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The Ratio of Intraoperative Red Blood Cell Transfusion to Blood Loss Associated with Early Postoperative Complications in Pediatric Liver Transplantation Patients

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Keywords

Pediatric liver transplantation · Blood loss · Red blood cell transfusion · Early postoperative complications · Intraoperative red blood cell transfusion to blood loss

Abstract

Introduction: Liver transplantation (LT) is an operation purposed to save the lives of children with acute or chronic liver diseases, hepatic tumors, and some genetic and metabolic diseases. However, patients who underwent LT have a significant risk of intraoperative blood loss and red blood cell (RBC) transfusion, especially in pediatric patients. ***Methods:*** In this study, 569 pediatric patients (<18 years old) who underwent LT at a tertiary university hospital between 2013 and 2020 were included. Multiple logistic regression was used to analyze the association between the ratio of intraoperative RBC transfusion to blood loss (IRTBL) and the complications after LT in pediatric patients. IRTBL was divided into quartiles in the adjusted model. Odds ratios, 95% confidence intervals, and *p* values for trends were calculated. Restricted cubic spline (RCS) regression was used to evaluate the nonlinear association between IRTBL and complications. ***Results:*** Compared with the lowest level and the highest level of IRTBL, Q2 and Q3 quartiles of IRTBL showed significantly positive association with early complications. A significantly nonlinear association was observed between the IRTBL and early complications in the RCS model with the multiple adjustments of potential covariates (*P* overall<0.01, *P* nonlinear<0.01). However, no significant association was observed between late complications and IRTBL. ***Conclusion:*** In this study, we found there was a nonlinear relationship between the ratio of IRTBL and early postoperative complications in pediatric LT patients, which provides a theoretical basis for RBC transfusion in pediatric LT patients.

Introduction

Pediatric liver transplantation (LT) is one of the most successful solid organ transplantations. It has become an advanced treatment strategy for children with end-stage liver disease [1–3]. More than 80% of children will survive and become adolescents and adults with good health-related quality of life [4]. Blood transfusion is indispensable in surgery, but it has the risks of infectious and noninfectious complications [5]. Clinical trials demonstrate blood transfusion with low hemoglobin levels is beneficial [6, 7]. Therefore, blood transfusion is often conservatively selected to maintain blood volume in children during the perioperative period, and hemoglobin is promptly supplemented. LT

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studies have demonstrated that red blood cell (RBC) transfusion and blood loss are independent risk factors that will impact outcomes in adult and pediatric patients [8–10], but there are few studies in pediatric LT patients regarding the association between intraoperative blood loss and RBC transfusion demand and postoperative complications. As intraoperative blood loss and RBC transfusion are interdependent, this study introduced a new concept – the ratio of intraoperative RBC transfusion to blood loss (IRTBL) for balance blood loss and RBC transfusion – and then analyzed and evaluated the relationship between IRTBL and clinical outcomes in pediatric LT patients.

Methods

Participants and Study Design

Pediatric patients who underwent LT at Beijing Friendship Hospital (Capital Medical University, Beijing, China) between 2013 and 2020 were enrolled in the present study. A total number of 569 pediatric patients (<18 years old) with complete and available medical records were ultimately analyzed in this retrospective study. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Beijing Friendship Hospital, Capital Medical University (Ethics code: 2022-P2-155-01).

From 2013 to 2020, a total of 1,190 patients underwent LT. Among the patients who underwent LT, 156 patients with incomplete basic information were excluded. We then excluded 423 patients over the age of 18 years old, 33 pediatric patients with incomplete operation information were also excluded. Finally, a total of 569 pediatric patients who underwent LT first time were ultimately analyzed in the present study (Fig. 1).

