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ORIGINAL ARTICLE

Factors associated with postoperative respiratory conditions and critical outcomes on pediatric liver transplantation: A single-center experience

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Abstract

Background: Orthotopic liver transplantation (OLT) is an established therapeutic option for pediatric end-stage liver disease (PELD). The postoperative respiratory conditions of OLT recipients may be associated with subsequent clinical outcomes including length of stay (LOS) in the pediatric intensive care unit (PICU). This study aimed to characterize the postoperative respiratory conditions, associated factors, and outcomes after pediatric OLT.

Methods: Clinical data of children receiving OLT from July 2014 to July 2020 were retrospectively collected. Postoperative respiratory conditions were defined as time to extubation, significant pleural effusion, and initial postoperative PaO_2/FiO_2 ratio. Logistic and multiple regressions were applied to analyze the associations among clinical factors, postoperative respiratory conditions, and clinical outcomes.

Results: Twenty-two patients with median age of 1.4-year-old (range: 25 days to 12 years old) were analyzed. Mortality within 28 days was 4.5% and median LOS in the PICU was 18 days. Of 22 patients, 11 patients (50.0%) were extubated over 24 hours after surgery, and 8 patients (36.4%) required drainage for pleural effusions. Longer LOS in the PICU were noted in patients extubated over 24 hours ($p = 0.008$), complicated with significant pleural effusions ($p = 0.02$) after surgery, and having low initial postoperative PaO_2/FiO_2 (<300 mmHg) ($p = 0.001$). Among clinical factors, massive intraoperative blood transfusion (>40 mL/kg) was significantly associated with prolonged intubations, significant pleural effusions, low initial postoperative PaO_2/FiO_2 and prolonged LOS in the PICU (>14 days). The initial postoperative PaO_2/FiO_2 significantly depended on age, disease severity (PELD score), and whether the patient received massive intraoperative blood transfusion.

Conclusion: Pediatric patients of OLT with poor postoperative respiratory conditions including low initial PaO_2/FiO_2 ratio, extubation over 24 hours or significant pleural effusions have longer LOS in the PICU, and the requirement of massive intraoperative transfusion was a risk factor for both poor postoperative respiratory conditions and prolonged LOS in the PICU.

Keywords: Massive blood transfusion; Orthotopic liver transplantation; Pediatric intensive care unit; Postoperative respiratory conditions; Prognosis

1. INTRODUCTION

In recent decades, orthotopic liver transplantation (OLT) has become a standard treatment for pediatric patients with fatal acute or chronic end-stage liver disease.[1,2] Although adequate organ preservation, skilled surgical technique, and new immunosuppressants improved the overall survival and long-term outcome of children after receiving OLT, perioperative management is still challenging and associated with some complications.[1–4] Pulmonary complications and prolonged postoperative mechanical ventilation have been reported as major and frequent contributing factors to postoperative mortality and long duration of stay in the intensive care unit (ICU) for both adult and pediatric OLT recipients.[4–10] However, very few pediatric studies focused on the postoperative respiratory conditions of pediatric OLT recipients, and the clinical factors associated with these pulmonary complications or respiratory conditions have not been consistent.[7,8,11] Therefore, this study aimed to characterize the postoperative respiratory conditions of OLT children, such as the lung function accessed via Horowitz index (arterial partial pressure of oxygen to fraction of inspired oxygen, PaO_2/FiO_2 ratio), time to extubation after surgery, and incidence of pulmonary complications such as pneumonia or significant pleural effusions, and to identify preoperative and intraoperative factors associated with these respiratory conditions as well as clinically important outcome such as the duration of intensive care.

