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Risk Factors for Transfusion after Orthotopic Liver Transplantation

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Keywords

Transfusion · Orthotopic liver transplantation · Risk factors · MELD score

Abstract

Background: Transfusion of blood products during orthotopic liver transplantation (OLT) is associated with increased morbidity and mortality. Although risk factors associated with intraoperative transfusion requirements have been widely assessed, published data on the prediction of postoperative transfusion requirements are sparse. ***Objectives:*** The aim of this study was to evaluate risk factors for postoperative allogeneic transfusion requirements in OLT. ***Methods:*** Clinical characteristics and intraoperative parameters of 645 consecutive adult patients undergoing OLT were retrospectively reviewed. Multivariate logistic regression was used to determine the main determinants for postoperative transfusion requirements. ***Results:*** Determinants of postoperative transfusion requirements of any blood product in the postoperative period were the number of blood products transfused in the intraoperative period (OR 1.17, 95% CI 1.08–1.28), warm ischemia time (OR 1.05, 95% CI 1.02–1.08), MELD score (OR 1.05, 95% CI 1.01–1.08) and hepatocellular carcinoma (OR 0.45, 95% CI 0.28–0.72). A dose-dependent effect between the number of units transfused in the intraoperative period and transfusion requirements in the postoperative period was also observed. The relative risk of postoperative allogeneic transfusion of any blood component was 5.9 (95% CI 3.4–10.4) for patients who received 1–2 units in the intraoperative period, 7.3 (95% CI 3.6–14.7) for those who received 3–5 units in the intraoperative period, and 11.1 (95% CI 4.7–26.4) for those who received 6 or more units, when compared to no intraoperative blood transfusion. ***Conclusion:*** Our study demonstrated an association between intraoperative transfusion and warm ischemia time with postoperative transfusion requirements. The identification of risk factors for transfusion in the postoperative period may improve management of these patients by increasing awareness to bleeding complications in this high-risk population and by expanding hemostasis monitoring to the postoperative period.

Introduction

Transfusion of blood products in orthotopic liver transplantation (OLT) has been related with poorer prognosis [1–3] since cohort studies consistently demonstrated that transfusion of blood products is associated with increased posttransplant morbidity and mortality [1–8].

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Intraoperative transfusion of packed red blood cell units have been dose-dependently associated with several posttransplant complications, such as increase in the risk of hepatic artery thrombosis [9], early surgical re-intervention after OLT [10, 11], reoperations for hemorrhage [12], higher rate of graft loss [1, 2], development of postoperative infections [4], prolonged hospital stay [13], and with significant decrease in the 1-year survival rate [14] and in overall survival [3]. Plasma-containing blood components, such as platelets and fresh frozen plasma (FFP), were also associated with increased risk of graft loss [6], reduced posttransplant survival rate [15], transfusion-related acute lung injury (TRALI) [4], and transfusion-associated circulatory overload [16]. Particularly, transfusion of platelets was related to early mortality due to TRALI [2] and this is probably the blood component most associated with increase in morbidity and mortality during OLT [2, 17, 18].

Not only intraoperative transfusion of blood products was associated with adverse outcomes after OLT. Postoperative bleeding is a prominent risk factor for intensive care unit readmission after OLT [19] and postoperative transfusion requirement has been associated with increased length of hospital stay and lower graft and patient survivals [7, 20, 21]. Particularly, the risk for postoperative bleeding may be evaluated by preoperative thromboelastometry results [21].

Although risk factors for transfusion requirements in the intraoperative period have been largely investigated, such as Model for End Stage Liver Disease (MELD) score, age, warm ischemia times, and Child Turcotte Pugh score [13], data on postoperative transfusion requirements are sparse.

The negative impact of blood product transfusion on the posttransplant prognosis underscores the need to recognize risk factors associated with transfusion requirements and to reduce blood product use during OLT [13]. Therefore, to better understand the risk factors associated with postoperative transfusion in OLT, we evaluated whether clinical characteristics before transplantation and factors during transplantation were associated with blood transfusion requirements in the postoperative period.

