Received: 29 July 2022 | Revised: 16 February 2023 | Accepted: 22 February 2023

DOI: 10.1111/petr.14499

ORIGINAL ARTICLE

WILEY

Fluid balance in pediatric postoperative liver transplant recipients

Jessica M. Winters[1] | Rebecca Brocks[2] | Catherine A. Chapin[3] | Caroline P. Lemoine[4] | Riccardo Superina[4] | Katherine A. Brandt[4] | L. Nelson Sanchez-Pinto[5] | Matthew F. Barhight[5]

[1]Division of Critical Care, Connecticut Children's, University of Connecticut School of Medicine, Hartford, Connecticut, USA

[2]Division of Pediatric General Surgery, Hospital Sainte-Justine – Mother-Child University Hospital Center, University of Montréal, Québec, Canada

[3]Division of Gastroenterology, Hepatology, and Nutrition, Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

[4]Division of Transplant and Advanced Hepatobiliary Surgery, Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

[5]Division of Critical Care, Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

Correspondence
Jessica M. Winters, Division of Critical Care, Connecticut Children's, University of Connecticut School of Medicine, 282 Washington St., Hartford, CT 06106, USA.
Email: jessmwinters13@gmail.com

Abstract

Background: Positive fluid balance (FB) is associated with poor outcomes in critically ill children but has not been studied in pediatric liver transplant (LT) recipients. Our goal is to investigate the relationship between postoperative FB and outcomes in pediatric LT recipients.

Methods: We performed a retrospective cohort study of first-time pediatric LT recipients at a quaternary care children's hospital. Patients were stratified into three groups based on their FB in the first 72 h postoperatively: <10%, 10–20%, and > 20%. Outcomes were pediatric intensive care unit (PICU) and hospital length of stay, ventilator-free days (VFD) at 28 days, day 3 severe acute kidney injury, and postoperative complications. Multivariate analyses were adjusted for age, preoperative admission status, and Pediatric Risk of Mortality (PRISM)-III score.

Results: We included 129 patients with median PRISM-III score of 9 (interquartile range, IQR 7–15) and calculated Pediatric End-stage Liver Disease score of 15 (IQR 2–23). A total of 37 patients (28.7%) had 10–20% FB, and 26 (20.2%) had >20% FB. Greater than 20% FB was associated with an increased likelihood of an additional PICU day (adjusted incident rate ratio [aIRR] 1.62, 95% CI: 1.18–2.24), an additional hospital day (aIRR 1.39, 95% CI: 1.10–1.77), and lower likelihood of a VFD at 28 days (aIRR 0.85, 95% CI: 0.74–0.97). There were no differences between groups in the likelihood of postoperative complications.

Conclusions: In pediatric LT recipients, >20% FB at 72 h postoperatively is associated with increased morbidities, independent of age and severity of illness. Additional studies are needed to explore the impact of fluid management strategies on outcomes.

KEYWORDS
fluid overload, fluid therapy, pediatric intensive care unit, postoperative management, solid organ transplant

Abbreviations: AKI, acute kidney injury; FB, fluid balance; GRWR, graft-to-recipient weight ratio; IRR, incident rate ratio; KDIGO, Kidney Disease Improving Global Outcomes Nonprofit Organization; LT, [orthotopic] liver transplant; POD, postoperative day; PRISM-III, Pediatric Risk of Mortality Score-III; RRT, renal replacement therapy; VFD at 28 days, ventilator-free days at 28 days- integer number of days patient is liberated from ventilator and alive in the first 28 days following liver transplantation.

1 | INTRODUCTION

Liver transplantation (LT) is the standard-of-care therapy for children with end-stage liver disease. During surgery, there are periods of hemodynamic instability with potential significant blood loss, reperfusion phase-induced hypotension frequently requiring active resuscitation, and risk of systemic inflammatory response with endothelial leak and extravascular fluid shifts.[1–3] Pediatric patients are postoperatively admitted the pediatric intensive care unit (PICU), where they receive ongoing resuscitation with close monitoring of hemodynamic status, frequent reassessment of intravascular status, and careful titration of medications.

