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ORIGINAL ARTICLE

Postoperative fluid balance and outcomes in pediatric living-donor liver transplant recipients: a retrospective cohort study

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Abstract

Purpose This study aimed to investigate the relationship between postoperative fluid balance (FB) and clinical outcomes in pediatric living-donor liver transplant (LDLT) recipients.

Methods This retrospective study was conducted at a tertiary care center. Patients aged ≤ 18 years who underwent LDLT between January 2010 and September 2023 were included. Postoperative FB was calculated as [(total fluid intake—total fluid output) / body weight] × 100 for 48 h. Patients were categorized into four groups: < 5%, 5–10%, 10–15%, and ≥ 15% FB. The primary outcome was ventilator-free days (VFD) within 30 days post-transplantation. Secondary outcomes included acute kidney injury (AKI), reintubation, hepatic arterial thrombosis, acute rejection, primary graft dysfunction, intensive care unit (ICU) length of stay (LOS), and mortality.

Results The study included 200 patients with a median weight of 9.0 (interquartile range [IQR]: 6.9–19.3) kg. Median VFD did not significantly differ across the FB groups: < 5% FB, 29.3 (IQR, 28.3–29.4) days; 5–10% FB, 29.3 (IQR, 28.3–29.4) days; 10–15% FB, 29.3 (IQR, 28.3–29.4) days; and ≥ 15% FB, 27.4 (IQR, 23.3–29.4) days ($p = 0.27$). However, multivariable analysis showed ≥ 15% FB was associated with 4.59 days shorter VFD ($p = 0.004$) and higher AKI incidence (odds ratio: 6.60, $p = 0.012$). Thrombosis occurred in 7 patients (3.5%) with no significant differences among groups ($p = 0.61$). Other secondary outcomes showed no significant differences.

Conclusion Excessive postoperative FB (≥ 15%) in pediatric LDLT recipients was significantly associated with reduced VFD and increased AKI incidence, whereas other adverse outcomes were not significantly affected.

Keywords Pediatric intensive care unit · Liver transplantation · Living donors · Fluid therapy · Postoperative management

Introduction

Liver transplantation (LT) is recognized as the definitive treatment for patients with end-stage liver disease. Over the past few decades, the number of pediatric LTs has increased [1], and the difficulty in finding appropriately sized brain-dead donor organs for pediatric patients has led to a severe organ shortage [2]. Living donor liver transplantation (LDLT) has predominantly been practiced in pediatric patients in Japan due to a shortage of brain-dead donors. Recently, LDLT has gained significant attention for its potential to reduce waitlist morality and optimize outcomes for pediatric LT candidates [2, 3].

Perioperative fluid management in LT is vital for graft recovery and complication prevention. Post-LT hypovolemia due to bleeding, inadequate fluid resuscitation, and increased vascular permeability results in decreased cardiac output and subsequent hypoperfusion, thereby impairing the recovery of the liver graft [4]. Reduced hepatic artery blood flow following vascular reconstruction is a significant predictor of early hepatic artery embolism post-LT [5]. However, hypervolemia caused by excessive fluid resuscitation and fluid

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retention leads to increased venous pressure, causing edema in organs and the graft [6].

Recently, fluid balance (FB) has become a crucial consideration in intensive care. Accumulating evidence supports the association of excessive FB with prolonged mechanical ventilation, renal impairment, and intensive care unit (ICU) length of stay (LOS) in adult LT populations [7–12]. Therefore, restrictive fluid management could be a recommended strategy for adult LT patients [13]. However, these considerations and evidence might not be applicable to pediatric LT patients. Since pediatric LT patients are particularly at risk of postoperative thrombosis due to their hypercoagulable state and smaller vessel sizes [14, 15], maintaining sufficient intravascular volume—potentially resulting in positive FB—has traditionally been a strategy to prevent thrombosis in these patients.

We hypothesized that excessive FB is associated with an increased duration of mechanical ventilation in pediatric LT patients. Therefore, this study aimed to investigate postoperative FB in pediatric LDLT patients and evaluate the association of postoperative FB with patients' outcomes, such as mechanical ventilation duration, acute kidney injury (AKI) incidence, and thrombotic complications.

Methods

Ethical approval

This study was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (approval number: # R4282) on December 7, 2023. Informed consent was waived due to the use of anonymized patient data, which followed the "Ethical Guidelines for Medical and Health Research Involving Human Subjects" issued by the Japanese Ministry of Health, Labor, and Welfare. All procedures performed in this study adhered to the tenets of the 1975 Helsinki Declaration.

Study design and setting

This retrospective study was conducted at a tertiary teaching hospital (Kyoto university hospital, Japan). Eligible participants were patients aged ≤ 18 years who underwent LDLT and were admitted to the ICU directly from the operation theater between January 2010 and September 2023. The following patients were excluded: patients with missing data on FB, those who were under preoperative mechanical ventilation, those who underwent multiple LT and had two or more ICU admissions, and those who underwent two or more surgical procedures during the same operative session and/or multiorgan transplantations.