Materials and Methods

Patient Population

We retrospectively reviewed the liver transplant procedures performed at Hospital Israelita Albert Einstein in São Paulo, Brazil, between January 2011 and December 2015. A total of 672 consecutive OLTs were performed in our center in that period. Patients who underwent combined organ transplantations ($n = 23$) or had relevant missing data ($n = 4$) were excluded. We considered relevant missing data: MELD at the time of transplantation, age, and unclear documentation of warm and cold ischemia times.

Characteristics of the patients and transfusion data were extracted from the medical records and the database of the Hemotherapy and Cell Therapy Department at Hospital Israelita Albert Einstein. Both registries are prospectively maintained. The study was approved by the institutional review board of Hospital Israelita Albert Einstein as secondary analysis of preexisting databases. The analysis was conducted ethically in accordance with the World Medical Association Declaration of Helsinki, and under Brazilian legal recommendations.

Hemostasis Management and Blood Transfusion Policy

Blood Components

In our institution, we perform universal irradiation and prestorage leukoreduction, and all components are prepared according to Brazilian National Health Agency regulations. RBC units are prepared from whole blood or apheresis collection, and the hemoglobin content of each unit is above 40 g. One dose of platelet concentrates can either be obtained through apheresis collection (minimum content of platelets is 3×10^{11} per apheresis product) or platelet pooled concentrates (6 units of random donor platelets are pooled into one bag, at least 5.5×10^{10} platelets per unit), with a medium volume of 240–300 mL per dose. FFP units have approximately 150 mL. One dose of cryoprecipitate (CRYO) is prepared by pooling of 7–10 units of CRYO, with a minimum fibrinogen content per unit of 150 mg in 10 mL. No pathogen inactivation method is performed.

The transfusion policy in our hospital is characterized by restrictive use of blood products. Transfusion and hemostatic management were performed according to the institutional goal-directed perioperative protocol for OLT. Rotational thromboelastometry (ROTEM®), prothrombin time (PT), activated thromboplastin time (aPTT), fibrinogen dosage, and total blood count are performed in the preoperative phase, at anesthesia induction, and at the end of surgery. Viscoelastic assays and hemoglobin quantification are repeated at each bleeding episode, post reperfusion of graft, and after each therapeutic approach to check the effectiveness of hemostatic intervention or transfusion performed. In the postoperative period, total blood count, aPTT, and PT are performed daily, while viscoelastic assays, hemoglobin, and conventional tests are collected only when bleeding episodes occur. Transfusion of RBC is performed to a target hemoglobin of 8 g/dL. Additionally, an intraoperative cell salvage device is used in selected patients. Infection and active neoplasia are contraindications for cell savage. Transfusion of other blood components such as platelets, FFP, and CRYO are performed when severe bleeding occurs coinciding with laboratory evidence of hemostatic derangement by rotational thromboelastometry or by conventional tests (prolonged PT or aPTT). Four-factor prothrombin complex concentrate (PCC) and fibrinogen concentrate are also used. PCC is avoided in cases of active thrombosis, thrombophilia, and malignant neoplasia because of the higher risk of thrombosis associated with those conditions [22, 23]. Therapeutic platelet transfusion is indicated when A10 EXTEM (tissue factor activated ROTEM assay), the amplitude or clot firmness obtained 10 min after coagulation time, is below 35 mm, and A10 FIBTEM (tissue factor activated ROTEM assay with elimination of platelet contribution to clot firmness by cytochalasin D) is above 8 mm. Additionally, platelets are transfused when significant bleeding occurs and there is clinical evidence of platelet dysfunction, such as prior use of antiplatelets or other thrombocytopathy. Although viscoelastic assays are superior in predicting the need for platelet transfusion [24–26], the method is not capable of detecting platelet dysfunction [27], a common situation among patients with end-stage liver disease [28], specifically after reperfusion [29]. Also, when major bleeding occurs