Studies have investigated the risks for patient morbidity and mortality in the intraoperative period, but there is limited data evaluating risk factors in the immediate postoperative period and how they may contribute to outcomes.[4,5] Positive fluid balance (FB) is well known to be associated with increased morbidity and mortality in other critically ill pediatric populations including patients with shock, acute lung injury, those postoperative from cardiac surgery.[6–10] In adult LT recipients, postoperative positive FB is associated with acute kidney injury (AKI), graft failure, and mortality.[11–13] The effects of postoperative FB have not been studied in pediatric LT recipients.

We sought to describe FB in the postoperative period for pediatric LT recipients and its association with outcomes. We hypothesized that positive FB is common and is associated with poor in-hospital clinical outcomes in pediatric LT recipients.

2 | MATERIALS AND METHODS

We performed a retrospective cohort study of patients 0–18 years-old who underwent a first-time orthotopic LT at a quaternary care free-standing children's hospital in Chicago, IL, USA from January 2009 to December 2018. Patients receiving preoperative renal replacement therapy (RRT), those undergoing repeat LT, initial and repeat LT during the same admission, multivisceral transplant, and those who died prior to postoperative day (POD) 3 were excluded. Data were collected from preexisting data sets and the electronic health record. Procedures were followed in accordance with ethical standards of Ann and Robert H. Lurie Children's Hospital Institutional Review Board (Outcomes Following Liver Transplantation, #2013–15357, approved 2/27/2015), which waived the need for informed consent, and in accordance with the Helsinki Declaration of 1975.

Our primary aim was to describe postoperative FB in pediatric LT recipients. Our secondary aim was to evaluate the relationship between postoperative FB and in-hospital clinical outcomes. Our primary outcome was PICU length of stay (LOS). Secondary outcomes were hospital LOS, ventilator-free days (VFD) at 28 days, in-hospital mortality, day 3 severe AKI, fluid-corrected day 3 severe AKI. Additional outcomes included were postoperative infections, biliary complications, and a vascular complication composite that consisted of postoperative hepatic arterial thrombosis and portal venous thrombosis. We also evaluated the number of repeat operations, time to permanent fascial closure, volume of postoperative blood product received in the first 72 h in mL/kg (excluding routine administration of fresh frozen plasma infusion which is used as drain output replacement at our institution), receipt of diuretics and enteral feeds during the first 72 h postoperatively, and time to full enteral feeds.

We included patient's most immediate preoperative calculated pediatric end-stage liver disease score or model end-stage liver disease score as well as medical priority exceptions recorded for United Network for Organ Sharing, in demographic data. We included each patient's diagnosis categorized into Organ Procurement and Transplantation Network liver diagnosis categories.[14] We characterized the patient's preoperative admission status, whether the patient was home or admitted to the hospital ward or PICU prior to LT, with the latter as a marker of higher acuity of illness or larger disease burden. We defined intraoperative transfusion as the cumulative volume of packed red blood cells and cell saver administered in the operating room, in mL/kg.

FB was defined as the cumulative FB in the first 72 h postoperatively using the patient's pre-transplant weight as their baseline weight in a formula described by Goldstein et al: [(total fluid intake (L) − total fluid output (L))/pre-transplant weight (kg)] × 100.[15] Patients were categorized into one of three groups based on their FB: <10% FB, 10–20% FB, and > 20% FB. These are consistent with FB categories used in other pediatric studies.[6,16,17] We also did an ad hoc analysis with FB as a continuous variable. PICU LOS days were calculated based on postoperative PICU admission, transfer, and discharge dates. Hospital LOS days were calculated using the patient's PICU admission following LT timestamp and their discharge from the hospital timestamp in the medical record.