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2. METHODS

2.1. Patients and clinic data

This retrospective cohort study following Institutional Review Board approval (number 2021-02-007CC) reviewed the medical records of all pediatric liver transplant recipients (age ≤ 12 years) from July 2014 to July 2020 in Taipei Veterans General Hospital, Taiwan. For each identified patient, the following demographic data were collected: age, weight (percentile of weight, weight PR), height (percentile of height, height PR), sex, preoperative pediatric end-stage liver disease (PELD) score for patient under the age of 12 years, and the underlying disease process. The intraoperative details included graft type (living or cadaver), duration of surgery, and the volume of blood loss as well as blood products infused during surgery. The postoperative data were collected as follows: the PRISM III[12] within 12 hours of admission to the ICU, duration of invasive mechanical ventilation, PaO_2/FiO_2 ratio within 1 hour after transfer to the pediatric intensive care unit (PICU), length of stay (LOS) in the PICU, and mortality within 28 days after the operation. The following respiratory complications were identified: significant pleural effusion, which required drainage and pneumonia (culture proven) within 28 days after OLT.

2.2. Statistical evaluation

Statistical analysis was performed with Statistical Package for the Social Sciences SPSS, version 22.0 (SPSS, Inc., Chicago, IL). The clinical data were described as medians with range or interquartile range (IQR 25%–75%) as indicated for skewed continuous variables and as percentages for categorical data. The Fisher's exact test was applied to compare differences in proportions for categorical variables and the Mann–Whitney U test was used to compare skewed continuous variables between two groups. Multivariable analysis was performed using logistic regression with age as continuous variables to calculate the age-adjusted odds ratios for each condition. Multiple regression models with initial postoperative PaO_2/FiO_2 ratio after transfer to the PICU as the dependent variables was computed for age, whether the patient received massive blood transfusion (> 40 mL/kg) during surgery, and PELD score as predictor variables in the regression to verify the association between these variables. A p value of <0.05 was considered statistically significant.

Table 1

Demographic profile with preoperative, intraoperative and postoperative status of study 22 patients

Age (year) *	1.4 (0.4–5.1)
Body weight (kg)*	8.0 (5.0–17.1)
PR*	6.7 (0.03–45.1)
Body height (cm)*	71.4 (58.4–100.6)
PR*	0.6 (0.02–11.19)
Male/female (%)*	9 (40.9%)/13(59.1%)
Living donor/Cadaver (%)	19 (86.4%)/3 (13.6%)
PELD score*	16.5 (3.8–32.2)
Etiology (%)	
Biliary atresia	6 (27.3%)
Inborn error of metabolism	7 (31.8%)
Methylmalonic academia	2 (9.1%)
Maple syrup urine disease	2 (9.1%)
Urea cycle disorder	2 (9.1%)
Glycogen storage disease	1 (4.5%)
Acute liver failure	3 (13.6%)
Hemochromatosis	1 (4.5%)
Alagille syndrome	1 (4.5%)
Protein C deficiency	1 (4.5%)
Primary sclerosing cholangitis	1 (4.5%)
Hepatoblastoma	1 (4.5%)
Progressive family intrahepatic cholestasis	1 (4.5%)
Duration of operation (h) *	10.3 (8.8–12.2)
Intraoperative blood loss (mL/kg) *	7.5 (5.0–36.4)
Intraoperative blood transfusion (mL/kg) *	34.6 (13.5–59.6)
PRISM III *	11.5 (8.8–16.2)
Initial postoperative PaO_2/FiO_2 (mmHg) *	339 (216.9–515.0)
Invasive respiratory support time (d) *	1 (1–3.5)
Significant pleural effusion (required drainage)	8 (38.1%)
PICU stay (d) *	18 (11–33.5)
Mortality in 28 d	1 (4.5%)

*Median (interquartile range, IQR), PELD = Pediatric End-Stage Liver Disease; PICU = Pediatric Intensive Care Unit; PR = percentile for age group.