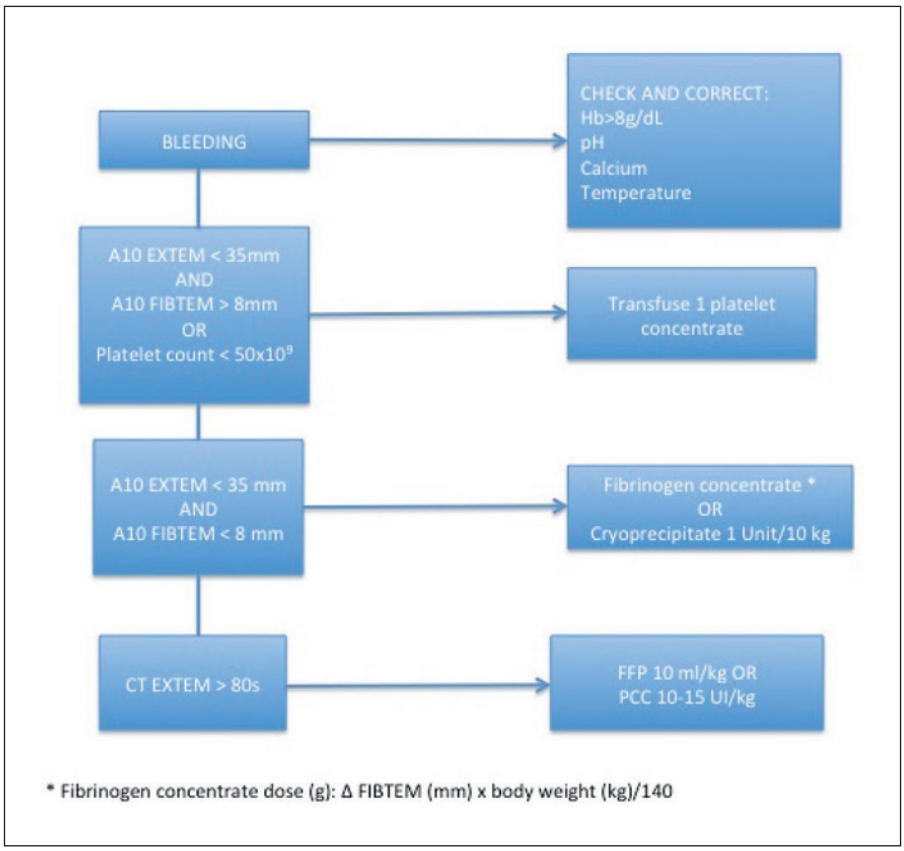

Fig. 1. Criteria for transfusion. Flow chart for transfusion indication according to clinical and laboratory criteria.

with platelet counts under 50×10^9/L, platelet transfusions are performed if ROTEM assays are not available. CRYO or fibrinogen concentrate are transfused when A10 EXTEM is below 35 mm and A10 FIBTEM is below 8 mm. Prophylactic platelet transfusion is not performed in the intraoperative period. In the postoperative period, prophylactic transfusion is performed for a platelet count of 10×10^9/L and before invasive procedures such as insertion of central venous lines, percutaneous liver biopsy, or major surgeries [30, 31].

Calcium, pH, and temperature were monitored and corrected if necessary. Venous thromboembolic (VTE) prophylaxis and antiplatelet therapy protocols are started on cessation of hemorrhagic risk, usually 24 h post-procedure. Enoxaparin is used for VTE prophylaxis, and doses are adjusted if renal impairment is observed. Dual antiplatelet therapy is used in patients with high-risk cardiovascular disease [32]. Reassessments are performed if bleeding or thromboembolic events were suspected. Figure 1 summarizes the criteria for transfusion.

Statistical Analysis

Baseline characteristics are presented as counts and percentages if they are categorical variables or mean ± standard deviation if they are continuous variables. Median and interquartile range were used to express continuous variables that were not normally distributed.

The association between potential risk factors with postoperative transfusion requirements was assessed by the multivariable logistic regression models. In each logistic regression model, odds ratios (OR) and the 95% confidence interval (CI) were used to estimate the association of the predefined risk factors with postoperative transfusion requirement. We considered as potential determinants (or risk factors) of postoperative blood product use the following variables: age, gender, body mass index, hepatocellular carcinoma (HCC) diagnosis, MELD score, warm and cold ischemia times, and intraoperative transfusion requirements. The primary outcome was the postoperative transfusion requirements of any allogeneic blood component. Autologous blood recovered from intraoperative cell salvage devices and coagulation factor concentrates were not considered in this analysis. The outcome was grouped into binary categories based on postoperative transfusion need: no transfusion or transfusion of at least one unit of any blood product.