Management

Intraoperative fluid management, as well as the use of vasoactive and inotropic agents, was determined by the anesthesiologist in charge based on the patient's condition, blood loss, and hemodynamic status. All patients were admitted to the ICU under sedation and mechanical ventilation postoperatively. Extubation was performed after a 30–120-min evaluation period using low-level ventilator support (positive end-expiratory pressure: 5 cm H_2O, fraction of inspired oxygen: 0.40, and pressure support: 6–8 cm H_2O in continuous positive airway pressure with pressure support ventilation). Reintubation was performed for severe hypoxia/hypercapnia and/or excessive respiratory effort that was not alleviated by non-invasive respiratory support or consciousness impairment affecting airway safety. Maintenance fluid infusion, calculated using the Holliday–Segar method [16], was administered along with corrective fluid for ascites and pleural effusion in the ICU. The volume of pleural and abdominal effusions was calculated over the last 4 h, and the percentage for correction of the effusions was decided by discussion between the surgeon and the pediatric intensive care physician. Subsequent adjustments to fluid volume and diuretic administration were made at the discretion of the attending physician based on daily overall assessments. Red blood cell concentrates and albumin were used to maintain the hemoglobin level above 7.0 g/dL and serum albumin level at 3.0 g/dL, respectively. Fresh frozen plasma was administered if the prothrombin time-international normalized ratio was ≥ 2 or fibrinogen levels were < 100 mg/dL. Antithrombin concentrate was administered to maintain levels above 80% in the absence of bleeding. Continuous renal replacement therapy was indicated for oliguria or hyperkalemia despite aggressive diuretic therapy, inotropic support optimization, and fluid status adjustment.

Echo-Doppler examinations were conducted two times daily in the initial post-transplant week, once daily in the second week, and subsequently as needed from the third week onwards to evaluate hepatic vascular thrombosis. Preoperative desensitization was performed for ABO-incompatible transplants as needed. Immunosuppressive therapy comprised three (tacrolimus, steroids, and mycophenolate mofetil) and two (tacrolimus and steroids) drugs for ABO-incompatible and ABO-compatible transplants, respectively. The target blood concentration of tacrolimus was 14 ng/mL during intravenous administration and a trough level of 12 ng/mL after switching to oral administration. Methylprednisolone was planned to be administered at 1 mg/kg for the first 3 days, 0.5 mg/kg on days 4–6, and 0.3 mg/kg on day 7, transitioning to oral prednisolone at 0.3 mg/kg on day 8.

Study variables and data sources

Data on study variables were obtained from the hospital and ICU electronic databases, whereas additional information was collected from electronic patient medical records. Preoperative data included patient demographics, diagnosis, onset of liver failure, presence of encephalopathy, baseline serum creatinine level, use of extracorporeal blood purification therapies (renal replacement therapy or plasma exchange), Pediatric end-stage liver disease (PELD) scores for patients aged ≤ 11 years, Model for end-stage liver disease (MELD) scores for those aged ≥ 12 years, and admission status (either admitted directly from home for transplantation or already hospitalized for other conditions). Encephalopathy was defined as the presence of overt hepatic encephalopathy symptoms prior to surgery, based on the criteria proposed by the international society for hepatic encephalopathy and nitrogen metabolism (ISHEN) [17]. The intraoperative data obtained included duration of surgery; volume of crystalloids, colloids, and blood products; urine output; and blood loss. Data on vasoactive and inotropic agents (dopamine, dobutamine, milrinone, norepinephrine, epinephrine, and vasopressin) used during surgery were collected, and the highest intraoperative vasoactive-inotropic score (VIS) was calculated [18]. The pediatric index of mortality 3 (PIM3) [19] at ICU admission was calculated. Fluid intake included oral and intravenous fluids, as well as transfusions administered within 48 h post-ICU admission. Fluid output included urine output, stool, and drain output during the same period. Postoperative data included peak serum creatinine level for the first 48 h and mechanical ventilation duration for the first postoperative 30 days.

The "exposure" in this study was FB within 48 h post-ICU admission calculated using the following formula: [(total fluid intake (L)−total fluid output (L))/pre-transplant weight (kg)] × 100. Additionally, the primary outcome was ventilator-free days (VFD) within 30 days post-transplantation, while the secondary outcomes included AKI, reintubation within 48 h post-extubation, hepatic arterial thrombosis, primary graft dysfunction, ICU LOS, and mortality. Hepatic arterial thrombosis was defined as thrombosis in the hepatic artery requiring intervention within 30 days post-transplantation. Acute rejection was diagnosed by biopsy or clinically suspected, requiring steroid pulse therapy within 30 days post-transplantation. AKI was diagnosed and classified within 48 h postoperatively using the creatinine criteria defined by the kidney disease improving global outcomes [20]. Primary graft dysfunction was defined as graft failure resulting in death or requiring re-transplantation within the first 7 postoperative days [21].

Statistical analysis

Data are presented as frequencies and proportions or medians (interquartile range [IQR]: 25% quartile, 75% quartile) as appropriate. According to previous studies on pediatric FB [22, 23], and with an emphasis on clinical interpretability, patients were categorized into the following four groups based on FB within the first 48 h postoperatively: < 5%, 5–10%, 10–15%, and ≥ 15% FB groups. For groupwise comparisons of continuous variables, the Wilcoxon rank-sum (two groups) or Kruskal–Wallis (more than two groups) test was used. Fisher's exact or the chi-square test was used for categorical variables as appropriate. Survival curves were generated and compared using the Kaplan–Meier method and Log-rank test, respectively.