Day 3 AKI was defined using kidney disease improving global outcomes (KDIGO) creatinine-based criteria. We used the highest serum creatinine level collected 48–72 h following LT compared to baseline creatinine, which was the lowest creatinine recorded in the electronic medical record within 3 months prior to admission. If no baseline creatinine was available, normal values for age and gender were used.[15,18] Day 3 severe AKI was defined as stage 2 or 3 AKI. Fluid-corrected severe AKI was calculated using a fluid-corrected creatinine equation: [fluid-corrected creatinine = serum creatinine * (1 + [net FB/total body water])] where total body water varied by age: 3 months-1 year = 0.8 × weight (kg), 1–2 years = 0.7 × weight (kg), and ≥2 years = 0.6 × weight (kg).[17,19,20] Finally, we performed descriptive subgroup analyses of our cohort by liver diagnosis and preoperative admission status.

2.1 | Statistical analysis

Statistical analyses were performed using Stata 16.1 (StataCorp LP). Statistical significance was set at p-Value <.05. Patient demographic data are displayed by FB percentage groups. Non-normal data are presented as median with interquartile range (IQR) or number with

percentages. Kruskal–Wallis and chi-squared tests were performed to compare FB percentage groups. Bonferroni correction was done to adjust for multiple comparisons. Negative binomial regression was used to explore the relationship between 10–20% FB and > 20% FB and PICU LOS, VFD at 28 days, and hospital LOS. Modified Poisson regression was used to evaluate the relative risk of day 3 severe AKI, day 3 fluid-corrected severe AKI, and postoperative complications including infections, biliary complications, and vascular complications.[21] In multivariate analyses, we adjusted for potential confounders defined a priori of age, Pediatric Risk of Mortality (PRISM)-III score, and preoperative admission status, as these have been shown to be associated with mortality.[22] We also performed an ad hoc analysis investigating the relationship between FB as a continuous variable and the clinical outcomes previously stated. For subgroup analyses, data were presented as median with IQR or number with percentages, Kruskal–Wallis or chi-squared tests were performed to compare FB percentage groups, and Bonferroni correction was used to account for multiple comparisons.

3 | RESULTS

3.1 | Demographics and clinical characteristics

From 2009 to 2018, 158 LTs were performed in 151 children at our institution. A total of 22 patients were excluded due to the following reasons: receiving RRT preoperatively ($n = 12$), repeat LT ($n = 5$), initial and repeat LT during same admission ($n = 2$), multivisceral transplant ($n = 1$), and death prior to POD 3 ($n = 2$). The remaining 129 patients were included in our analyses.

Demographics and clinical characteristics for all patients as well as comparisons between FB strata are shown in Table 1. Median age at LT was 20.8 months (IQR 9.4–105.1), 50.4% ($n = 65$) were female, the most common primary liver diagnosis for LT was biliary atresia (47.3%, $n = 61$), and 30.2% ($n = 39$) were admitted to the hospital or PICU preoperatively. At 72 h postoperatively, 51.2% patients ($n = 66$) had <10% FB, 28.7% patients ($n = 37$) had 10–20% FB, and 20.2% patients ($n = 26$) had >20% FB. Compared to patients with <10% FB, patients with 10–20% and > 20% FB were younger, had higher PRISM-III scores on admission to the PICU, and received a larger volume of intraoperative transfusion.

3.2 | Clinical outcomes

Patients with 10–20% and > 20% FB had a longer median PICU LOS compared with patients who had <10% FB (Table 2, <10%: 6 days [IQR 3–10], 10–20%: 10 days [IQR 5–16], >20%: 12 days [IQR 9–27]). After adjusting for age, PRISM-III score, and preoperative admission status in multivariate analyses, 10–20% and > 20% FB was associated with an increased likelihood of an additional PICU day (Table 3, 10–20%: adjusted incidence rate ratio [aIRR] 1.37, 95% CI: 1.04–1.81; >20%: aIRR 1.62, 95% CI: 1.18–2.24).