Additionally, subgroup analyses were performed to determine the risk factors associated with the use of RBC, platelets, FFP, and CRYO, separately. We performed multivariable logistic regression analyses to determine the association between the predefined potential risk factors for transfusion (age, gender, body mass index, HCC diagnosis, MELD score, warm and cold ischemia times, intraoperative transfusion requirements, and duration of hospital stay) and transfusion requirements of each blood product. Blood products were grouped into binary categories based on no transfusion or transfusion of at least one unit. The association of potential risk factors with transfusion requirements was expressed as OR and 95% CI.

A dose-dependent relationship between intra- and postoperative blood product use was also assessed by logistic regression analysis. Intraoperative transfusion was grouped into 4 categories (no transfusion, 1–2 units, 3–5 units- or 6 and above 6 units), according to the cut-offs previously defined [4, 5], which were entered into the model as determinants. Postoperative blood transfusion and transfusion of RBC, platelet concentrates, FFP, and CRYO were entered as dependent variables. All analyses were performed with SPSS version 20.0 (IBM, Chicago, USA).

Table 1. Baseline characteristics of patients before OLT

Characteristics	*N* (%) or median (IQR)
Age	55 (46–61)
Male	452 (71)
Body mass index	26 (23–29)
MELD score	29 (24–31)
Primary diagnosis	
Virus-related liver cirrhosis[1]	236 (36.5)
Cirrhosis due to other causes[2]	216 (33.5)
Metabolic diseases[3]	32 (5)
Miscellaneous[4]	32 (5)
Primary nonfunction	18 (2.8)
Autoimmune diseases[5]	60 (9.3)
Vascular complications[6]	36 (5.6)
Fulminant hepatitis	16 (2.5)
Hepatocellular carcinoma	195 (30.2)

OLT, orthotopic liver transplantation; IQR, interquartile range; MELD, model for end-stage liver disease. [1] Virus-related cirrhosis: hepatitis B virus and hepatitis C virus. [2] Cirrhosis due to other causes: alcoholic cirrhosis, nonalcoholic steatohepatitis, cryptogenic. [3] Metabolic diseases: hemochromatosis, alpha 1 anti-trypsin deficiency, familial amyloid polyneuropathy, Wilson's disease. [4] Miscellaneous: hemangioendothelioma, Caroli's disease, schistosomiasis, polycystic liver disease, adenomatosis, neuroendocrine tumor. [5] Autoimmune diseases: biliary atresia, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, ductopenic cholestasis, primary nonfunction. [6] Vascular complications: Budd-Chiari syndrome, hepatic artery thrombosis, portal vein thrombosis.

Table 2. Intraoperative parameters and length of hospitalization

Parameters	*N* (%) or median (IQR)
Warm ischemia, min	40 (35–45)
Cold ischemia, h	8 (6.8–9.4)
Total transfusion requirements	
0	225 (43)
1–2 units	144 (24)
3–5 units	102 (17)
6 or more	90 (15)
Days in hospital	12 (8–22)

IQR, interquartile range.

Results

Study Population

Patient baseline characteristics are shown in Table 1. Intraoperative parameters and length of hospitalization are presented in Table 2.

Transfusion of Blood Products

One hundred thirteen patients (17.5%) did not receive any blood product during the entire hospitalization period. Three hundred and twenty-six patients (50.5%) received transfusion in both intraoperative and postoperative period, whereas one hundred and sixty-seven patients (25.8%) received blood transfusions only in the postoperative period. Thirty-nine patients (6.2%) received transfusion only in the preoperative period. The total number of RBC units transfused in the intraoperative period was 1,623 units, less than half of the amount transfused in the postoperative period (3,576 RBC units). Similarly, 480 units of FFP were transfused in the intraoperative period, while almost twice as many units (798 FFP units) were transfused in the postoperative period. Transfusion requirements of all blood components was higher in the postoperative period. Transfusion requirements in the intraoperative and postoperative period are shown in Table 3. Postoperative transfusion requirements per diagnosis is detailed in Table 4.

Risk Factors for Postoperative Transfusion Requirements

The determinants of blood transfusion requirements are detailed in Table 5.

