	2 (0-4)	8 (6-13)	**0.0000**
FFP, units	0 (0-4)	9 (5-12)	**0.0000**
PLT, units	0 (0-0)	1 (0-2)	**0.0000**
Fibrinogen, grams	4.5 (2.2-7)	7 (5-8)	**0.0027**
Tranexamic acid, grams	2 (0-2)	3.5 (2-4)	**0.0005**
Crystalloids, ml	5500 (5000-6500)	6500 (5000-10000)	**0.0124**
Colloids, ml	1050 (500-2000)	2000 (800-3000)	**0.0010**

HCC: hepatocellular carcinoma; MELD: Model for End-Stage Liver Disease; D-MELD: Donor age x MELD; RBC: red blood cells; PVT: portal vein thrombosis; TIPS: trans-jugular intrahepatic portosystemic shunt; INR: international normalized ratio; aPTT: activated partial thromboplastin time; FFP: fresh-frozen plasma; PLT: platelets. Other diseases include polycystic, autoimmune and metabolic diseases.

Table III. Multivariate analysis for a high transfusion requirements.

Variable	*p*-value	Odds Ratio	95% CI
Portal vein thrombosis	0.0156	4.00	1.30-12.31
Hemoglobin, g/dL	<0.0001	0.67	0.57-0.79
INR	0.0010	2.40	1.42-4.06
Veno-venous by-pass	0.0048	3.82	1.50-9.70

INR: International Normalized Ratio.

We found that previous portal vein thromboses (OR 4.20, 95% CI 1.37-12.86, p= 0.0119), Hb concentration (OR 0.71, 95% CI 0.60-0.83, p<0.0001), and INR value (OR 2.14, 95% CI 1.26-3.64, p=0.0047) at transplant independently predicted intraoperative HTR. We then added to the model the VVBP, the only surgical variable that at univariate analysis was associated with HTR. All the above-mentioned variables and VVBP retained a significant effect in predicting HTR during LT (Table III).

Effect of High Transfusion Requirements on Transplant Outcomes

Table IV illustrates the effect of HTR on various post-transplant outcomes. On day 90, 107 out of 125 patients in the HTR group and 92 out of 94 patients in the non-HTR group were alive (85.6 % versus 97.8%, OR 0.129, 95% CI 0.029-0.572; p=0.0016). Excluding from the analysis 4 HTR patients deceased during surgery, the rate of survival at day-90 in the HTR group was 88.4% (OR 0.166, 95% CI 0.036 to 0.750, p=0.0086). HTR was constantly associated with poorer outcomes, including higher SAPS-II at ICU admission (p=0.0005), higher rates of pulmonary infections (p=0.0015) and early rejection (p=0.0176), longer requirement of mechanical ventilation, (p<0.0001), more frequent need for hemodialysis after transplantation (p=0.0036). In addition, patients receiving a higher transfusion support, most likely needed further RBC and PLT transfusions in the first post-transplant week (Table IV). Overall, the detrimental effect of HTR resulted in a longer stay in ICU (p<0.0001). We examined the effect of RBC transfusions on day-90 survival in a multivariate regression model incorporating HTR and other variables with known or conceivable effect on the outcome (recipient age, BMI lower than 18.5 or higher than 30, diabetes, pre-transplant intubation, values of MELD, creatinine, and INR at transplant, number of intraoperative PLT transfusions, pre- or post-transplant hemodialysis, post-transplant pulmonary infections and duration of mechanical ventilation). We found that HTR (OR 0.18, 95% CI 0.03-0.95, p=0.0442), high or low BMI (OR 0.23, 95% CI 0.06-0.91, p=0.0360), recipient age (OR 0.90, 95% CI 0.84-0.98, p=0.0132), and post-transplant pulmonary infections (OR 0.20, 95% CI 0.05-0.82, p=0.0252) all had a detrimental effect on the rate of day-90 survival. The impact of transfusions was confirmed by replacing in the same model the HTR status by the number of RBC units, show-

Table IV. Effect of high transfusion requirement (HTR) on main clinical outcomes obtained at day-90 follow-up.