3. RESULTS

3.1. Characteristics of patients

A total of 22 patients who received OLTs from July 2014 to July 2020 were identified. The demographic and clinical features are summarized in Table 1. The median age at the time of transplant was 1.4-year-old (range: 25-day-old to 12-year-old), which included 10 (45.4%) infants with age below 1-year-old as shown in Fig. 1A. The median body weight was 8 kg (range: 3.5–26.6 Kg), and there are 7 (31.8%) patients with bodyweight less than 6 kg when receiving OLT as shown in Fig. 1B. Nineteen (86.4%) transplantations involved living donors, whereas the remaining involved cadaveric donors. Biliary atresia was the most frequent indication, accounting for 27.3% of recipients, and the median PELD score for all patients was 16.5 (range: 0–63). During surgery, the median blood loss was 7.5 (range: 2.3–300) milliliter per kilogram (mL/kg) and median blood transfusion was 34.6 (range: 0–368) mL/kg. For total transfused blood components, whole blood, packed red blood cells, fresh frozen plasma, and platelets accounted for 50%, 27.1%, 18.4%, and 4.5% respectively. The median duration of operation was 10.3 hours (range: 7.5–18.2 hours). After surgery, all patients were transferred to the PICU under intubated and ventilated status. In the PICU, the initial arterial gas analysis was performed within 1 hour, and the median initial postoperative PaO_2/FiO_2 ratio was 339.4 (range: 131.3–567.5) mmHg, in which acute lung injury defined as PaO_2/FiO_2 ratio < 300 was noted in eight patients (36.4%). The median PRISM III within 12 hours of admission to the PICU was 11.5 (range: 2–34). The median (IQR) duration of mechanical ventilation was 1 (1–3.5) day and 11 (50.0%) patients received successful extubations within 24 hours after surgery. One (4.5%) patient developed pneumonia with *Haemophilus influenzae* growth in the sputum culture at postoperative day (POD) 2 and was successfully extubated at POD 7 after adequate antibiotics treatment. Eight (36.4%) patients developed significant pleural effusion with the requirement of drainage for symptoms relief, and the median (IQR) duration of drainage was 12 (6.5–33.5) days. After the median (IQR) stay of 18 (11–33.5) days in the PICU, pediatric OLT recipients were transferred to the protective isolated ward. Till August 2020, 2 patients died. One died within 12 hours after surgery with suspicion of acute intra-abdominal bleeding complicated with shock, and the other died from uncontrolled hemophagocytic lymphohistiocytosis induced multi-organ failure. Thus, the overall patient survival rate was 91%, and the mortality rate in 28 days was 4.5%.

Compared to other patients, infant recipients with age below 1 year old had higher PELD score (p = 0.001), more intraoperative blood transfusion (p = 0.014), lower initial postoperative PaO_2/FiO_2 ratio (p = 0.001), and longer length of PICU stay (p = 0.008). However, there were no significant difference in duration of operation (p = 0.123), intraoperative blood loss