Multivariable linear or regression analysis was performed to examine the associations of FB with outcomes as appropriate. Cox proportional hazards model was used to estimate the hazard ratio (HR) and 95% confidence interval (CI). The following variables that could affect both FB and patients' clinical outcomes were included in the models as confounders: weight, onset of liver failure, admission status, PELD/MELD score, graft-to-recipient weight ratio (GRWR), presence of preoperative encephalopathy, preoperative serum creatinine level, preoperative extracorporeal blood purification therapies, highest intraoperative VIS, intraoperative FB, and PIM3. Since this study included a wide range of aged patients and the association between FB and VFD in infants might differ from that in older patients, subgroup analyses were performed for patients aged < 1 year. Statistical significance was set at $p < 0.05$, and all analyses were performed using R software (version 4.3.2, R foundation for statistical computing, Vienna, Austria).

Results

Participants

Overall, 227 pediatric patients were eligible for this study. After excluding 27 patients based on the exclusion criteria, 200 were included in the final analysis (Fig. 1). Table 1 summarizes the patient demographics and clinical characteristics, along with FB strata comparisons. Significant differences were observed in age, weight, GRWR, PELD/MELD score, preoperative serum creatinine level, intraoperative FB, and PIM3 across the FB groups.

Ventilator-free days and reintubation

Table 2 and Fig. 2 show the outcomes with a comparison among patients categorized by FB. No significant differences in VFD were observed across the FB groups ($p = 0.27$).

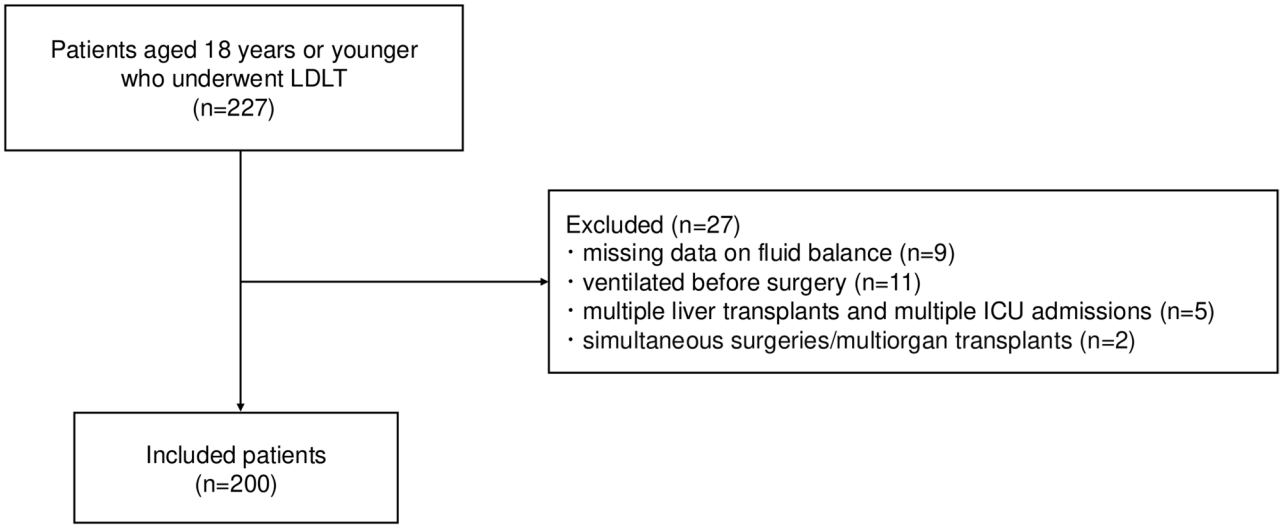

Fig. 1 Flowchart of patient selection *ICU* Intensive care unit, *LDLT* Living-donor liver transplantation

Table 3 presents the results of multivariable linear regression analysis with VFD as the outcome. Patients with FB ≥ 15% had 4.59 days shorter VFD than those with FB < 5% as a reference group ($p = 0.004$). Meanwhile, no significant difference in VFD was observed for patients with FB 5–10% and 10–15% compared with the reference group ($p = 0.21$and $p = 0.32$, respectively). Details on the subgroup analysis for patients aged < 1 year are provided in Tables 4 and 5. In this subgroup, a multivariable linear regression analysis demonstrated a non-significant trend towards shorter VFD in patients with FB ≥ 15% than in the reference group with FB < 5% ($p = 0.15$).

Six (3.0%) patients were reintubated within 48 h post-extubation. No significant differences in reintubation rate were found across the FB groups (Table 2). Among the six cases, one patient was reintubated due to agitation and hypoxemia associated with elevated ammonia levels. The remaining five required reintubation for worsening respiratory status that could not be alleviated by non-invasive respiratory support. Chest radiographs showed possible pulmonary edema in three of these patients: one in the FB < 5% group, one in the FB 10–15% group, and one in the FB ≥ 15% group. Multivariable logistic regression analysis showed no significant difference in reintubation rates among patients with FB 5–10%, 10–15%, or ≥ 15% compared to the reference group with FB < 5% (Table 6).

