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The effect of high-volume intraoperative fluid administration on outcomes among pediatric patients undergoing living donor liver transplantation

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Abstract

Background Pediatric patients undergoing liver transplantation are particularly susceptible to complications arising from intraoperative fluid management strategies. Conventional liberal fluid administration has been challenged due to its association with increased perioperative morbidity. This study aimed to assess the impact of intraoperative high-volume fluid therapy on pediatric patients who are undergoing living donor liver transplantation (LDLT).

Methods Conducted at the Children's Hospital of Chongqing Medical University from March 2018 to April 2021, this retrospective study involved 90 pediatric patients divided into high-volume and non-high-volume fluid administration groups based on the 80th percentile of fluid administered. We collected the perioperative parameters and postoperative information of two groups. Multivariable logistic regression was utilized to assess the association between estimated blood loss (EBL) and high-volume FA. Kaplan-Meier survival analysis was used to compare patient survival after pediatric LDLT.

Results Patients in the high-volume FA group received a higher EBL and longer length of stay than that in the non-high-volume FA group. Multivariate logistic regression analysis indicated that hours of maintenance fluids and fresh frozen plasma were significantly associated risk factors for the occurrence of EBL during pediatric LDLT. In addition, survival analysis showed no significant differences in one-year mortality between the groups.

Conclusions High-volume fluid administration during LDLT is linked with poorer intraoperative and postoperative outcomes among pediatric patients. These findings underscore the need for more conservative fluid management strategies in pediatric liver transplantations to enhance recovery and reduce complications.

Keywords Pediatric, Living donor liver transplantation, Fluid administration, Intraoperation, Outcomes

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Introduction

Biliary atresia (BA) is the most common indication for liver transplantation in the pediatric population, and living donor liver transplantation (LDLT) and deceased donor liver transplantation (DDLT) have been established as radical treatments for BA [1]. During LT surgery, there are periods of hemodynamic instability with potential significant blood loss, so perioperative fluid management is important for effective intravascular volume and hemodynamic stability [2].

The conventional approach to perioperative fluid management involves the administration of generous amounts of fluids to achieve optimal blood volume and sufficient tissue perfusion. Nevertheless, this traditional strategy has come under scrutiny due to its potential to result in fluid overload. The adverse consequences of fluid overload include the development of interstitial edema, impaired gastrointestinal motility, delayed wound healing, compromised coagulation, and the onset of cardiopulmonary complications [3–5]. Recent research has demonstrated the advantages of implementing restrictive fluid therapy in postoperative recovery, including the reduction of hospitalization duration [6, 7], mitigation of pulmonary edema risk [8], and decreased perioperative blood loss and transfusion needs [9]. However, importantly, the majority of data supporting these fluid management strategies has been derived from studies conducted on adult patients [10, 11]. Despite these advancements, there remains a notable gap in pediatric-specific research, particularly concerning the unique body fluid dynamics in children, such as total body water and extracellular fluid volumes, which differ significantly from adults [12]. These differences underscore the critical need to evaluate whether these adult-derived fluid management strategies are applicable or need adjustment for the pediatric population undergoing LDLT. Therefore, this study aims to bridge this knowledge gap by investigating the impact of high-volume versus restrictive fluid administration on intraoperative and postoperative outcomes in pediatric LDLT recipients. By focusing on this pediatric cohort, the study seeks not only to evaluate the direct effects of fluid volume on surgical outcomes but also to contribute to the broader understanding of optimal fluid management strategies in pediatric liver transplantation, potentially influencing practice guidelines and improving patient recovery trajectories.

Materials and methods

Data source

The data for this study were obtained from the UniDMR Browser database (case system of our hospital). We retrospectively analyzed the cases of pediatric patients diagnosed with BA who underwent LDLT at Children's Hospital of Chongqing Medical University from March 2018 to April 2021. The research procedures adhered to the ethical standards set by the Approval Letter of the Institutional Review Board, Children's Hospital of Chongqing Medical University (2023-35), which exempted the study from obtaining informed consent. A standardized form was utilized for data collection.

Population data

The study sample consisted of pediatric patients classified as ASA III-IV, aged between 3 months and 12 months, who underwent LDLT. The transplanted livers are all the left half of the donor's liver. Patients undergoing repeat LT or those with other severe congenital diseases were excluded from the study. These patients were divided into two groups: the high-volume FA group, which had standardized fluid intake greater than the 80th percentile; and the non-high-volume FA group, which had standardized fluid intake below the 80th percentile.