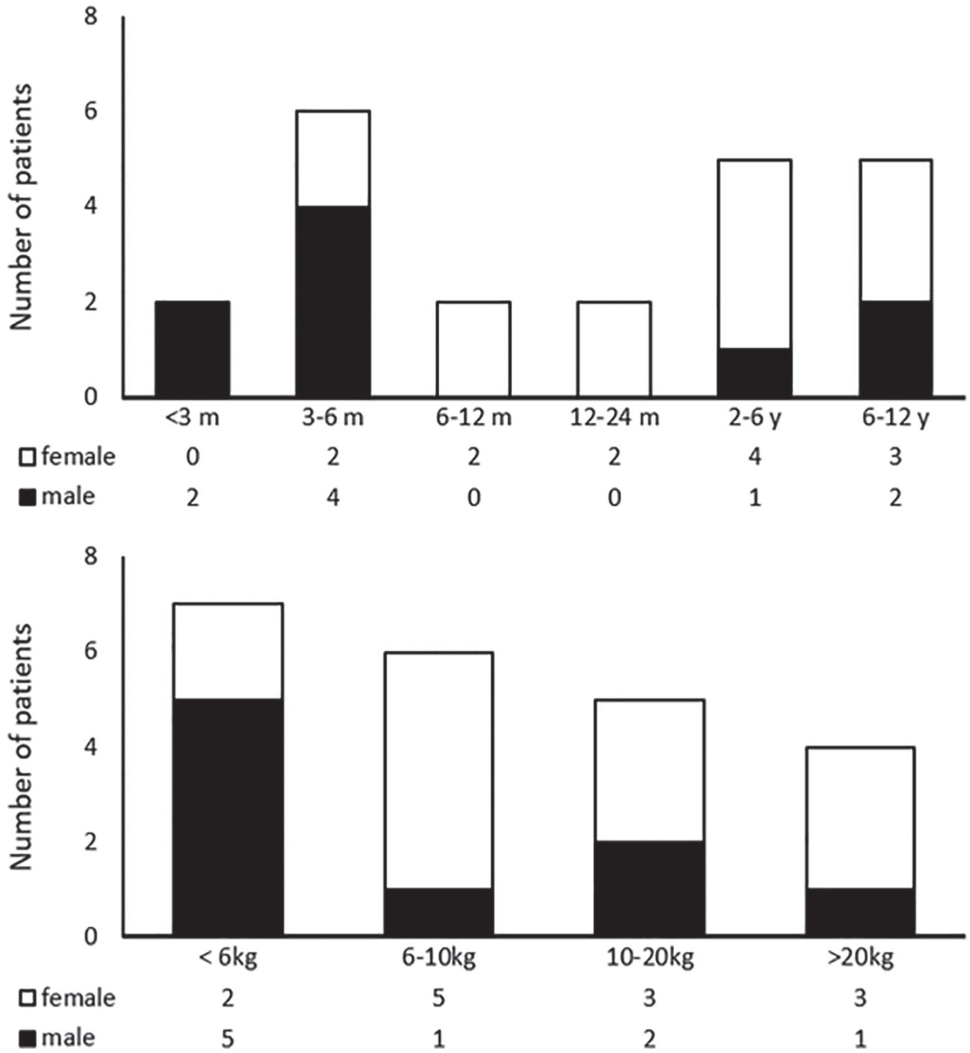

Fig. 1 Age (A) and body weight (B) distributions of pediatric patients who underwent orthotopic liver transplantation (OLT). Ten infant patients (45.4%) with age below 1 year and 7 patients (31.8%) with body weight below 6 kg underwent OLT in this cohort respectively.

(p = 1.000), proportions of patients extubated over 24 hours after surgery (p = 0.086), nor significant pleural effusion (p = 0.387) between infant patients and older children (Table 2).

3.2. Postoperative respiratory conditions of OLT

After surgery, 8 (36.4%) patients experienced acute lung injury, defined as an initial PaO_2/FiO_2 ratio < 300 on arterial blood gas analysis within 1 hour after admission to the PICU.[13] Similarly, patients with initial postoperative PaO_2/FiO_2 ratio < 300 were with younger age (p = 0.001), higher PELD score (p = 0.001), more intraoperative blood transfusion (p = 0.001), higher proportions of extubated over 24 hours after surgery (p = 0.008), and longer length of PICU stay (p = 0.001) than those of their counterparts (Table 2).

Eleven (50.0%) patients who received extubation over 24 hours after surgery were younger (p = 0.01) and had a higher PELD score (p = 0.029), more intraoperative blood transfusion (p = 0.045), lower initial postoperative PaO_2/FiO_2 ratio (p = 0.002), and longer length of PICU stay (p = 0.008) than those able to be extubated within 24 hours after surgery (Table 3).

Eight (36.4%) patients who developed significant pleural effusion with requirement of drainage for symptoms relief had longer duration of operation (p = 0.02), more intraoperative blood transfusion (p = 0.025), lower initial postoperative PaO_2/FiO_2 ratio (p = 0.025), and longer length of PICU stay (p = 0.02) than those without significant pleural effusions (Table 3).