The main determinants of postoperative transfusion requirements of any blood component were the number of blood units transfused in the intraoperative period (OR 1.21, 95% CI 1.10–1.34), MELD score (OR 1.05, 95% CI 1.01–1.08), and warm ischemia time (OR 1.05, 95% CI 1.02–1.08). HCC was a protective factor for postoperative transfusion (OR 0.45, 95% CI 0.28–0.72). Intraoperative transfusion was a major determinant of postoperative transfusion requirements regardless of the type of blood component used during the surgery. Age, gender, BMI, virus-related cirrhosis, and cold ischemia time were not associated with the risk of postoperative blood transfusion.

As shown in Table 5, determinants of postoperative transfusion of packed RBC were female gender, MELD score, virus-related cirrhosis, number of blood component units used in the intraoperative period, and warm ischemia time. The determinants of postoperative platelet transfusion requirements were MELD score and volume of intraoperative blood transfusion. Transfusion of FFP was related to the number of units of blood components used in the intraoperative period, while CRYO usage was determined by BMI, number of units of blood components used in the intraoperative period, and cold ischemia time. HCC was a protective factor for transfusion of RBC, FFP, and CRYO.

As volume of intraoperative transfusion per unit was a major determinant for transfusion requirements in the postoperative period, we further investigated whether there was a dose-dependent association between the number of units transfused in the intraoperative period and transfusion requirements in the postoperative period

Table 3. Overall transfusion requirements during hospitalization for OLT

Blood components	Intraoperative transfusion, median (range)	Total intraoperative transfusions, *n*	Postoperative, median (range)	Total postoperative transfusions, *n*
Total blood transfusion, UI	1 (0–35)	1,623	3 (0–56)	3,576
RBC, UI	1 (0–22)	906	2 (0–27)	1,962
FFP, UI	0 (0–18)	480	0 (0–25)	798
Platelets, UI	0 (0–5)	155	1 (0–25)	701
Cryoprecipitate, UI	0 (0–2)	82	0 (0–6)	115

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

Table 4. Postoperative transfusion requirements per diagnosis

Diagnosis	Postoperative units of RBC transfusion		Postoperative units of FFP transfusion		Postoperative units of CRYO transfusion		Postoperative units of platelet transfusion	
	mean	SD	mean	SD	mean	SD	mean	SD
Etiological diagnosis								
Virus-related liver cirrhosis	3.22	4.34	1.70	3.64	0.24	0.66	1.28	2.20
Cirrhosis due to other causes	3.00	3.79	1.25	2.85	0.15	0.46	1.01	1.50
Metabolic diseases	2.75	4.24	0.44	1.08	0.19	0.47	0.91	1.82
Miscellaneous	5.13	5.07	2.84	5.38	0.34	0.60	1.66	1.93
Primary nonfunction	10.22	6.73	6.56	7.50	0.50	0.86	2.06	2.10
Autoimmune diseases	4.93	4.73	1.92	4.32	0.20	0.82	1.38	2.01
Vascular complications	5.50	4.78	2.58	3.81	0.36	0.72	1.39	2.14
Fulminant hepatitis	4.25	5.05	2.00	2.68	0.13	0.34	2.44	6.14
Hepatocellular carcinoma								
Present	1.67	2.43	0.78	2.45	0.1	0.48	0.71	1.12
Absent	4.70	4.98	2.21	4.15	0.28	0.66	1.51	2.43

SD, standard deviation; RBC, red blood cells; FFP, fresh frozen plasma; CRYO, cryoprecipitate.

Table 5. Risk of postoperative transfusion according the baseline characteristics and intraoperative parameters