The infused fluids consisted of Ringer acetate and albumin 5%. Correction of coagulation defects was only undertaken in cases of uncontrolled surgical bleeding detected through thromboelastometry. Hemoglobin levels were maintained above 8 gm/dl. The utilization of cell savers was implemented for all patients. Infusions of norepinephrine and dopamine were administered as necessary to sustain a mean arterial pressure exceeding 50 mmHg. All procedures were conducted by a single surgical team. A uniform immunosuppressive therapy protocol was adhered to for all patients.

Standardized fluid administration calculation

According to the method provided by Sanford et al. [13], the standard fluid administration was calculated. The total fluids of each patient were calculated as crystalloid + (colloid × 1.5). This total was adjusted for surgical duration by subtracting the product of the maintenance rate (as determined by the 4-2-1 rule) and surgical time. The adjusted total fluids administered were then divided by the maintenance rate to normalize for patient size-related metabolic requirements, resulting in hours of maintenance fluids (HMF). That is, the derived unit=crystalloid + (colloid × 1.5)- (the maintenance rate× surgical time)]/the maintenance rate; standardized fluids administered=the maintenance rate ×the derived unit.

Clinical information collection

We collected several parameters of the two groups, including age, sex, weight, previous abdominal surgery (Kasai), surgical procedure, intraoperative blood loss (estimated by the Cell saver), blood products, urine output (UOP) total, peak and minimum central-venous pressure (CVP), postoperative length of stay (LOS), duration of ventilator support, intensive care unit (ICU) admission time, acute kidney injury (AKI) as indicated by

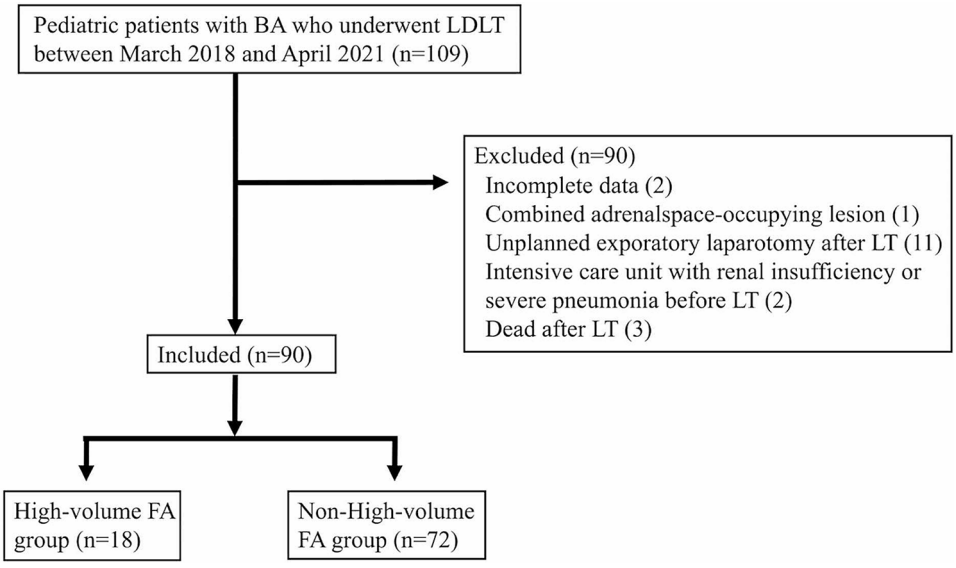

Fig. 1 Study flow chart. A total of 109 unique patients with BA were identified, 19 patients were excluded due to meeting the exclusion criteria. Finally, 90 patients were included in the study, and divided into two groups: High-volume FA group ($n=18$) and non-High-volume FA ($n=72$)

preoperative and postoperative day 3 creatinine levels, and significant chest X-ray findings defined as pulmonary edema, pneumonia, and pulmonary effusion.

Statistical analysis

For continuous variables, data were expressed as median (interquartile range); while for categorical variables, data were expressed as n (%). The Mann–Whitney U test was used for the comparison of continuous variables, and the chi-squared test was used for categorical variables. The Spearman Rho correlation between the amount of fluids given and EBL was calculated. The most relevant risk factors associated with intraoperative EBL were selected in the univariate logistic regression analysis. Variables with a P value < 0.2 in the univariate logistic regression analysis were included in the final multivariate logistic regression analysis. Kaplan–Meier survival analysis with a log rank test was used to compare patient survival within 1 year of LDLT between the high-volume FA group and the nonhigh-volume FA group. Data were analyzed using IBM SPSS Statistics 26.0 (SPSS, Inc., Chicago, IL). P value < 0.05 was considered to indicate statistical significance.