Twelve (54.5%) patients who stayed in the PICU for over 2 weeks (14 days) were younger (p = 0.015) and had a higher PELD score (p = 0.028), more intraoperative blood transfusion (p = 0.018), and lower initial postoperative PaO_2/FiO_2 ratio (p = 0.03) than those able to transfer to the protective isolated ward within 14 days after surgery (Table 3).

To sum up, pediatric OLT patients with poor postoperative conditions, defined as a low initial postoperative PaO_2/FiO_2 ratio (<300 mmHg), extubation over 24 hours after surgery, and significant pleural effusion requiring drainage, had a longer LOS in the PICU than those without these poor postoperative conditions.

3.3. Associated factors analysis

Among all clinical variables, patients who received more intraoperative blood transfusion tended to have poor postoperative respiratory conditions including extubation over 24 hours after surgery as well as significant pleural effusion, and LOS in the PICU over 14 days. Furthermore, both infant recipients and patients with initial postoperative PaO_2/FiO_2 < 300 mmHg also

Table 2

Comparison of clinic conditions of infant recipients versus children recipients and patients with low initial postoperative PaO_2/FiO_2 ratio (<300 mmHg) versus adequate PaO_2/FiO_2 (≥300 mmHg)

	Age < 1-year-old		Initial postoperative PaO_2/FiO_2 < 300 mmHg	
	Yes (N = 10)	No (N = 12)	Yes (N = 8)	No (N = 14)
Age (y)	0.4* (0.2 to 0.5)	4.6*(2.3 to 8.3)	0.4* (0.12 to 0.45)	4.2* (1.6 to 7.2)
Body weight PR	6.1 (0.0 to 43.3)	13.6 (2.0 to 48.2)	3.3 (0.0 to 44.6)	7.9 (2.6 to 46.0)
Male sex	6 (60%)	3 (25%)	5 (62.5%)	4 (28.6%)
PELD score	33.5* (15.5 to 37.5)	6.0* (−1.7 to 16.8)	36.0* (21.3 to 40.5)	7.5* (−1.3 to 17.8)
PRISM score	13.5 (10.8 to 22.8)	11 (8.0 to 15.2)	14.5 (11.5 to 24.3)	11.0 (8.0 to 13.8)
Preoperative respiratory support	5* (50%)	0* (0%)	5* (62.5%)	0* (0%)
Operation time (min)	542 (493 to 636)	682 (564 to 745)	560 (530 to 709)	675 (502 to 735)
Intraoperative blood loss (mL/kg)	7.4 (5.0 to 25.9)	10.4 (4.8 to 41.1)	9.6 (5.3 to 42.8)	7.4 (4.9 to 36.4)
Intraoperative blood transfusion (mL/kg)	51.2* (36.2 to 105.0)	16.5* (9.5 to 26.1)	56.7* (47.1 to 150.0)	16.5* (8.8 to 28.6)
PaO_2/FiO_2 ratio after surgery (mmHg)	209* (172 to 307)	510* (364 to 525)	190* (150 to 251)	509* (352 to 531)
Extubated in 24 h after surgery	3 (30%)	8 (66.7%)	1* (12.5%)	10* (76.9%)
Pleural effusion required drainage	5 (50%)	3 (25%)	5 (62.5%)	3 (23.1%)
PICU stay (d)	26* (19 to 63)	14* (9 to 18)	36.5* (20.5 to 101.3)	15.0* (9.0 to 20.5)

The data are presented as medians and interquartile ranges. PR = percentile for age group.
* $p < 0.05$.