Clinical parameters	Postoperative transfusion of any blood component (compared to no postoperative transfusion)			Postoperative RBC transfusion ≥1 U (compared to no postoperative RBC transfusion)			Postoperative platelet transfusion ≥1 U (compared to no postoperative platelet transfusion)			Postoperative FFP transfusion ≥1 U (compared to no postoperative FFP transfusion)			Postoperative cryoprecipitate transfusion ≥1 U (compared to no postoperative cryoprecipitate transfusion)		
	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Age	1.00	0.98; 1.02	0.90	1.00	0.99; 1.02	0.62	1.01	0.99; 1.02	0.37	1.00	0.98; 1.01	0.90	1.02	0.99; 1.04	0.10
Gender	1.10	0.66; 1.85	0.70	1.66	1.02; 2.71	0.04	1.02	0.69; 1.52	0.92	1.21	0.81; 1.83	0.35	1.09	0.62; 1.91	0.76
BMI	1.03	0.98; 1.07	0.25	1.01	0.97; 1.05	0.76	1.04	0.99; 1.08	0.10	1.02	0.98; 1.06	0.25	1.03	1.00; 1.05	0.03
MELD score	1.05	1.01; 1.08	0.02	1.07	1.03; 1.10	<0.001	1.02	1.00; 1.04	0.05	1.00	0.98; 1.02	0.73	1.02	0.99; 1.04	0.13
Hepatocellular carcinoma	0.45	0.28; 0.72	<0.001	0.41	0.27; 0.64	<0.001	0.72	0.48; 1.08	0.12	0.39	0.24; 0.64	<0.001	0.29	0.13; 0.64	<0.001
Virus-related cirrhosis	1.72	0.86; 3.40	0.18	2.44	1.24; 4.81	0.01	1.59	0.97; 2.59	0.06	1.44	0.88; 2.38	0.43	1.26	0.69; 2.31	0.45
Volume of intraoperative blood transfusion	1.21	1.10; 1.34	<0.001	1.20	1.10; 1.31	<0.001	1.16	1.10; 1.24	<0.001	1.17	1.11; 1.23	<0.001	1.13	1.08; 1.19	<0.001
Warm ischemia time	1.05	1.02; 1.08	<0.001	1.05	1.03; 1.08	<0.001	1.01	1.00; 1.03	0.14	1.01	0.99; 1.03	0.17	1.01	0.99; 1.03	0.84
Cold ischemia time	1.02	0.97; 1.14	0.71	1.02	0.92; 1.14	0.68	1.08	0.99; 1.19	0.09	1.02	0.91; 1.13	0.77	1.17	1.02; 1.35	0.03

OR, odds ratio; CI, confidence interval; RBC, red blood cells; FFP, fresh frozen plasma.

Table 6. Risk of postoperative transfusion according intraoperative transfusions

Total intraoperative transfusion required	Postoperative transfusion (any transfusion)			Postoperative RBC transfusion			Postoperative platelet transfusion			Postoperative FFP transfusion			Postoperative CRYO transfusion		
	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
0	reference			reference			reference			reference			reference		
1–2 units	5.9	3.4; 10.4	<0.001	5.4	3.3; 8.9	<0.001	2.7	1.8; 4.1	<0.001	2.5	1.5; 4.2	<0.001	4.4	2.1; 9.4	<0.001
3–5 units	7.3	3.6; 14.7	<0.001	6.1	3.4; 11.1	<0.001	5.4	3.2; 8.8	<0.001	2.6	1.5; 4.6	<0.001	3.8	1.7; 8.7	0.001
6 or more	11.1	4.7; 26.4	<0.001	11.7	5.4; 25.2	<0.001	7.3	4.2; 12.8	<0.001	10.4	5.9; 18.1	<0.001	11.7	5.5; 24.5	<0.001

OR, odds ratio; CI, confidence interval; RBC, red blood cells; FFP, fresh frozen plasma; CRYO, cryoprecipitate.

(Table 6). The OR for postoperative transfusion of any blood component was 5.9 (95% CI 3.4–10.4) for patients who received 1–2 units in the intraoperative period, 7.3 (95% CI 3.6–14.7) for those who received 3–5 units in the intraoperative period, and 11.1 (95% CI 4.7–26.4) for those who received 6 or more units, when compared to no intraoperative blood transfusion. A similar dose-dependent effect was also observed regarding transfusion of platelet concentrates, FFP, and CRYO (Table 6).

Discussion/Conclusion

Several studies have demonstrated the negative impact of blood transfusion in OLT, with increased rates of morbidity and mortality, longer hospital stay, and higher costs [1, 9]. So far, most of the studies have analyzed predictors of blood transfusion only in the intraoperative period [7, 20, 33, 34].