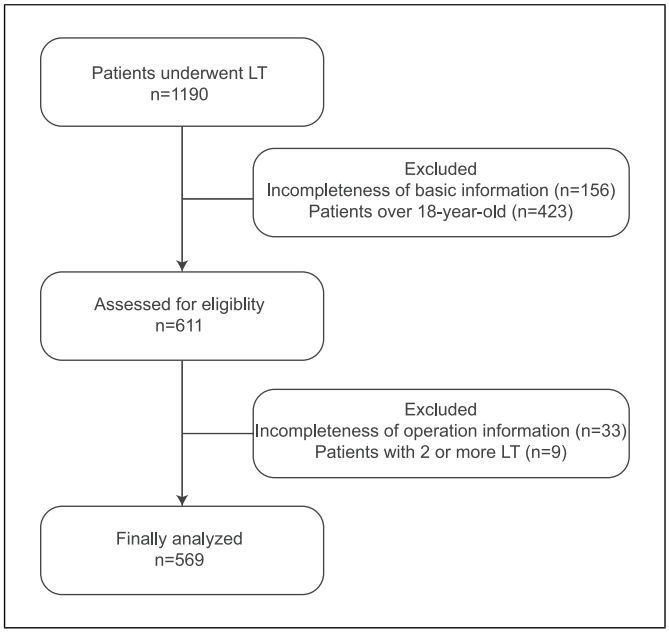

Fig. 1. Flow diagram.

Definition of IRTBL and Classification of Postoperative Complications

The complication examination during hospitalization is determined by the doctor according to the laboratory examination every day. Early complications refer to complications occurring within 30 days after LT, including intraperitoneal hemorrhage, hepatic artery embolism, portal vein occlusion, hepatic vein/inferior vena cava stenosis/embolism, bile leakage, anastomotic biliary stricture, intrahepatic biliary stricture, primary graft nonfunction, graft function delay, intraperitoneal effusion/abscess, pulmonary infection, pleural effusion, pulmonary edema, catheter sepsis, urinary tract infection, wound infection, renal failure, opportunistic infection, and death. Late complications refer to the complications that occur after 30 days after LT and will be followed up for life, including cyclosporine A toxicity, FK506 toxicity, hepatic vein/inferior vena cava stenosis, hepatic artery embolism portal vein stenosis/thrombosis, bile leakage, biliary anastomotic stenosis, intrahepatic biliary stricture, chronic rejection, opportunistic infection, posttransplant lymphoproliferative disease, graft-versus-host reaction, and death.

The anesthesiologist estimated the intraoperative blood loss according to the amount of liquid in the drainage bottle and the weighing of the blood-soaked gauze. The amount of RBC transfusion during the operation is also recorded by the anesthesiologist. Therefore, IRTBL is the radio of intraoperative RBC transfusion (unit) to blood loss (mL). IRTBL ranged from 0 to 6.7 in the present study. Median (Q1, Q3) of IRTBL in all the participants was 0.53 (0.20, 0.91).

Statistical Analysis

Quantitative data with a normal distribution are expressed as the mean ± standard deviation, and comparisons between the two groups were performed by *t* test. Median and interquartile range were used for the quantitative data that did not follow a normal distribution, and the comparisons between the two groups were performed by Wilcoxon test. Categorical data were expressed as n (%) and were compared by χ^2 tests. The association between IRTBL and postoperative complications of LT in pediatric patients was analyzed by a multiple logistic regression model. The regression model was adjusted by age, gender, blood type, clinical diagnosis, graft source, relationship between recipient and donor, and Child-Pugh classification of the patients. In addition, body weight, height, operation duration, and cold ischemia time, were also enrolled in the adjusted model. Categorical covariates were transformed into dummy variables in the analysis. IRTBL was divided into quartiles in the analysis, and odds ratios (ORs) and 95% confidence intervals (CIs) for the complications of LT were calculated. The nonlinear relationship between IRTBL ratio and the complications of LT was assessed by the restricted cubic spline (RCS) regression model with the adjustment of all the potential covariates. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA). A *p* value <0.05 was considered statistically significant.

Results

Participants Characteristic

The general characteristics and potential covariates of the pediatric patients who underwent LT are presented in Table 1. There were no significant differences in age, gender, graft source, relationship between recipient and donor, clinical diagnose, blood type, body weight, and height between the LT patients with and without complications (*p* value >0.05), while significant differences were observed in the Child-Pugh stages of LT patients

Table 1. General characteristics of participants[1]