Results

Clinical characteristics of patients

A total of 109 unique patients with BA were identified. 19 patients were excluded due to meeting the exclusion criteria. Two patients had incomplete data, 1 patient had a combined adrenal space-occupying lesion, 11 patients had an unplanned exploratory laparotomy after LT, 2 patients were transferred to the intensive care unit with renal insufficiency or severe pneumonia before LT, and 3 patients died after LT. Finally, 90 patients were included in the study, and divided into two groups: High-volume FA group ($n=18$) and non-High-volume FA ($n=72$) (Fig. 1).

Table 1 Comparison of population characteristics between two groups

	High-volume FA group($n=18$)	non-High-volume FA($n=72$)	*P*-value
Sex (male/female)	11/7	37/35	0.460
Age (mouth)	6.0 (5.0–9.0)	5.0 (4.0–11.0)	0.081
Weight(kg)	6.3 (5.0–10.0)	7.0 (4.8-9.0)	0.360
ASA III or IV	18 (100%)	72 (100%)	NS
Previous abdominal surgery	1	10	0.573

ASA, American Society of Anesthesiologists physical status classification

We compared the population characteristics and perioperative laboratory parameters of the two groups. Demographics showed a balanced sex distribution with slight variations in age and weight; High-volume FA patients averaged 6 months and 6.3 kg, while Non-High-volume FA patients averaged 5 months and 7.0 kg. All were classified as high risk (ASA III or IV) (Table 1). Baseline clinical metrics included hemoglobin levels averaging 94.0 g/L in the High-volume FA group versus 97 g/L in the Non-High-volume FA, with platelet counts and fibrinogen levels showing no significant differences between the groups. Baseline serum creatinine and instances of pulmonary disease were also similar (all $P>0.05$, Table 2).

Table 2 Comparison of perioperative laboratory parameters between two groups

	High-volume FA group($n=18$)	non-High-volume FA($n=72$)	*P*-value
Baseline Hb	94.0 (76.0-119.0)	97 (70.0-145.0)	0.570
Baseline platelet count ($\times10^9$/l)	230.0 (68.0-423.0)	214.5 (91.0-486.0)	0.870
Baseline fibrinogen (mg/dl)	1.5 (0.6–3.9)	1.9 (0.8–4.4)	0.101
Baseline Serum creatinine level	16.0 (8.0–34.0)	15.00 (9.0–33.0)	0.256
Baseline pulmonary disease	3	29	0.054

Hb, Hemoglobin

Table 3 Comparison of perioperative relevant clinical parameters between two groups

	High-volume fluid administration group ($n=18$)	non-High-volume FA($n=72$)	*P*-value
HMF (h)	109.1 (59.5–187.0)	57.7 (28.3-118.4)	< 0.001
UOP (ml/kg/h)	8.4 (1.8–30.0)	4.4 (0.6–19.4)	0.018
Dosage of 5% sodium bicarbonate (ml/kg)	6.6 (1.8–14.7)	4.8 (0-12.5)	0.040
Durations of dopamine (min)	322.7 (5.0-505.0)[a]	225.5 (0-470.0)	0.023
Durations of norepinephrine (min)	217.5 (20.0-405.0)	152.5 (0-470.0)	0.094
Anesthesia times (h)	9.0 (12.3-8.0)	9.1 (5.8–14.7)	0.940
Operative time (h)	8.4 (7.1–13.4)	7.3 (4.6–10.7)	< 0.001
Peak CVP (cmH_2O)	17.0 (13.0–19.0)	15.0 (9.0–19.0)	0.001
Minimum CVP (cmH_2O)	6.5 (4.0–14.0)	6.5 (3.0–10.0)	0.399
PRBC transfusion (ml/kg)	108.2 (47.0-327.6)	93.2 (40.5-242.9)	< 0.001
EBL (ml/kg)	92.6 (7-230.8)	46.9 (16.7-171.4)	< 0.001
FFP	16/2	41/31	0.012
Cryoprecipitate	6/12	12/60	0.211
LOS (d)	38.5 (19.0–61.0)	32.5 (18.0–63.0)	0.046
Time of ventilator support (h)	25.0 (12-156.2)	20 (9.7–156.0)	0.670
ICU admission time (d)	5.5 (2.5–12.5)	4.8 (2.0–31.0)	0.580
Pneumonia complications			
pneumonia edema	14/4	32/36	0.030
Pneumonia	5/15	24/44	0.549
pleural effusion	7/11	26/42	0.960
Renal function damage (Serum creatinine levels)			
The immediate postoperative phase	15.8 (13.3–24.6)	16.8 (13.3–33.0)	0.227
3 days after operation	21.3 (13.3-33.25)	18.40 (13.3–66.9)	0.402