Variable	No HTR (n = 94)	HTR (n =1 25)	*p*-value
SAPS-II	31 (23-47)	39 (31-51)	0.0005
Mechanical ventilation, hours	18 (14-24)	36 (18-68)	<0.0001
Pulmonary infections	3 (3.2)	20 (16)	0.0015
Hemodialysis post-LT	0	10 (8.0)	0.0036
^Early rejection	11 (11.7)	27 (21.6)	0.0176
ICU LoS, days	4 (3-6)	6 (4-10)	<0.0001
post-LT RBC, units	0 (0-1)	1 (0-2)	0.0003
post-LT FFP, units	0 (0-0)	0 (0-0)	0.5487
post LT PLT, units	0 (0-0)	0 (0-1)	<0.0001
*Day-90 survival, %	97.8 (92.5-99.7)	85.6 (78.2-91.2)	0.0016

^data of 5 patients were missing. *Data are expressed as mean (95% CI), median with interquartile range (IQR), or N (%). SAPS-II: Simplified acute physiology score -II; LT: Liver Transplantation; ICU: Intensive Care Unit; LoS: length of stay; RBC: red blood cell; FFP: fresh frozen plasma; PLT: platelet.

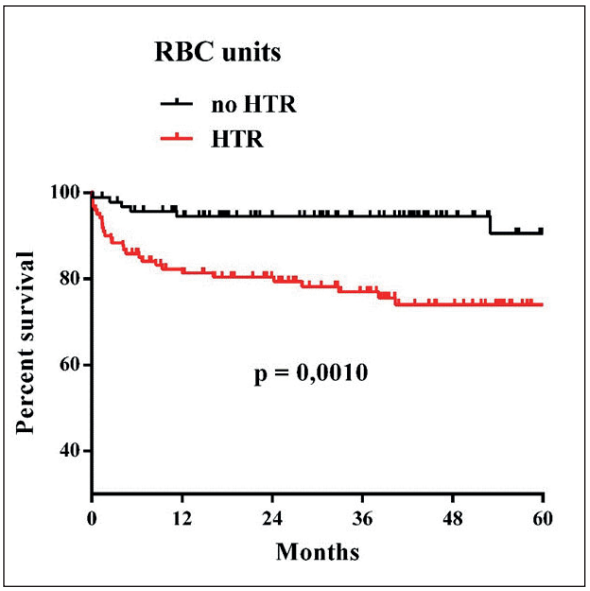

Figure 3. Overall survival analysis in 219 adult patients submitted to liver transplantation from deceased donors. Patients are grouped according to the intraoperative RBC unit requirements (<5 or ≥5 units). The p value at log-rank test is shown.

ing that increasing number of RBC transfusions proportionally reduced day-90 survival (OR 0.87, 95% CI 0.82-0.94, p=0.0001). The results were confirmed also excluding from the analysis 4 patients who died during surgery. Finally, the burden of transfusions also affected the overall survival of LT patients, with a HR of 3.92 (95% CI 1.58-6.09, p=0.0010) for patients in the HTR group (Figure 3).

Discussion

The blood product requirements in LT patients are greatly variable, ranging from none to many units[3]. In our series of LT patients, 13.2% of cases were transplanted without transfusion, whereas the majority of those receiving blood products (67.5%) were given 5 or more RBC units. Numerous studies[6,7,9,12,13,19-27] have tried to identify which factors reliably predict a greater blood product need. In our set, we used the threshold of 5 or more RBC units to investigate potentially modifiable risk factors for the high blood product demand[6,7,19-27]. In general, comparison among different studies may be biased by differences in transfusion triggers, as well as by changes in clinical practices that occur over the time. A positive aspect of our analysis is the homogeneous management of investigated patients, due to the presence of well consolidated anesthesiologic procedures, as well as the same surgeons' and anesthesiologists' team during the entire investigated periods.

The results of the present analysis, incorporating several pre- and intraoperative variables, show that pre-transplant Hb concentration, INR value, and presence of preexisting portal vein thrombosis were the most relevant risk factors for HTR. The risk for HTR was also increased when the VVBP instead of the piggy-back technique was adopted during surgery. Unfortunately, both PVT and VVBP represent risk factors hardly modifiable in the clinical practice. The effect of pre-existing portal vein thrombosis on blood product consumption during LT can be attributable to the portal hypertension, with more pronounced bleeding from tortuous and congested venous collateral circles[26]. At variance with our results, it has also been hypothesized that VVBP would lead to spare blood products[1,28]. However, in our experience, VVBP was used in more complex surgical cases with longer surgery duration, finally increasing the blood product demand.