In bivariate analyses, there was a significant difference between FB groups for VFD at 28 days and hospital LOS (Table 2). In adjusted multivariate analyses, >20% FB was associated with an increased likelihood of an additional hospital day (aIRR 1.39, 95% CI: 1.10–1.77) as well as fewer VFD at 28 days (Table 3, aIRR 0.85, 95% CI: 0.74–0.97). In ad hoc adjusted multivariate analyses with FB as a continuous variable, FB was associated with an increased likelihood of an additional hospital day as well (Table S6, aIRR 1.03, 95% CI: 1.0001–1.06). Only one patient died during the follow-up period of our study. Therefore, mortality rate and risk were not calculated.

There were no differences between the rates and risk of postoperative infections, biliary complications, or composite vascular complications among FB strata in bivariate and multivariate analyses (Tables S1 and S2). Compared to patients with <10% FB, patients with 10–20% and > 20% FB received diuresis-promoting medications more often during the first 72 h postoperatively (Table S1).

At 72 h postoperatively, 11.6% ($n = 15$) of patients had stage 1 AKI, 7.8% ($n = 10$) had stage 2 AKI, and 5.4% ($n = 7$) had stage 3 AKI. Therefore, 13.2% ($n = 17$) patients had day 3 severe AKI (Table 2). In unadjusted multivariate analyses, 10–20% and > 20% FB was associated with an increased risk of developing day 3 severe AKI compared with <10% FB (Table 3, 10–20%: relative risk [RR] 4.16, 95% CI: 1.13–15.21; >20%: RR 5.92, 95% CI: 1.65–21.28). After adjusting for confounders, there was no difference in the risk of day 3 severe AKI between FB strata (Table 3). However, in ad hoc adjusted multivariate analyses of FB as a continuous variable, higher FB was found to be associated with an increased risk of developing day 3 severe AKI (Table S6, aRR 0.40, 95% CI: 0.36–0.45). When creatinine was adjusted for FB in order to evaluate the fluid-corrected severe AKI, day 3 severe AKI was diagnosed in an additional 6 patients (Table 2, details: Table S3). In total, day 3 fluid-corrected severe AKI was diagnosed in one patient (1.5%) with <10% FB compared with 11 patients (29.7%) with 10–20% FB and 11 patients (42.3%) with >20% FB. In adjusted multivariate regression, 10–20% and > 20% FB was associated with increased risk of day 3 fluid-corrected severe AKI (Table 3, 10–20%: aRR 16.76, 95% CI: 1.95–144.19; >20%: aRR 22.16, 95% CI: 2.40–204.43).

Subgroup bivariate analysis by primary liver diagnosis (Table S4) and preoperative admission status (Table S5) had similar findings to the entire cohort. There was a significant difference between FB groups for day 3 fluid-correct AKI among all liver diagnosis subgroups (biliary atresia, metabolic diseases, and malignant neoplasms diagnoses) and patients home preoperatively. In addition, patients home preoperatively had a difference between FB groups for PICU LOS, hospital LOS, and VFD at 28 days. In the metabolic diseases subgroup, there was a difference between FB groups for PICU LOS and VFD at 28 days.

4 | DISCUSSION

In this retrospective single-center study of pediatric LT recipients, we found independent associations between positive FB and poor

TABLE 1 Pediatric liver transplant recipient demographic and clinical characteristics by cumulative fluid balance strata.