Rejection and thrombotic complications

Acute rejection occurred in 58.0% of all patients in this study. However, no significant difference was found in the incidence of acute rejection across the FB groups ($p = 0.20$). Hepatic arterial thrombosis occurred in seven (3.5%) patients, with no significant differences across the FB groups ($p = 0.61$). Multivariable logistic regression analyses demonstrated no significant differences in the odds of acute rejection and hepatic arterial thrombosis (Table 6).

Other clinical outcomes

In this cohort, 35 (17.5%) patients had postoperative AKI. A significant difference was found in AKI incidence across the FB groups (Table 2, $p = 0.004$). Pairwise comparisons showed a significantly higher AKI incidence in patients with FB ≥ 15% than in those with FB < 5% ($p = 0.009$), 5–10% ($p < 0.001$), and 10–15% ($p = 0.02$). Likewise, multivariable regression analysis showed a significantly higher AKI incidence in patients with FB ≥ 15% than in the reference group with FB < 5% (Table 6; OR: 6.60, 95% CI 1.50–29.0; $p = 0.012$). Primary graft dysfunction did not occur in any patients across all FB groups.

The median ICU LOS was 4.6 (IQR: 3.6–4.6) days. No significant difference was found in ICU LOS across the FB groups ($p = 0.11$). Multivariable regression analyses showed no significant differences in ICU LOS across the FB groups.

Figure 3 presents the Kaplan–Meier survival curves of the patients categorized by FB. No significant differences were observed in the survival curves across the FB groups ($p = 0.82$). Cox proportional hazards analysis, after adjusting for potential confounders, indicated a higher risk of adverse events in the FB ≥ 15% group than in the FB < 5% group, without statistical significance (Table 7; HR: 2.77, 95% CI 0.20–38.19; $p = 0.45$).

Table 1 Patient demographics and clinical characteristics

Variables	Total ($n=200$)	<5% FB ($n=67$)	5–10% FB ($n=66$)	10–15% FB ($n=45$)	≥15% FB ($n=22$)	*p*
Age, year, median (IQR)	1.3 (0.7–6.3)	5.21 (1.5–8.9)	1.77 (0.8–8.1)	0.77 (0.6–1.3)	0.65 (0.6–0.9)	<0.001
Male, *n* (%)	81 (40.5)	31 (46.3)	22 (33.8)	19 (42.2)	9 (40.9)	0.62
Weight, kg, median (IQR)	9.0 (6.9–19.3)	16.60 (10.0–25.0)	9.68 (7.4–22.7)	7.20 (6.2–8.5)	6.09 (5.8–7.5)	<0.001
Indication for LT, *n* (%)						0.04
Cholestatic	156 (78.0)	45 (67.2)	58 (87.9)	36 (80.0)	17 (77.3)	
Hepatocellular	2 (1.0)	0 (0.0)	0 (0.0)	1 (2.2)	1 (4.5)	
Vascular	4 (2.0)	2 (3.0)	0 (0.0)	2 (4.4)	0 (0.0)	
Neoplastic	16 (8.0)	7 (10.4)	5 (7.6)	4 (8.9)	0 (0.0)	
Metabolic	13 (6.5)	9 (13.4)	2 (3.0)	1 (2.2)	1 (4.5)	
Other	9 (4.5)	4 (6.0)	1 (1.5)	1 (2.2)	3 (13.6)	
Onset of liver failure, *n* (%)						0.99
Acute	5 (2.5)	2 (3.0)	1 (1.5)	1 (2.2)	1 (4.5)	
Acute-on-chronic	5 (2.5)	2 (3.0)	2 (3.0)	1 (2.2)	0 (0.0)	
Chronic	190 (95)	63 (94.0)	63 (95.5)	43 (95.6)	21 (95.5)	
Pre-hospitalized patients, *n* (%)	48 (24.0)	12 (17.9)	16 (24.2)	13 (28.9)	7 (31.8)	0.44
Blood type incompatibility, *n* (%)	30 (15.0)	10 (14.7)	11 (16.7)	5 (11.1)	4 (18.2)	0.83
GRWR, %, median (IQR)	2.6 (1.6–3.5)	1.9 (1.3–3.0)	2.4 (1.3–3.3)	3.3 (2.5–3.9)	3.5 (3.2–3.8)	<0.001
PELD/MELD score, median (IQR)	9.4 (6.0–16.7)	6.00 (6.0–12.4)	8.5 (6.0–15.7)	12.5 (6.0–19.7)	17.5 (11.0–21.3)	<0.001
Pre-encephalopathy, *n* (%)	7 (3.5)	1 (1.5)	3 (4.5)	1 (2.2)	2 (9.1)	0.27
Pre-Cre, mg/dL, median (IQR)	0.2 (0.2–0.3)	0.3 (0.2–0.4)	0.2 (0.2–0.3)	0.2 (0.1–0.2)	0.2 (0.1–0.2)	<0.001
Pre-blood purification therapies, *n* (%)	10 (5.0)	3 (4.5)	4 (6.1)	1 (2.2)	2 (9.1)	0.58
Operation time, min, median (IQR)	687 (611–804)	709 (623–830)	696 (613–822)	669 (606–728)	678 (597–742)	0.45
Intraoperative FB, mL/kg, median (IQR)	12.3 (8.0–18.4)	15.4 (10.2–19.9)	11.0 (8.1–19.0)	9.4 (4.4–15.9)	10.9 (3.6–16.1)	0.005
Intraoperative VIS, median (IQR)	0.0 (0.0–2.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–4.0)	0.0 (0.0–0.9)	0.14
PIM3, predicted death rate (%), median (IQR)	0.7 (0.6–0.8)	0.6 (0.6–0.8)	0.7 (0.6–0.8)	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.007