Characteristic	Early complication		*p* value	Late complication		*p* value
	yes	no		yes	no	
Age, years			0.5581			0.8173
<6	150 (76.92)	302 (80.75)		107 (77.54)	345 (80.05)	
6–14	39 (20)	63 (16.84)		27 (19.57)	75 (17.4)	
14–18	6 (3.08)	9 (2.41)		4 (2.9)	11 (2.55)	
Gender			0.1463			0.6908
Male	110 (56.41)	187 (50)		70 (50.72)	227 (52.67)	
Female	85 (43.59)	187 (50)		68 (49.28)	204 (47.33)	
Graft source			0.1911			0.2244
Living-donor liver	141 (73.82)	259 (68.52)		84 (75)	316 (69.15)	
Cadaveric liver[2]	50 (26.18)	119 (31.48)		28 (25)	141 (30.85)	
Relationship			0.1419			0.5284
Parents	136 (71.2)	246 (65.08)		78 (69.64)	304 (66.52)	
Nonparents	55 (28.8)	132 (34.92)		34 (30.36)	153 (33.48)	
Diagnose			0.4811			0.3696
Biliary atresia	105 (54.97)	196 (51.85)		55 (49.11)	246 (53.83)	
Others	86 (45.03)	182 (48.15)		57 (50.89)	211 (46.17)	
Blood type						0.6412
A	53 (27.75)	96 (25.4)	0.8073	25 (22.32)	124 (27.13)	
B	55 (28.8)	122 (32.28)		37 (33.04)	140 (30.63)	
AB	26 (13.61)	46 (12.17)		17 (15.18)	55 (12.04)	
O	57 (29.84)	114 (30.16)		33 (29.46)	138 (30.2)	
Child-Pugh stage			0.9001			0.0238
A	17 (8.9)	38 (10.05)		8 (7.14)	47 (10.28)	
B	66 (34.55)	131 (34.66)		51 (45.54)	146 (31.95)	
C	108 (56.54)	209 (55.29)		53 (47.32)	264 (57.77)	
Weight, kg	10 (7,17.4)	9.65 (7,15.5)	0.3930	10 (7.4,17.2)	9.6 (7,16)	0.4993
Height, cm	80 (66,110)	75 (66,102)	0.5963	79 (66,109.5)	75 (66,103)	0.3961
Operation duration (min)	410 (360,480)	405 (345,471)	0.1853	402 (360,490)	405 (350,471)	0.6657
Cold ischemia time (min)	95 (65,160)	98 (60,315)	0.6826	100 (72,171)	96 (60,226)	0.2968

[1]Quantitative data are shown as median and quarterlies, and categorical data are shown as *n* (%). [2]Cadaveric liver was from the donation after citizens death.

with and without late complications (p value <0.05). Compared with the LT patients without late complication, the patients with late complications showed lower percentage in the A stage of Child-Pugh stage (7.14 vs. 10.28%) and C stage (47.32 vs. 57.77%); and higher percentage in the B stage (45.54 vs. 31.95%)

Patients with Early Complication Showed Higher Level of IRTBL

Several indicators related to RBC transfusion were compared between the patients with and without complications after LT (Table 2). No significant differences in operation duration, cold ischemia time, RBC transfusion, and IRTBL were observed between the patients with and without early complications. Compared with the patients without early complications, the total blood loss in the patients with early complications was slightly lower (150 mL vs. 250 mL, $p < 0.001$). In addition, no significant differences in those indictors were observed between the patients with and without late complications.

Classification and Rank of Complications in Pediatric Patients

Early complications and late complications were classified and ranked in LT patients (Fig. 2). Intra-abdominal abscesses or effusion was the most common early complication. Lung infections and pleural effusion were ranked as the second and third common complications at the early posttransplant stage. Opportunistic infections, posttransplant lymphoproliferative disease, and death were the most common complications at the late posttransplant stage.

Association between IRTBL and Complications after LT in Pediatric Patients

Multiple logistic regression was used to assess the association between IRTBL and complications, and the results are presented in Table 3. Quartiles of the IRTBL were analyzed in the adjusted models. Compared with the lowest level of IRTBL, Q2 and Q3 quartiles of IRTBL showed significantly positive association with early

Table 2. Differences among blood transfusion-related indicators among patients with and without complications

Blood transfusion-related indicators	Early complication		*p* value	Late complication		*p* value
	yes (*N* = 195)	no (*N* = 374)		yes (*N* = 138)	no (*N* = 431)	
Operation duration (min)	410 (360, 480)	405 (348, 471)	0.2541	402.5 (350, 490)	405 (350, 470)	0.6707
Cold ischemia time (min)	95 (65, 161)	98 (60, 300)	0.7296	101 (65, 345)	95 (60, 178)	0.2057
Blood loss, mL	150 (100, 300)	250 (150, 350)	<0.0001	200 (130, 350)	200 (120, 300)	0.5665
RBC transfusion (unit)	1 (0, 2.00)	1.30 (0.60, 2.00)	0.1855	1.13 (0.75, 2.00)	1.30 (0.50, 2.00)	0.4991
IRTBL	0.67 (0, 1.00)	0.52 (0.24, 0.80)	0.0752	0.57 (0.25,0.86)	0.53 (0.11,0.93)	0.7108

complications (OR_{Q2} = 2.164, 95% CI = 1.242–3.769, OR_{Q3} = 2.056, 95% CI = 1.180–3.585). However, the highest quartile of IRTBL showed no significant association with early complication. In addition, no significant association was observed between IRTBL and late complications.