EBL, estimated blood loss; HMF, Hours of Maintenance Fluids; LOS, longer length of stay; CVP, central-venous pressure; PRBC, packed red blood cell; FFP, Fresh frozen plasma; UOP, urine output

[a]Median value (IQR)

Comparison of intraoperative parameters of two groups

We analyzed the intraoperative parameters of two groups. The high-volume FA group received a higher median of 109.1 HMF compared to that in the non-High-volume FA groups (57.7 h, $P<0.001$). High-volume FA group has significantly increased dosages of sodium bicarbonate and UOP compared with non-High-volume FA groups ($P<0.05$). The durations of dopamine and operative time were significantly longer in the high-volume FA group than in the non-high-volume FA group ($P<0.05$). In addition, patients in the high-volume group had a significantly higher peak CVP than those in the non-high-volume group (Table 3). However, there was no significant difference in the minimum CVP between the two groups, with both groups having a median value of 6.5 cmH_2O ($P=0.399$).

High-volume FA group received a higher EBL compared to that of the non-high-volume FA group ($P<0.001$). We also found significant differences in the transfusion of blood products: the PRBC transfusion rate was 100% in the 2 groups; and the high-volume FA group received a higher median of 108.2 ml/kg, compared to 93.2 ml/kg in the non-high-volume FA group ($P<0.001$). The FFT transfusion rate was 88.9% in the high-volume FA group, compared to 56.9% in the non-high-volume FA group. The cryoprecipitate rate was not different between the 2 groups. (Table 3).

Logistic multifactor analysis of factors influencing of intraoperative EBL

The Spearman Rho correlation showed an association between the high-volume FA given and EBL ($R=0.592$, $P<0.01$). The results of logistic regression analysis are summarized in Table 4. Age, weight, fibrinogen, platelets, transfuse FFP, transfuse cryoprecipitate and operation time were selected for inclusion in the multivariate logistic regression analysis ($P<0.2$). The results of multivariate logistic regression analysis indicated that HMF (OR=11.355, 95%CI: 4.273–30.179, $P<0.001$) and FFP (OR=5.125, 95%CI: 2.030-12.939, $P=0.008$) were significantly associated risk factors for the occurrence of EBL during pediatric LDLT.

Association between high-volume fluid administration and secondary outcomes

The chest X-ray showed more pulmonary edema in the high-volume FA group than that in the nonhigh-volume FA group ($P<0.05$). The serum creatinine levels did not increase significantly in the immediate postoperative phase or 3 days after the operation between the high-volume FA group and the non-high-volume FA group ($P>0.05$). Patients in the high-volume FA group experienced increased LOS compared with non-high-volume FA group ($P<0.05$). The time of ventilator support and

Table 4 Univariate and multivariate analyses of factors intraoperative EBL

Variable	OR	95% CI	*P*-value
Univariate analysis			
HMF	11.355	4.273–30.179	< 0.001
Anesthesia Times (h)	1.070	0.6838–1.797	0.797
Operative time (h)	2.896	1.219–6.884	0.016
Age (mouth)	0.868	0.645–1.164	0.349
Weight (kg)	0.603	0.395–0.921	0.019
Baseline platelet count	1.000	0.995–1.004	0.981
Baseline fibrinogen	0.673	0.38–1.193	0.175
Baseline Hb	0.993	0.965–1.021	0.611
FFP	5.125	2.030-12.939	0.001
cryoprecipitate	8.000	1.714–37.349	0.008
PRBC transfusion (ml/kg)			
High-volume fluid administration	17.971	2.270-142.286	0.006
Multivariate analysis			
HMF	11.411	1.489–14.381	< 0.001
FFP	4.628	1.489–14.381	0.008

EBL, estimated blood loss; HMF, Hours of Maintenance Fluids; PRBC, packed red blood cell; FFP, Fresh frozen plasma. OR, odds ratio; 95% CI, 95% confidence interval

ICU admission time were longer in the high-volume FA group than in the control group, but there was no difference in either (Table 3). The mortality rate within 1 year of LDLT (Fig. 2) did not differ significantly between the high-volume fluid administration group and the control group (5.6% vs. 4.2%, $P=0.793$).