FB fluid balance, *IQR* interquartile range, *LT* Liver transplantation, *GRWR* graft-to-recipient weight ratio, *PELD* pediatric end-stage liver disease score, *MELD* model for end-stage disease score, Pre-encephalopathy, hepatic encephalopathy prior to surgery, *Pre-Cre* serum creatinine level before surgery, *Pre-blood purification therapies* preoperative use of renal replacement therapy or plasma exchange, *PIM3* Pediatric Index of Mortality 3, *VIS* vasoactive-inotropic score

Discussion

Our study demonstrated that patients with more positive postoperative FB within the first 48 h post-pediatric LDLT tended to have shorter VFD and that FB ≥ 15% was significantly associated with shorter VFD in the multivariate analysis. While significant associations were found between FB and postoperative AKI, our analyses did not show any significant association of FB with thrombosis, reintubation, acute rejection, or ICU LOS.

Growing evidence supports the association between excessive FB and prolonged mechanical ventilation and/or pulmonary complications in adult LT populations [7–9, 12, 24, 25]. However, to the best of our knowledge, only one study has investigated FB post-pediatric LT. Winters et al. retrospectively reviewed postoperative FB in 129 children who underwent LT, more than 70% of whom were deceased donors. They found a significant difference in VFD at 28 days among patients categorized based on FB ($p < 0.001$) and a significantly lower likelihood of VFD for patients with FB > 20% in the multivariate analysis (adjusted incident rate ratio: 0.85 [0.74–0.97]) [23]. However, we included only LDLTs, and our multivariable

Table 2 Primary and secondary outcomes

Variables	Total ($n=200$)	$<5\%$ FB ($n=67$)	5–10% FB ($n=66$)	10–15% FB ($n=45$)	$\geq 15\%$ FB ($n=22$)	p
VFD at 30 days, median (IQR)	29.3 (27.5–29.4)	29.3 (28.3–29.4)	29.3 (28.3–29.4)	29.3 (28.3–29.4)	27.4 (23.3–29.4)	0.27
Reintubation (48 h), *n* (%)	6 (3.0)	3 (4.5)	1 (1.5)	1 (2.3)	1 (4.5)	0.78
Acute rejection, *n* (%)	116 (58.0)	36 (53.7)	42 (63.6)	29 (64.4)	9 (40.9)	0.20
Hepatic arterial thrombosis, *n* (%)	7 (3.5)	1 (1.5)	3 (4.5)	2 (4.4)	1 (4.5)	0.61
AKI(stage 1–3), *n* (%)	35 (17.5)	11 (16.4)	6 (9.1)	8 (17.8)	10 (45.5)	0.004
Primary graft dysfunction, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
ICU LOS in days, median (IQR)	4.6 (3.6–4.6)	4.6 (3.6–4.6)	3.6 (3.6–4.6)	3.6 (3.6–4.6)	4.6 (3.6–6.6)	0.11
One-year mortality, *n* (%)	8 (4.0)	2 (3.0)	2 (3.0)	3 (6.7)	1 (4.5)	0.67

FB fluid balance, *VFD* ventilator-free days, *IQR* interquartile range, *AKI* acute kidney injury, *LOS* length of stay, *NA* not applicable (no events occurred in any group)