tended to receive more intraoperative blood transfusion. Massive blood transfusion in children, defined as blood transfusion over 40 mL/kg in 12 hours leads to many complications such as transfusion-related acute lung injury.[13,14] Univariate analysis showed that intraoperative massive blood transfusion (>40 mL/kg) was significantly associated with extubation over 24 hours after surgery, significant pleural effusion, acute lung injury defined as a PaO_2/FiO_2 ratio below 300 mmHg, and LOS in the PICU over 14 days with odds ratio of 10.5 (p = 0.024), 38.5 (p = 0.002), 42.0 (p = 0.001), and 16.0 (p = 0.024), respectively (Fig. 2). Due to the significant association between intraoperative blood transfusion and age, logistic regression was applied to calculate age-adjusted odds ratio, which still showed significant associations between intraoperative massive blood transfusion and significant pleural effusion, postoperative acute lung injury (PaO_2/FiO_2 < 300), as well as LOS in the PICU over 14 days with adjusted odds ratios of 41.4 (p = 0.01), 24.3 (p = 0.035), and 12.8 (p = 0.033), respectively (Fig. 2). To access the effect of age, disease severity defined by the PELD score and massive intraoperative blood transfusion on initial postoperative lung function (PaO_2/FiO_2) in pediatric OLT patients, a multiple regression analysis was performed and demonstrated that initial postoperative lung function (PaO_2/FiO_2) was independently significantly positively correlated to age (p = 0.014) and negatively correlated to the PELD score (p = 0.003) as well as the massive intraoperative blood transfusion (p = 0.004) (Table 4).

4. DISCUSSION

This retrospective study described associated factors as well as clinically important outcomes of respiratory conditions after pediatric OLT in a single center. The proportions of extubation over 24 hours after surgery, incidence of significant pleural effusions, and initial postoperative PaO_2/FiO_2 ratio were investigated, and poor postoperative respiratory conditions were defined as extubation over 24 hours after surgery, the occurrence of significant pleural effusions, and low initial postoperative PaO_2/FiO_2 ratio (<300). All these poor postoperative respiratory conditions were linked to the longer length of PICU stay. Many preoperative and intraoperative factors were identified to be associated with these poor respiratory conditions, including younger age, higher PELD score, longer operation time, and more intraoperative blood transfusion. Among these factors, more intraoperative blood transfusion during OLT was significantly linked to all poor postoperative respiratory conditions as well as prolonged LOS in the PICU, which was also demonstrated in other reports.[8,9] Our further analysis

Table 3

Comparison of clinic conditions in patients with different respiratory conditions and length of stay in PICU

	Extubated in 24 h after surgery		Pleural effusion required drainage		Length of stay in PICU > 14 d	
	Yes (N = 11)	No (N = 11)	Yes (N = 8)	No (N = 14)	Yes (N = 12)	No (N = 10)
Age (y)	4.0* (0.8 to 6.2)	0.4*(0.2 to 1.3)	0.4 (0.3 to 1.6)	2.7 (0.6 to 5.5)	0.4* (0.3 to 1.5)	4.0* (1.7 to 5.5)
Body weight PR	6.8 (2.9 to 36.8)	24.6 (0.0 to 47.3)	9.1 (0.0 to 45.3)	6.8 (3.4 to 45.9)	6.1 (0.0 to 44.7)	9.1 (3.4 to 47.1)
Male sex	3 (27.3%)	5 (45.5%)	4 (50.0%)	4 (28.6%)	6 (50.0%)	2 (20.0%)
PELD score	8.0* (5.0 to 17.0)	33.5* (13.2 to 37.5)	19.0 (8.2 to 40.5)	16.0 (2.5 to 27.0)	25.5* (9.0 to 36.0)	7.0* (−1.0 to 18.5)
PRISM score	11.0 (8.0 to 15.0)	12.0 (9.8 to 22.8)	13.0 (11.0 to 14.8)	11.0 (8.0 to 16.5)	13.0 (9.2 to 20.2)	11.0 (8.0 to 14.0)
Preoperative respiratory support	0* (0%)	5* (45.5%)	2 (25.0%)	3 (21.4%)	5* (41.7%)	0* (0%)
Operation time (min)	565 (480 to 685)	640 (530 to 746)	712* (574 to 851)	540* (488 to 678)	582 (530 to 741)	635 (495 to 702)
Intraoperative blood loss (mL/kg)	7.4 (5.5 to 16.7)	9.6 (4.5 to 45.4)	27.6 (5.3 to 83.3)	7.4 (4.7 to 15.0)	7.1 (4.6 to 42.8)	7.5 (5.6 to 25.3)
Intraoperative blood transfusion (mL/kg)	18.4* (9.2 to 31.4)	51.2* (31.0 to 105.0)	56.6* (47.1 to 72.6)	18.4* (8.4 to 34.6)	51.2* (33.0 to 80.9)	15.4* (8.4 to 24.5)
PaO_2/FiO_2 ratio after surgery (mmHg)	510* (364 to 525)	209* (172 to 307)	266* (189 to 307)	510* (270 to 538)	242* (184 to 398)	512* (339 to 538)
PICU stay (d)	11* (7 to 21)	21* (18 to 63)	26* (20 to 42)	14* (8 to 20)	26* (20 to 43)	11* (7 to 14)