Discussion

This retrospective cohort study aimed to assess the potential correlation between extensive intraoperative fluid administration and EBL, as well as various complications, in pediatric patients undergoing LDLT. Our findings indicate that conventional intraoperative fluid management approaches may contribute to fluid overload, resulting in adverse effects such as increased blood loss, subsequent blood transfusion requirements, pulmonary edema, and length of hospital stay. However, no significant associations were observed between high-volume fluid administration and AKI, time to extubation, ICU discharge, or one-year mortality rate.

The normalization steps in the standardized fluid administration calculation were essential to accurately assess the impact of fluid volume on intraoperative and postoperative outcomes. By normalizing fluid administration, we adjusted for the unique physiological differences in pediatric patients, such as total body water and extracellular fluid volumes, which differ significantly from adults. This approach provided a more robust and meaningful analysis, allowing us to evaluate the direct effects of fluid volume on surgical outcomes. The results of our study underscore the importance of tailored fluid management strategies in pediatric liver transplantation to improve recovery and reduce complications.

During the duration of LT operations, blood loss poses a significant challenge, making it exceedingly difficult to maintain effective hemodynamic stability [2]. The administration of fluids during the intraoperative period, aimed at preserving intravascular volume and hemodynamic stability, can lead to a substantial rise in fluid overload. This, in turn, can have detrimental consequences on tissue perfusion and prognosis. Our study indicates that the implementation of aggressive fluid infusion is correlated with heightened blood loss and, consequently, a higher requirement for intraoperative packed red blood cell

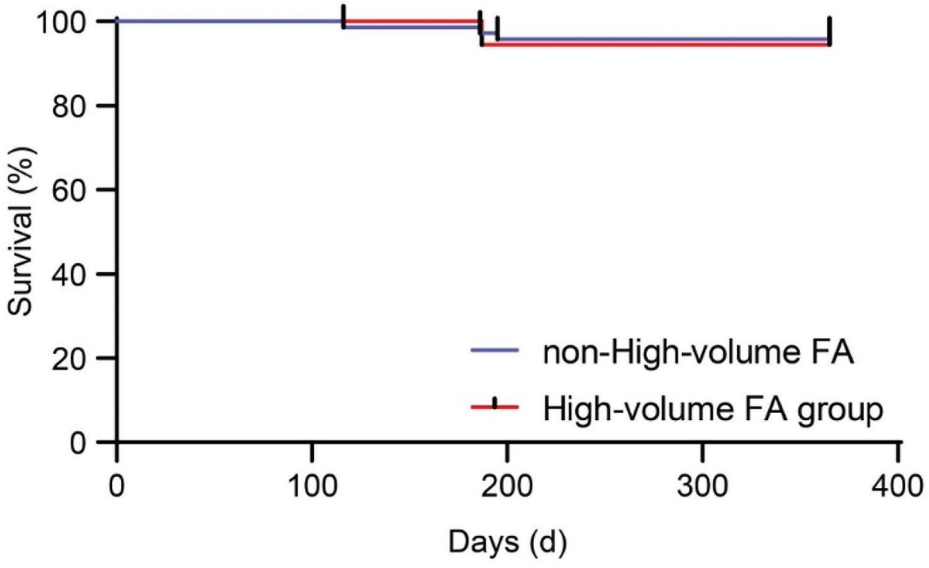

Fig. 2 Kaplan-Meier curves of patient survival within 1 year of the pediatric liver transplantation

transfusions in pediatric patients undergoing LDLT. Our results are in line with Lekerika's findings that demonstrated that the liberal fluid strategy group's blood losses and transfusion of PRBCs were greater [9]. The potential consequences of aggressive fluid infusion include the development of hypervolemia, an elevation in CVP, and subsequently an increase in blood loss [13, 14]. As a result, the prevention of excessive blood loss and the subsequent need for multiple transfusions have emerged as significant objectives in the perioperative care of liver transplantation patients [15–17]. Moreover, we found that the rate of transfusion of FFP was also higher in the high-volume FA group, probably due to the high-volume and more blood losses caused by the high-volume effects of coagulation. However, Lekerika's study shows that aggressive fluid infusion, including FFP, may increase rather than prevent blood loss in LT patients [9]. In our study, logistic regression showed that aggressive fluid infusion and transfusion of FFP are two strong risk factors, increasing the probability of blood loss.