Subgroup analysis was performed to discuss the association between IRTBL and the most popular early complications (intra-abdominal abscesses/effusion, lung infections, and pleural effusion), and the results are presented in Table 4. Quartiles of the IRTBL were analyzed in the adjusted models. Compared with the lowest level of IRTBL, Q3 quartiles of IRTBL showed significantly positive association with intra-abdominal abscesses/effusion (OR_{Q3} = 1.885, 95% CI = 1.020–3.482). However, no significant association was observed between IRTBL and the other most popular early complications, including lung infections and pleural effusion.

Nonlinear Association between IRTBL and Early Complications in Pediatric Patients

Further analysis of the relationship between IRTBL and complications was performed in the RCS model (Fig. 3). With the full adjustment of potential covariates, a statistically significant overall association was observed between IRTBL and early complications (Fig. 3a, $p < 0.01$). Furthermore, the association showed significantly nonlinear characteristics (Fig. 3a, $p < 0.01$). Meanwhile, no significant association between IRTBL and late complications was observed in the RCS model with full adjustment of potential covariates (Fig. 3b).

Discussion

For many years, intraoperative transfusion has been a controversial topic. In this study, IRTBL plays an important role in maintaining the homeostasis of blood volume, and we found that there is a nonlinear relationship between IRTBL and early postoperative complications in pediatric LT, suggesting that IRTBL has guiding significance for postoperative recovery. In addition, we found that IRTBL is related to the early complications after LT, but not to the late complications after LT. This may be because the complications caused by transfusion-related factors often occur within 1 month. For example, the delayed hemolytic transfusion reaction usually occurs within 1–2 weeks after blood transfusion, and the standardized and systematic treatment after operation will reverse the postoperative complications caused by transfusion-related factors.

Despite guidelines based on many years of experience and recommendations of consensus conferences on the use of pediatric blood products, there is still a huge gap between clinical practice and the recommendations of the medical community. Neonatal and pediatric patients are physiologically different from adults, so transfusion indications and clinical management may present unique challenges [11, 12]. Since the amount of blood used during surgery or massive RBC transfusion may be equal to the total blood volume of the newborn, neonatal patients are more vulnerable to the electrolyte and metabolic consequences of blood transfusion (e.g., hyperkalemia, hypocalcemia) [11, 13, 14]. In this single-center retrospective analysis, we focused on the pathological process of LT in pediatric patients, but due to the limitations of this cross-sectional study, we can only suggest that IRTBL shows a nonlinear relationship with clinical outcomes, suggesting that there is an undisclosed relationship. In future studies, we will conduct a multicenter study to clarify the relationship between IRTBL and clinical outcomes.

Many studies have shown that RBC transfusion is independently associated with an increased risk of postoperative morbidity. Some studies have also shown or implied an increase in postoperative mortality [15–18]. In addition, most of these works did not specify the storage time of blood transfusion RBCs. During storage, change in the structure and function of RBCs, known as the "storage lesion", may impair the function and diminish the vitality of RBCs, and increase free hemoglobin, potassium, lactic acid, and inflammatory factors in packaged red cells, thereby increasing the incidence rate and mortality risk [19–21]. Several recent randomized controlled trials in adults have compared the outcome of fresh and old red cells in different critical