The data are presented as medians and interquartile ranges.
*$p < 0.05$.

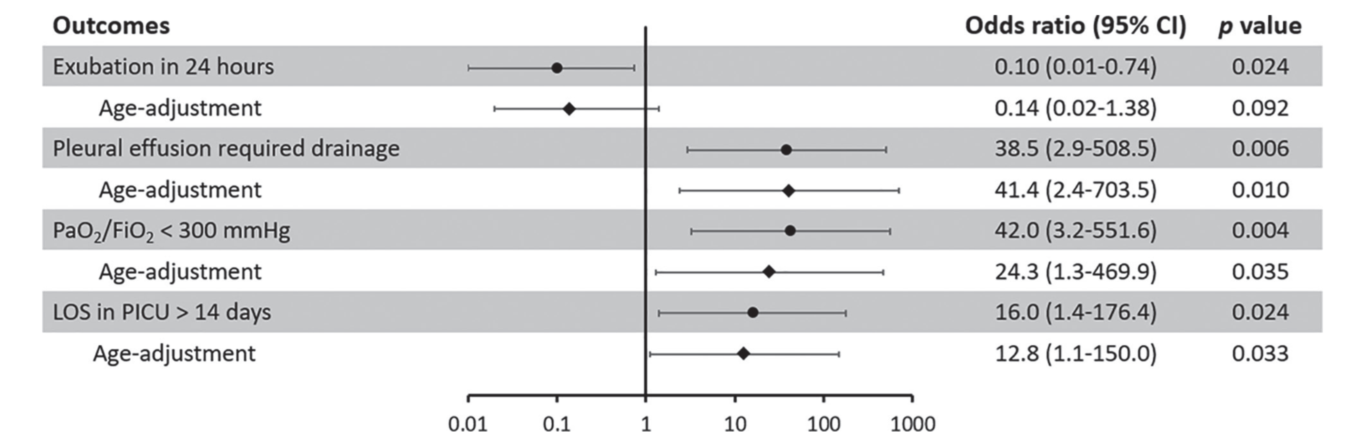

Fig. 2 Forest plot of the impact of massive intraoperative blood transfusion (> 40ml/kg) on clinical outcomes including postoperative respiratory conditions and length of stay (LOS) in the PICU. The data was presented as odds ratio with 95% confidence interval, and age-adjusted odds ratio was calculated via logistic regression with age as continuous variables. The calculated *p* value was considered to be statistically significant when the *p* value less than 0.05.