In contrast to PVT and VVBP, the preoperative values of Hb and INR could represent a potential target for intervention to reduce the transfusion requirements in LT candidates. Ramos et al[7] investigated 324 LT recipients and identified Hb at transplant as the only significant driver for RBC transfusion. Analogously, pre-operative anemia was associated with a high transfusion burden in a large series reported by Massicotte et al[24]. More recently, a retrospective analysis of 591 patients, found that pre-operative Hb ≤10 g/dl was the main determinant for an increased RBC transfusion, also predicting the need for massive transfusion[27]. In other studies, both Hb and INR have been identified as blood use predictors, either preoperatively or during the entire hospitalization[22,29]. Finally, another study[30] reported that INR, but not Hb, correlated with the need for transfusions. Despite the thresholds for a HTR was different in the studies above, ranging from more than 2 units to a massive transfusion, all of them were concordant on the relevance of Hb level at transplant. At variance with our results, other studies[6,7,24] failed to demonstrate an association between INR values and blood product requirements. A recent retrospective analysis[31] of 25 LT patients transplanted while receiving antivitamin K agents (AVK) as anticoagulants, failed to demonstrate a significant difference in intraoperative blood loss and transfusions in

comparison with the control group. Our study population included nine patients in AVK therapy: a non-significant proportion of them was in the HTR group (6 out of 9, 67%, p=0.5579), but, overall, they had similar INR values as non-HTR patients. INR is a variable part of the MELD score that has been rarely associated with increased perioperative blood product requirement[22,32]. In our study both scores MELD and its derivative donor age per MELD[15,33] significantly differed in HTR and non-HTR patients but at multivariate analysis their effect was overcome by INR and Hb values. Finally, in contrast to studies[34-36] suggesting that thromboelastography, more than INR and other classical coagulative tests, may reduce blood product consumption in LT, we could not confirm this finding in our patients.

Transfusion[13] burden has a relevant impact on the outcome of LT patients, influencing both morbidity and mortality[6-9,37-39]. In our analysis, 85.6 % of HTR patients *vs.* 97.8% of non-HTR group were alive at post-transplant day 90. Overall, HTR patients had a significantly longer ICU stay than others, facing an increased rate of pulmonary infections, longer periods of mechanical ventilation, and higher rate of renal failure needing hemodialysis. The burden of transfusions also affected the overall survival of LT patients, with a HR of 3.92 (95% CI 1.58-6.09) for patients in the HTR group. Our findings confirm those presented in other studies. In fact, higher rates of transfusion have been variably associated with prolonged length of hospital stay, higher rates of infections, graft failure, and mortality[7,27,37,38,40-42]. It is challenging to establish whether patients needing more intraoperative blood products represent a more severely ill population with higher postoperative morbidity and mortality, or whether their poor outcome directly depends on blood products received. Interestingly, in reference to this issue, Avolio et al[8] have recently identified a correlation between numbers of RBC units transfused during surgery and incidence of early allograft failure in a large multicenter international study. Notably, the EASE score developed by the authors, incorporating beside RBC transfusions other variables related to the donor quality and post-operative thrombosis, achieved a C-statistic of 0.87%[8]. In general, the detrimental effects of transfusions have been ascribed to the storage lesions accumulating in preserved red cells. Biochemical, morphologic, and omics investigations suggest that stored RBCs show a series of lesions that make them qualitatively different from fresh RBCs[43]. The ensuing biochemical changes can elicit in RBC recipients the activation of the innate immune system and an inflammatory response, also affecting the graft function[44]. This effect, known as transfusion-related immunomodulation (TRIM), is mediated by several components released by senescent cells, including RBC microparticles, cytokines, reactive oxygen species, and free iron[44]. Indeed, a combination of both patient-related and blood product-related factors underlies transfusion-associated circulatory overload and transfusion-related acute lung injury, two acute respiratory distress syndromes typically occurring a few hours after blood transfusion[45]. In addition, TRIM might explain the increased susceptibility to pneumonia that we found in HTR patients, confirming our previous data on respiratory failure in LT patients and paralleling other observations connecting transfusion burden and sepsis[37,46]. Similarly, an increased inflammatory response evoked by transfused products could explain the increased rate of early rejection observed in HTR patients[47].

In our series of patients, the RBC unit consumption correlated with that of PLT and FFP units. Both blood products have been associated with a detrimental effect in the LT setting, including sepsis or even graft survival[48-51]. In particular, it has been shown that PLT transfusions contribute to ischemia-reperfusion injury initially after liver transplantation, by induction of sinusoidal endothelial cell apoptosis[52]. Nevertheless, in this series, we failed to demonstrate an effect of PLT transfusions on patient survival at multivariate analysis, in agreement with other studies showing that the impact of this blood product on several surgical outcomes remains difficult to be quantified[53,55].

Conclusions

Despite the limitations due to the retrospective single center design, this study identifies Hb level and INR at transplant as potential target for intervention to reduce blood need in LT patients. Given the negative impact exerted by blood products on LT outcome, prospective investigations are worth to assess whether a patient blood management program aimed at correcting Hb concentration and high INR before the LT may effectively reduce blood product utilization and improve prognosis.

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Conflict of Interests

The authors declare that they have no conflicts of interest.

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