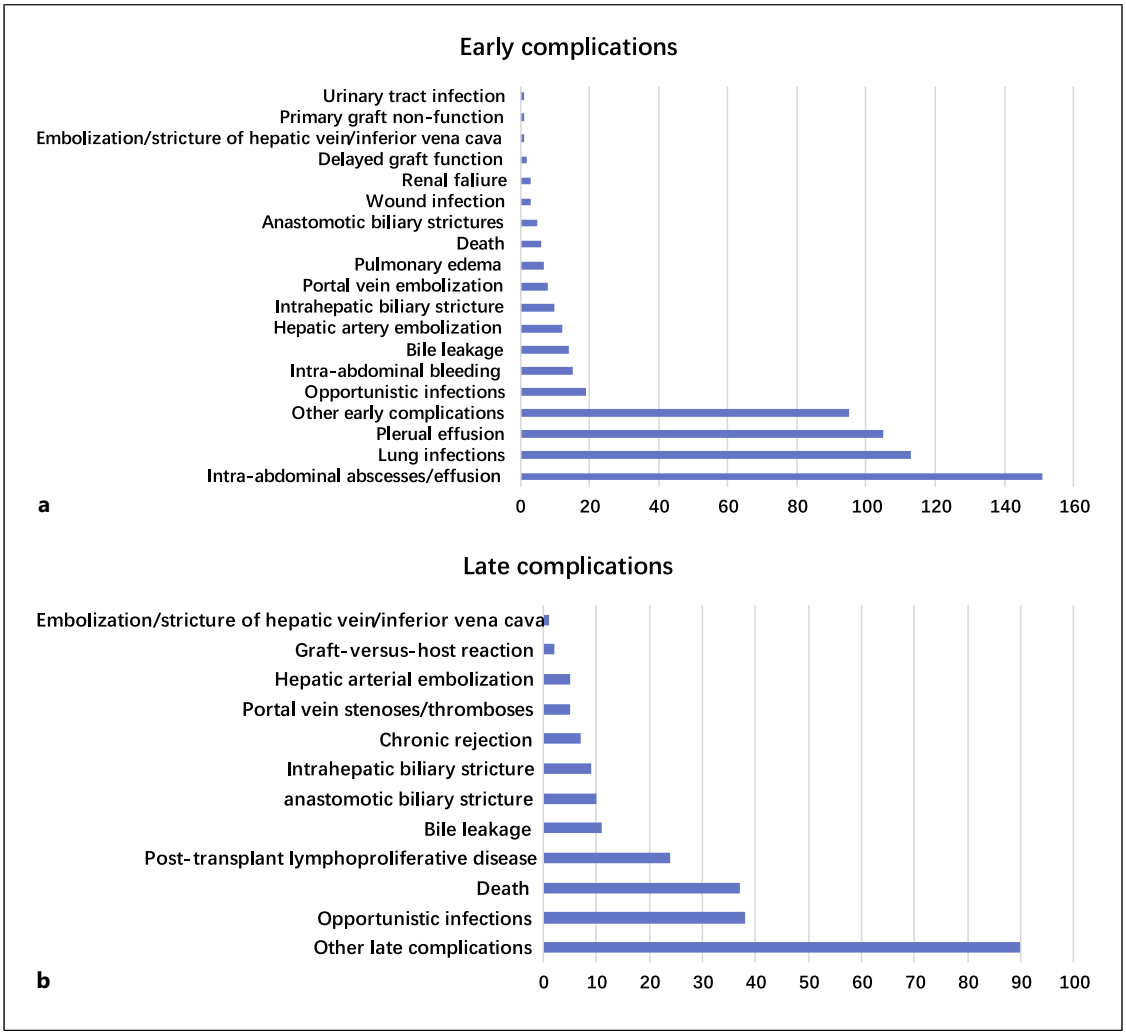

Fig. 2. Classification and rank of early complications (**a**) and late complications (**b**).

Table 3. Association between IRTBL and complication among pediatric patients with LT in the logistic regression model[1]

Complication	IRTBL										
	Q1	Q2			Q3			Q4			
	Ref	OR	95% CI		OR	95% CI		OR	95% CI		*p* for trend
Early complication	1	2.164	1.242	3.769	2.056	1.180	3.585	0.709	0.423	1.186	0.0934
Late complication	1	0.919	0.507	1.667	0.870	0.477	1.586	0.932	0.509	1.707	0.7997

[1]Regression models were adjusted by age-group, gender, blood type, clinical diagnosis, graft source, relationship between recipient and donor, and Child-Pugh classification, body weight, height, operation duration, and cold ischemia time.

populations and found that "fresh" blood transfusion has no survival advantage [22–25]. However, the results of adult studies may not be applicable to children because the host characteristics and differences in fertility may have a significant impact on the risk and benefits of anemia and blood transfusion in this population [26].