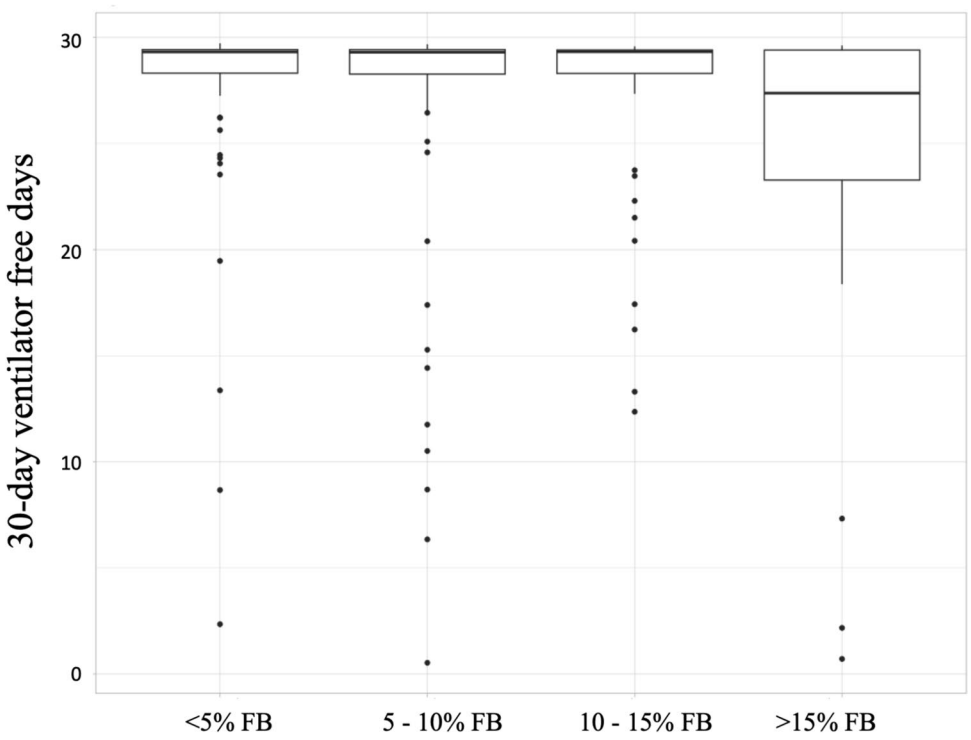

Fig. 2 30-day ventilator-free days across fluid balance groups *FB* fluid balance

analysis revealed that patients with FB $\geq 15\%$ have significantly shorter VFD than those with FB $< 5\%$.

One of the plausible reasons for the association between fluid overload (FO) and VFD is that FO impairs respiratory function. FO damages the endothelial glycocalyx, leading to fluid leakage into the interstitial space and pulmonary edema and impairing gas exchange [26]. Although the relationship between FB and oxygenation in our study is unclear due to insufficient data, this causality logically explains the association. However, postoperative patients under mechanical ventilation require the administration of sedatives and analgesics, many of which can cause vasodilation and fluid administration for relative dehydration. Therefore, the possibility that prolonged mechanical ventilation and the use of sedatives resulted in positive FB cannot be ruled out.

Hepatic arterial thrombosis is a fatal complication post-LT, and a hypothetical consideration regarding dehydration and thrombosis exists. LT patients typically exhibit physiological characteristics, such as portal hypertension and highly permeable capillaries [12], and risks of postoperative hemorrhage and ascites [27, 28], leading to a higher risk of dehydration. Additionally, pediatric patients have smaller vessel sizes and are subject to postoperative hypercoagulation states, with a higher risk of thrombosis [15, 29,

Table 3 Multivariable linear regression analyses for ventilator-free days and length of stay in the intensive care unit

Variable	β	SE	p value
VFD at 30 days			
FB 5–10%	−1.29	1.02	0.21
FB 10–15%	−1.21	1.20	0.32
FB ≥ 15%	−4.59	1.58	0.004
ICU LOS			
FB 5–10%	0.25	3.03	0.93
FB 10–15%	3.22	3.58	0.37
FB ≥ 15%	3.72	4.76	0.43

Each model was adjusted for weight, onset of liver failure, admission status, PELD/MELD score, GRWR presence of preoperative encephalopathy, preoperative serum creatinine level, preoperative extracorporeal blood purification therapies, intraoperative fluid balance, intraoperative VIS, and PIM3

FB < 5% was set as a reference in the models

β regression coefficient, *SE* standard error, *VFD* ventilator-free days, *FB* fluid balance, *GRWR* graft-to-recipient weight ratio, *PELD* pediatric end-stage liver disease score, *MELD* model for end-stage liver disease score, *PIM3* Pediatric Index of Mortality 3, *LOS* length of stay, *VIS* vasoactive-inotropic score

30]. Despite the absence of universally adopted guidelines regarding postoperative fluid management post-LT, maintaining intravascular volume and potentially positive FB is commonly adopted to prevent thrombosis, particularly in pediatric patients. In our study, no significant association was observed between post-transplant FB and thrombosis incidence. However, due to the low incidence of thrombosis and limited statistical power, our findings cannot definitively determine the optimal fluid therapy for thrombosis prevention.

Our study also revealed a significant association between post-LT FB and AKI incidence. These findings are consistent with those observed in adult [10–12] and pediatric LT patients [23]. Patients with liver dysfunction have low colloid osmotic pressure, and perioperative fluid resuscitation aggravates tissue edema and possibly renal congestion. On the other hand, reduced glomerular filtration rate and kidney injury can lead to FO. Establishing causation beyond the association between the potentially concomitant and interacting events of FO and AKI is difficult in this retrospective study. Although many recent studies have shown the association of FO with poor outcomes, including mortality and AKI in critically ill pediatric patients [22, 31, 32], establishing optimal fluid management with targeted FB for pediatric LT recipients requires a prospective interventional study.

The strength of this research lies in its innovative emphasis on FB post-pediatric LDLT, an area previously underexplored in medical research. This study is at the forefront of evaluating FB in pediatric LDLT recipients. While the insights gained from this research were inconclusive, our findings raise questions regarding traditional fluid management strategies for this population in terms of respiratory function, thrombotic complications, and organ dysfunctions. Another strength of this study is the accuracy of FB calculations using data from fluid intake and output. For example, fluid creep, acting as the vehicle for drugs, is an essential source of fluid load for critically ill patients [33, 34], particularly critical in pediatric patients [35], where even small fluid volumes can significantly affect FB. Most previous studies on LT do not specify whether fluid creep was accounted for in FB calculations. Furthermore, comprehensive medical records of all fluid intake and output—including infusion volumes, fluid creep, gastric drainage, stool output, and other relevant components—enabled more accurate analyses of the associations between FB and outcomes.