Anemia and hemostatic derangements are also common situations in the postoperative period, contributing to transfusion requirements. Early postoperative bleeding is the most frequent life-threatening complication of OLT [12, 35]. These bleeding episodes demand reoperation in 10–15% of patients and increase costs [36]. Rotational thromboelastometry parameters, such as CFT INTEM, A10 FIBTEM, and MCF FIBTEM, were recently identified as predictors of postoperative nonsurgical bleeding in OLT in a retrospective analysis [21]. Standard coagulation test, such as aPTT and PT, may also predict postoperative bleeding, while fibrinogen concentration, platelet count, and other ROTEM variables failed to identify bleeding risk [21]. Although these risk factors associated with transfusion requirements in the postoperative period have been reported by previous studies [21], clinical evidence on this issue remains sparse.

In this study, we aimed to determine predictors of transfusion requirements in the postoperative period. We included a large number of severe acutely ill patients and those with mild abnormalities of liver function, which provided a wide range of transfusion requirements. We observed that the volume of blood components transfused in the postoperative period was higher than that in the intraoperative period. The number of RBC and FFP units transfused was 2.2 times increased and the number of platelets transfused were 4.5 times increased in the postoperative period when compared with the intraoperative period. This observation suggests that the need for therapeutic transfusions was more pronounced in the postoperative period. Although it is possible to argue that the differences between intra- and postoperative platelet transfusion guidance may have had an impact on transfusion indication [37–39], that would only be true for prophylactic platelet transfusion because both post- and intraoperative therapeutic transfusion were only guided by viscoelastic tests. Furthermore, the same guidance for intra- and postoperative RBC and FFP transfusion was applied.

Posttransplant thrombocytopenia is a common situation that affects the majority (90%) of patients immediately after the procedure [40, 41]. Nadir of thrombocytopenia is expected on days 3–5, when platelet counts may drop as low as 60% of the baseline, followed by full recovery within 14 days [42]. The use of standard laboratory tests to guide prophylactic platelet transfusion in the postoperative period and the occurrence of a transient thrombocytopenia may explain our findings of increased platelet transfusion need in the postoperative period. However, they would not explain the increase in packed RBC and FFP transfusion.

We observed that the main determinants of postoperative blood transfusion requirement were volume of blood transfused in the intraoperative period, warm ischemia time, and MELD score. Besides these determinants, female gender and virus-related cirrhosis were also risk factors for the need of packed RBC transfusion, and cold ischemia time and BMI for CRYO transfusion. HCC was a protective factor for postoperative transfusions for all components, except for platelets.

We observed that the diagnosis of virus-related liver cirrhosis was a risk factor for RBC transfusion requirement in the postoperative period. This result was unexpected because hepatitis C infection is associated with increased platelet activity [43, 44], which suggests that the disease leads to a procoagulant state. Nevertheless, volumes of platelets, CRYO, or FFP transfused were not associated with virus-related cirrhosis.

Intraoperative transfusion was dose-dependently associated with postoperative transfusion requirements when considering all blood products and in subgroup analyses of each product. This observation suggests that the determinants of postoperative transfusion requirements are similar to those of intraoperative transfusion, which are age [20, 33], preoperative hemoglobin and coagulation tests results [7, 20, 33, 34], bilirubin [3, 7], previous surgery [3, 5], and MELD score [20, 34].

Besides sharing the same risk factors, it is also possible that intraoperative transfusion is directly associated with the risk of postoperative transfusion. Severe coagulopathy may occur following hepatic revascularization due to prolonged ischemia times [20], thrombocytopenia, heparin-like effect [45], hyperfibrinolysis, and coagulation factor deficiencies [8, 46]. These disorders may cause intraoperative and postoperative bleeding [11, 12], affecting the risk of both intraoperative and postoperative transfusion requirements. The association between intraoperative transfusion requirement and postoperative bleeding has been determined before [8, 11, 12, 15]. In a retrospective study, intraoperative blood transfusion was dose-dependently associated with the risk of reoperation due to bleeding [12].

In our study, warm ischemia time was also a determinant for blood transfusion requirement in the postoperative period. Warm ischemia has been described as a risk factor for intraoperative transfusion requirements [3, 5]. A previous cohort study showed that prolonged warm ischemia time affects immediate graft function, which leads to reperfusion blood loss and transfusion need [3]. The risk of receiving massive transfusion during the surgery increased by 11% for each additional minute of warm ischemia time [3].