Liver transplant recipients suffer many postoperative complications. Postoperative respiratory disorders are also very common after LT and are a major cause of mortality. Some studies have demonstrated that intraoperative fluid overload is a strong risk factor for pulmonary complications [18–20]. However, these data were derived from adults, and minimal data were reported in pediatric patients. We observed an association between a higher fluid balance and pulmonary edema but no differences in pneumonia and pleural effusion. Additionally, in adult patients, postoperative AKI also has a high incidence following liver transplantation [21, 22], and intraoperative fluid management has been associated with postoperative AKI in many surgical populations [18, 23, 24]. However, our study showed no differences in AKI or hemofiltration. The results showed that serum creatinine levels did not increase significantly in the immediate postoperative phase or 3 days after the operation. This result is consistent with what Carrier et al. [25] reported, and we observed no association between intraoperative fluid balance and postoperative AKI. Furthermore, we observed an association between a higher fluid balance and LOS, and this result is consistent with Ethan L. Sanford et al.'s study showing that high-volume fluid administration is associated with a longer LOS for pediatric patients [13].

In our present analysis, the mortality rate within 1 year of LDLT did not differ significantly between the high-volume FA group and the non-high-volume FA group among pediatric patients. However, previous studies showed that positive fluid balance was associated with increased mortality in other critically ill pediatric populations [26, 27], including patients with shock and those postoperative from cardiac surgery. Moreover, a postoperative positive fluid balance was associated with mortality in adult LT recipients [28, 29]. In our study, while the liberal fluid administration was associated with increased estimated blood loss and longer lengths of stay, similar to findings in adults, the absence of significant differences in mortality rates and acute kidney injury highlights the need for pediatric-specific studies. The discrepancies between pediatric and adult responses underscore the critical need for ongoing research to develop evidence-based fluid management protocols that are specifically tailored to pediatric liver transplantation patients.

One strength of this study was the utilization of a cell saver to estimate the bleeding loss protocol and the implementation of all operations by a team under comparable conditions. Nonetheless, some limitations need to be acknowledged. (1) As a retrospective study, our findings are inherently limited by the nature of data collection, which was not originally intended for this research. This may lead to potential biases in data integrity and completeness, affecting the reliability of the conclusions. (2) The retrospective nature of the study restricts our ability to control for all potential confounding variables that might have influenced the study outcomes. (3) Small sample sizes and data from a single center may not reflect broader demographic and clinical variations, limiting the generalizability of our results. Future research should include prospective multicenter studies to enhance data diversity and relevance, and randomized controlled trials to better ascertain causal relationships between fluid management strategies and patient outcomes.

Conclusion

There exists a statistically significant correlation between fluid administration and blood loss. Furthermore, patients in the high-volume FA group exhibited substantial clinical disparities in terms of pulmonary edema and LOS, indicating compromised recovery when subjected to large volumes of intravenous fluid during surgery. Consequently, the adoption of goal-directed fluid administration, guided by dynamic measurements associated with fluid responsiveness, may effectively prevent excessive fluid administration. Additional future research should be conducted to examine the safety and potential advantages of various fluid management approaches in pediatric patients undergoing LDLT.

Abbreviations

LT	liver transplantation
LDLT	living donor liver transplantation
EBL	estimated blood loss
HMF	Hours of Maintenance Fluids
LOS	longer length of stay
CVP	central-venous pressure
PRBC	packed red blood cell
FFP	Fresh frozen plasma
UOP	urine output
AKI	acute kidney injury

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Author contributions
MMZ and ZZT designed and supervised the study. ZZT collected the data. ZZT and DXK conducted the data analysis. LB, DWH and JS analyzed and interpreted the result. All authors approved submitted version.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The research procedures adhered to the ethical standards set by the Approval Letter of the Institutional Review Board, Children's Hospital of Chongqing Medical University (2023-35).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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