This study has some limitations. First, this was a retrospective, single-center study, which may limit the generalizability of the findings to different settings. Second, a wide age range of participants was included in this study. Therefore, the size of patients could be confounding the association

Table 4 Bivariate analyses of outcomes based on fluid balance within 48 h postoperatively in patients aged < 1 year

Variables	Total (n = 84)	< 5% FB (n = 14)	5–10% FB (n = 24)	10–15% FB (n = 29)	≥ 15% FB (n = 17)	p
VFD at 30 days, median (IQR)	29.3 (26.2–29.4)	29.1 (26.2–29.3)	29.3 (26.5–29.4)	29.4 (28.9–29.4)	27.4 (23.2–29.4)	0.14
Reintubation (48 h), *n* (%)	3 (3.7)	1 (7.7)	0 (0.0)	1 (3.7)	1 (5.9)	0.59
Acute rejection, *n* (%)	47 (56.0)	6 (42.9)	12 (50.0)	22 (75.9)	7 (41.2)	0.054
Hepatic arterial thrombosis, *n* (%)	4 (4.8)	1 (7.1)	2 (8.3)	0 (0.0)	1 (5.9)	0.42
AKI (Stage 1–3), *n* (%)	22 (26.2)	5 (35.7)	2 (8.3)	6 (20.7)	9 (52.9)	0.01
Primary graft dysfunction, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
ICU LOS in days, median (IQR)	4.6 (3.6–5.6)	5.6 (4.6–6.6)	3.6 (3.6–4.6)	3.6 (3.6–4.6)	4.6 (4.4–6.9)	0.02
One-year mortality, *n* (%)	3 (3.6)	1 (7.1)	0 (0.0)	1 (3.4)	1 (5.9)	0.59

FB fluid balance, *VFD* ventilator-free days, *IQR* interquartile range, *AKI* acute kidney injury, *LOS* length of stay, *NA* not applicable

Table 5 Multivariable linear regression analyses for ventilator-free days in patients aged < 1 year

Variable	*β*	SE	*p*
VFD at 30 days			
FB 5–10%	−0.52	2.22	0.82
FB 10–15%	0.01	2.20	1.00
FB ≥ 15%	−3.61	2.50	0.15

The model was adjusted for weight, onset of liver failure, admission status, PELD/MELD score, GRWR, presence of preoperative encephalopathy, preoperative serum creatinine level, preoperative extracorporeal blood purification therapies, intraoperative fluid balance, intraoperative VIS, and PIM3

FB < 5% was set as a reference in the models

β regression coefficient, *SE* standard error, *VFD* ventilator-free days, *FB* fluid balance, *GRWR* graft-to-recipient weight ratio, *PELD* pediatric end-stage liver disease score, *MELD* model for end-stage liver disease score, *PIM3* pediatric index of mortality 3, *VIS* vasoactive-inotropic score

Table 6 Multivariable logistic regression analyses for of acute kidney injury, reintubation, acute rejection, and hepatic vascular thrombosis

Variable	Odds ratio	95% CI	*p*
Reintubation (48 h)			
FB 5–10%	0.32	0.02–4.73	0.40
FB 10–15%	0.66	0.04–10.4	0.76
FB ≥ 15%	5.02	0.15–166.0	0.37
Acute rejection			
FB 5–10%	1.25	0.59–2.66	0.56
FB 10–15%	1.39	0.57–3.40	0.47
FB ≥ 15%	0.44	0.13–1.43	0.17
Hepatic arterial thrombosis			
FB 5–10%	6.97	0.20–241.0	0.28
FB 10–15%	2.95	0.12–75.8	0.51
FB ≥ 15%	0.76	0.00–121.0	0.91
AKI			
FB 5–10%	0.59	0.17–2.04	0.40
FB 10–15%	1.43	0.41–5.03	0.57
FB ≥ 15%	6.60	1.50–29.0	0.012

Each model was adjusted for weight, onset of liver failure, admission status, PELD/MELD score, GRWR, presence of preoperative encephalopathy, preoperative serum creatinine level, preoperative extracorporeal blood purification therapies, intraoperative fluid balance, intraoperative VIS, and PIM3

FB < 5% was set as a reference in the models

CI confidence interval, *AKI* acute kidney injury, *GRWR* graft-to-recipient weight ratio, *PELD* pediatric end-stage liver disease score, *MELD* model for end-stage liver disease score, *PIM3* pediatric index of mortality 3, *VIS* vasoactive-inotropic score