Table 4. Subgroup analysis of the association between IRTBL and the most popular early complication among pediatric patients with LT in the logistic regression model

Complication	IRTBL										
	Q1	Q2			Q3			Q4			
	Ref	OR	95% CI		OR	95% CI		OR	95% CI		*p* for trend
Intra-abdominal abscesses/effusion	1	1.361	0.755	2.453	1.885	1.020	3.482	0.934	0.529	1.649	0.8945
Lung infections	1	1.610	0.781	3.319	1.189	0.600	2.357	0.811	0.417	1.576	0.2295
Pleural effusion	1	0.918	0.475	1.774	1.644	0.799	3.385	0.796	0.410	1.544	0.8348

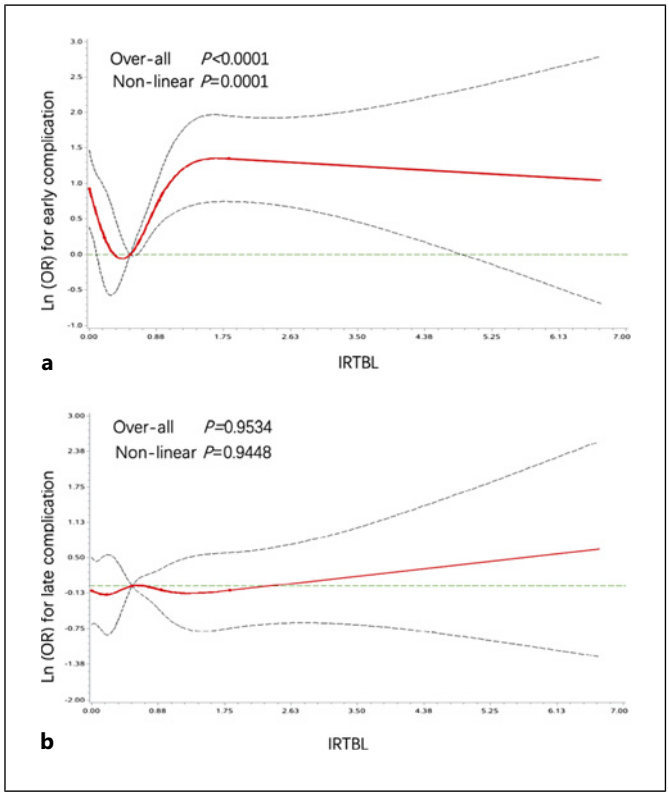

Fig. 3. Nonlinear association between IRTBL and complications among pediatric patients with LT in the RCS model. Nonlinear association between IRTBL and early complications (**a**) and nonlinear association between IRTBL and early complications among pediatric patients with LT (**b**). RCS models were adjusted by age-group, gender, blood type, clinical diagnosis, graft source, relationship between recipient and donor, and Child-Pugh classification, body weight, height, operation duration, and cold ischemia time.

In two randomized controlled trials published in the pediatric population, the tissue oxygenation by transfusion in severe anemia with lactic acidosis trial failed to show the difference in the increase of blood lactic acid level in children with severe anemia who received RBCs with longer storage time [27]. Therefore, we should pay more attention to RBC transfusion, especially postoperative RBC transfusion in pediatric patients; we should consider the correlation between IRTBL and postoperative complications in other operations, and whether IRTBL should be widely promoted as an indicator of precision medicine.

There are the following limitations in this study: all patients come from only one unit, and the results may be affected by the unique practice of the hospital. More than half of pediatric patients suffer from biliary atresia, which may result in biased selection of results. These limitations will provide a useful platform for future efforts to conduct prospective multicenter research and evaluate the safety of LT in patients compared with other surgical models.

Conclusions

In LT of pediatric patients, we found a nonlinear relationship between IRTBL and early postoperative complications. This suggests that we should associate RBC transfusion with blood loss to provide a new basis for blood transfusion guidance in pediatric LT.

Acknowledgments

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Statement of Ethics

This study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki, and no informed consent was required, and was reviewed and approved by the Ethics Committee of Beijing Friendship Hospital, Capital Medical University (Ethics code: 2022-P2-155-01).

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author Contributions

Dr. Ma and Prof Li contributed equally to design of the study, interpret data, and draft the manuscript. Dr. Sun provided all the data of patients receiving LT and reviewed the manuscript. Dr. Li coordinated and supervised data collection, and critically revised the manuscript of important contents. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Data Availability Statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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