demonstrated that the massive intraoperative blood transfusion (>40 mL/kg) was highly associated with significant pleural effusions and postoperative acute lung injury defined as PaO_2/FiO_2 < 300 mmHg after age adjustment. The requirement of massive blood transfusion implies high intraoperative blood loss and relative cardiovascular instability during surgery. Furthermore, massive blood transfusion may result in poor lung function via transfusion-related acute lung injury or transfusion-associated circulatory overload.[14–16] The multiple regression analysis also demonstrated the significant effect of age, disease severity (PELD score), and massive blood transfusion on initial postoperative lung function assessed via initial postoperative PaO_2/FiO_2. Unlike other intuitive factors such as age or the PELD score, which reflected as either part of the pathological process or severity of the underlying disease, some modifications may be applied to massive intraoperative blood transfusion to improve postoperative respiratory conditions, including adequate ratio of blood products or use of fresh whole blood.[14] Further studies are required to verify the effect of this modification of massive intraoperative blood transfusion on postoperative respiratory outcomes of pediatric OLT.

Compared with previous cohorts,[17] our cohort had three different demographical factors. First, a high proportion (31.8%) of inborn errors of metabolism was diagnosed in recipients, even though the single leading indication for OLT was biliary atresia (27.3%). Second, the majority (86.4%) of liver donors were living donors rather than cadaveric donors, which became more common recently. Finally, 10 (45.4%) infant recipients underwent OLT, of whom the youngest age was 25-day-old and the bodyweight of 7 infant patients (70%) was less than 6 kg. For these infant patients, the duration of surgery and overall survival rate were similar to that of the elder children, indicating the experienced surgical technique.

Prolonged mechanical ventilation after OLT was linked to longer length of ICU stay and higher posttransplant mortality.[8] Therefore, many studies suggested early or even immediate extubation in the operating room.[17] In our cohort, all patients were transferred to the PICU under intubation with ventilation, and approximately half of the patients received extubation within 24 hours (most within 12 hours) after surgery at the PICU. Except for the anesthetic policy, younger age is a risk factor for prolonged postoperative mechanical ventilation (PPMV), and 6 (27.3%) out of 22 patients in our study had PPMV (≥ 4 days), which is similar to the previously reported rate (25%).[8] Pleural effusion, especially right side, was a common pulmonary complication after pediatric OLT and may result from local reactions in the surgical side. Compared to previous studies, a higher proportion (36.4%) of pleural effusions required drainage, but the concurrent allograft rejection was not identified in our cohort.[3–6] The median (18 days) LOS in the PICU was longer than those (around 7 days) shown in other study reports. Younger age and higher proportion of low body weight in our patients were the possible causes. In addition, public insurance was associated with a longer LOS in the hospital in pediatric OLT patients,[18] and people in Taiwan were included in an affordable and accessible national public health insurance, which may be another possible explanation for our longer length of PICU stay.

In conclusion, pediatric patients after OLT with poor postoperative respiratory conditions including postoperative acute lung injury (initial postoperative PaO_2/FiO_2 ratio <300), extubation over 24 hours after surgery, or significant pleural effusion tended to have prolonged LOS in PICU. Among clinic factors, the requirement of massive intraoperative blood transfusions increased risks of poor postoperative respiratory conditions such as postoperative acute lung injury and significant pleural effusions required drainage, and prolonged LOS in PICU after age adjustment. Furthermore, the requirement of massive intraoperative blood transfusions is the independent factors along with age and PELD score for initial postoperative PaO_2/FiO_2 ratio as initial lung function index after OLT.

Table 4

Multiple regression analysis assessing the relative effect of predictive variables for PaO_2/FiO_2 after surgery

	PaO_2/FiO_2 after surgery (mmHg)		
	B	Beta	*p*
Age (y)	13.9 (3.1 to 24.5)	0.32	0.014
PELD score	−3.7 (−6.0 to −1.5)	−0.43	0.003
Intraoperative blood transfusion > 40 mL/kg	−116.4 (−189.9 to −42.9)	−0.38	0.004

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