We observed that increase in postoperative transfusions was associated with increased length of hospital stay. It is noteworthy that there is an association between post-OLT complications and longer hospitalization periods. Therefore, length of hospital stay may be regarded as a surrogate marker of post-OLT complications. From that perspective, our study suggests that post-OLT adverse outcomes are associated with the risk of postoperative transfusion.

Our subgroup analyses on the risk factors for the use of packed RBC, FFP, and CRYO in the postoperative period yielded similar results as those on the risk for blood products altogether, except for adjusted MELD, which appeared as risk factor for packed RBC transfusion and platelets, and HCC, which was a protective factor for all blood components, except for platelets.

The role of HCC in OLT prognosis is controversial and may be dependent on the stage of the disease. Although selected patients with stage 1–2 HCC may have long-term survival after OLT [47], it has also been reported that HCC patients may require more blood products than those suffering from other pathologies [33]. In our center, most of HCC patients are prioritized for transplantation because of additional MELD points gained due to the tumor and, therefore, they spend a shorter period on the waiting list. These recipients had preserved liver function, little or no hemostatic derangements, and almost no coagulopathy. Furthermore, patients with HCC may have a hypercoagulable state due to chronic inflammation and circulating tissue factor-bearing cells [48–53], which may contribute to lower transfusion requirements. Indeed, we had a relatively elevated incidence of patients with HCC (30.2%), with elevated adjusted MELD, but mild disease and minimum impairment on liver function.

The association between MELD score and transfusion requirements is also controversial [54, 55, 47]. In our study, MELD score was only associated with packed RBC and platelet requirements. In previous studies, blood product use and reoperation due to hemorrhage was more frequent in patients with higher MELD scores [10, 12], probably due to a persistent coagulopathy. However, we had a significant proportion of patients with HCC (33%), whose adjusted MELD score were high because of the tumor and not because of a more compromised liver function. A previous study that included a high proportion of patients with HCC (16%) also reported no association between adjusted MELD score and transfusion requirements [54]. Likewise, no significant correlation between MELD score and coagulopathy measured by thromboelastometric parameters was established [56], suggesting a rebalanced hemostasis in such patients, irrespective of the extent of liver failure [56].

Our study has several limitations, which are addressed in the following paragraph. First, this is a retrospective study and some information on baseline characteristics are missing, such as blood tests before the OLT. However, we were still able to accurately evaluate the clinical conditions of the patients because this information was summarized in the adjusted MELD score. Second, as we aimed to evaluate determinants of allogeneic transfusion, we did not evaluate the use of cell salvage and the use of blood products such as PCC and fibrinogen concentrates. It is possible, however, that these therapies have an effect on transfusion requirements in the postoperative period. Third, this is a single-center study where OLT has been performed by the same team of surgeons and anesthesiologists for the last 5 years. Although single-center studies provide limited variability of practices and standardized procedures, it may also comprise the generalizability of the results. Finally, our findings suggest that blood product use in the intraoperative period increases postoperative transfusion requirements. Since blood transfusion is associated with increased short- [2, 4, 11] and long-term [5, 13, 14] morbidity and mortality, restrictive transfusion strategies and methods to decrease blood loss

[57] may potentially benefit the patients. However, these strategies have to be evaluated in further studies.

In conclusion, our study demonstrated that there is an association of intraoperative transfusion, warm ischemia time, and length of hospitalization with postoperative transfusion requirements. The identification of risk factors for transfusion in the postoperative period may improve management of these patients by increasing the awareness to bleeding complications in this high-risk population and by expanding hemostasis monitoring to the postoperative period. This may result in improved outcomes and reduced morbidity and costs.

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Statement of Ethics

The study protocol has been approved by Hospital Israelita Albert Einstein committee on human research. The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

A.P.H. Yokoyama designed the study, collected the information of patients, and drafted the manuscript. J.M. Kutner contributed to analyzing data and revised the manuscript. A.M. Sakashita, C.Y. Nakazawa, T.A.O. de Paula, R.P.C. Zamper, P.T. Pedroso, S.P. Meira Filho, and M.D. de Almeida revised the manuscript. F.A. Orsi designed the study, designed and performed the statistical analysis, and revised the manuscript. All authors read and approved the final manuscript.

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