between FB and outcomes. Different associations between FB and outcomes may also exist across ages. However, multivariable analysis adjusting for weight demonstrated a significant association between FB and VFD, and the subgroup analysis of children aged < 1 year showed a similar trend of reduced VFD in patients with more positive FB. Third, confounding factors might not have been adequately adjusted. For example, the associations between FB and outcomes were adjusted for preoperative PELD/MELD scores and PIM3, which might not sufficiently reflect the severity of conditions such as portal hypertension. Additionally, PELD and MELD scores were treated as equivalent severity indicators in our study, as was done in previous research [23]; however, this approach is debatable as these scoring systems are derived through different methodologies. Fourth, our study treated various fluids, such as crystalloids, colloid solutions, free water, transfusions, urine output, stool, hemorrhage, pleural effusion, and ascites, as having equivalent volume, which may have been physiologically inappropriate. In addition, this study does not reveal the components of FB that were associated with outcomes. For instance, FO could be attributable to excess fluid administration and a small amount of fluid output, such as oliguria. However, additional adjustment for these components of FB in the regression models posed a risk of collinearity, which could lead to false negatives, and was, therefore, avoided. Furthermore, the effects of an intervention to control FB, including the administration of colloid, transfusion, and diuretics and the induction of renal replacement therapy, remains unclear. Therefore, it should be noted that postoperative FB is not an intervention but rather a result of interventions and patients' conditions over time. In conclusion, our study demonstrated significant associations of FB within the first 48 h postoperatively with reduced VFD and increased AKI incidence, but not with thrombotic complications. These findings underscore a potential relationship between perioperative FB and clinical outcomes in pediatric LT recipients, highlighting the need for further research to explore optimal fluid management strategies in this population.

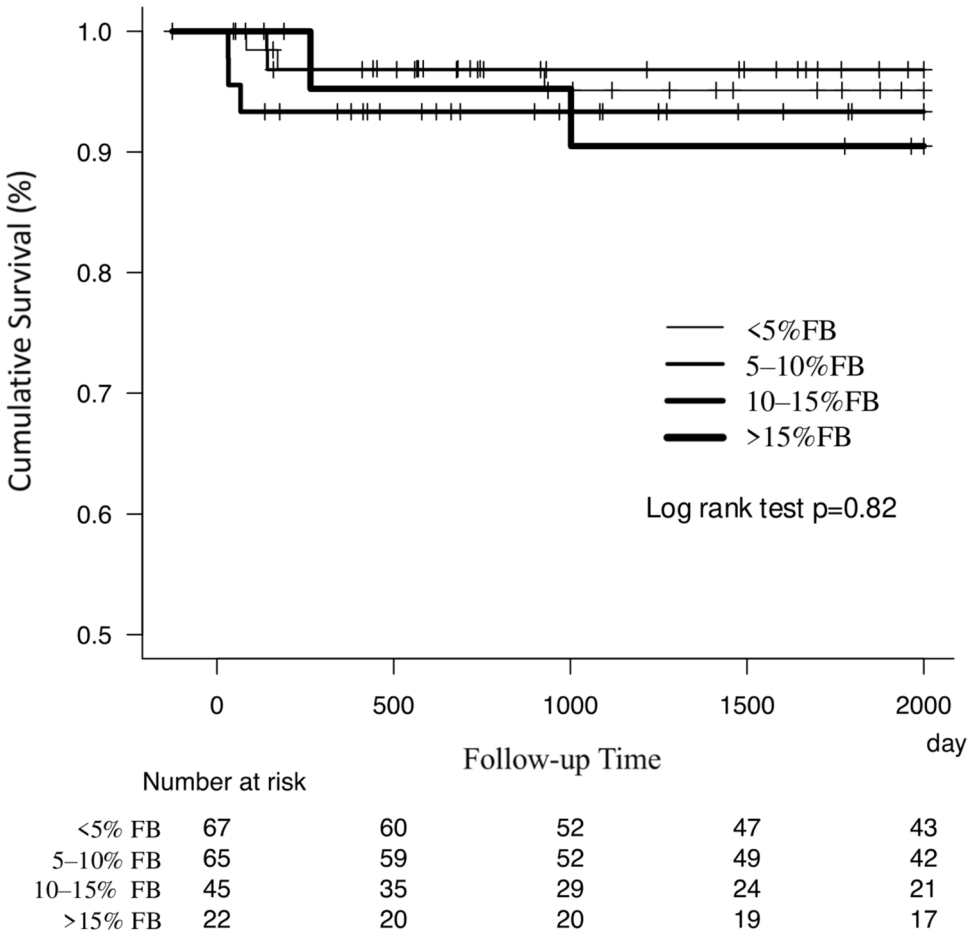

Fig. 3 Comparison of Kaplan–Meier survival curves across fluid balance groups *FB* fluid balance

Table 7 Cox proportional hazard model analysis of survival time based on postoperative fluid balance

Group	Hazard ratio	95% Confidence interval	*p*
FB (reference < 5%)			
5–10%	0.77	0.16–3.83	0.75
10–15%	2.06	0.39–10.97	0.40
≥15%	2.77	0.20–38.19	0.45

Model was adjusted for weight, onset of liver failure, admission status, PELD/MELD score, GRWR, presence of preoperative encephalopathy, preoperative serum creatinine level, preoperative extracorporeal blood purification therapies, intraoperative fluid balance, intraoperative VIS, and PIM3

FB fluid balance, *GRWR* graft-to-recipient weight ratio, *PELD* pediatric end-stage liver disease score, *MELD* model for end-stage liver disease score, *PIM3* pediatric index of mortality 3, *VIS* vasoactive-inotropic score

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Declarations

Conflict of interest All authors declare no financial disclosures or conflicts of interest.

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