Demographics and clinical characteristics	Total ($n = 129$)	<10% FB ($n = 66$)	10–20% FB ($n = 37$)	>20% FB ($n = 26$)	*p*-Value
Age, months, *median* (*IQR*)	20.8 (9.4–105.1)	39.9 (15.7–134.3)	12.0 (8.8–80.3)	8.9 (6.3–18.7)	<.001
Immediate preoperative weight, kg, *median* (*IQR*)	11.2 (7.4–24.6)	15.1 (9.3–32.4)	9.4 (6.8–21.9)	7.5 (6.3–10.4)	<.001
Female sex, *n* (%)	65 (50.4)	38 (57.6)	21 (56.8)	6 (23.1)	.008
Diagnosis, *n* (%)					
Non-cholestatic cirrhosis	8 (6.2)	2 (3.0)	3 (8.1)	3 (11.5)	0
Cholestatic liver disease/cirrhosis	6 (4.7)	4 (6.1)	1 (2.7)	1 (3.9)	
Biliary atresia	61 (47.3)	27 (40.9)	21 (56.8)	13 (50.0)	
Acute hepatic necrosis	5 (3.88)	4 (6.1)	1 (2.7)	0 (0)	
Metabolic diseases	28 (21.7)	15 (22.7)	6 (16.2)	7 (26.9)	
Malignant neoplasms	11 (8.5)	8 (12.1)	2 (5.4)	1 (3.9)	
Other	10 (7.8)	6 (9.1)	3 (8.1)	1 (3.9)	
Calculated PELD/MELD, *median* (*IQR*)	15 (2–23)	10 (0–20)	18 (10–27)	18.5 (−1–24)	.05
Medical priority exceptions, *n* (%)					
Status 1A	9 (7.0)	6 (9.1)	1 (2.7)	2 (7.7)	.5
Status 1B	20 (15.5)	9 (13.6)	6 (16.2)	5 (19.2)	
Donor, graft type, *n* (%)					
Donor, whole	29 (22.5)	21 (31.8)	7 (18.9)	1 (3.9)	.08
Donor, split	48 (37.2)	22 (33.3)	12 (32.4)	14 (53.9)	
Donor, reduced	18 (14.0)	8 (12.1)	5 (13.5)	5 (19.2)	
Living	34 (26.4)	15 (22.7)	13 (35.1)	6 (23.1)	
Calculated PELD/MELD, *median* (*IQR*)	15 (2–23)	10 (0–20)	18 (10–27)	18.5 (−1–24)	.05
GRWR ($n = 97$), %, *median* (*IQR*)	2.9 (1.8–3.8)	2.4 (1.7–3.1)	3.2 (1.8–4.1)	3.7 (2.8–4.5)	.001
PRISM-III, *median* (*IQR*)	9 (7–15)	8 (5–11)	12 (8–16)	14 (7–19)	.002
Admitted preoperatively, *n* (%)	39 (30.2)	13 (19.7)	15 (40.5)	11 (42.3)	.03
Intraoperative blood transfusion volume, mL/kg, *median* (*IQR*)	53.6 (29.8–110.3)	39.4 (24.0–64.3)	95.7 (37.9–140.4)	101.2 (60.6–143.1)	<.001

Note: Cumulative fluid balance was measured in the first 72 h postoperatively. Kruskal-Wallis and chi-square were used to generate *p*-Value, as appropriate.

Abbreviations: FB, fluid balance; GRWR, graft-to-recipient weight ratio; MELD, model end-stage liver disease score; PELD, pediatric end-stage liver disease score; PRISM-3, Pediatric Risk of Morality Score-3.

in-hospital clinical outcomes. After adjusting for covariates including severity of illness, we found that >20% FB at 72 h postoperative was associated with an increased the likelihood of longer PICU and hospital LOS, day 3 fluid-corrected AKI, and decreased number of VFD at 28 days. Furthermore, in subgroup analyses by primary liver diagnosis and preoperative admission status, the relationship between higher positive FB and in-hospital clinical outcomes remained.

Similar to our findings, Zhang et al demonstrated in adult LT that FB at 72 h postoperatively is a risk factor for development of AKI and postoperative complications.[11] Furthermore, Jeong et al demonstrated in a large cohort of LT patients that early postoperative weight gain was associated with early allograft dysfunction, graft failure, and mortality.[12,16] Similar to these adult LT recipient studies, as well as research done in other populations of critically ill children, we found that positive FB after pediatric LT is associated with a more complicated and prolonged postoperative course.[6,7,9,10,23] Positive FB puts patients at risk for several multiorgan system complications including pulmonary edema with prolonged intubation and oxygen requirement, interstitial edema with delayed wound healing, and bowel wall edema with impaired bowel function and prolonged receipt of IV fluids or parenteral nutrition, contributing to prolonged postoperative ICU and hospital LOS.[24]

Vascular thromboses are a feared complication following solid organ transplantation. In pediatric LT, thromboses are associated with graft failure and mortality.[25,26] Studies show that LT recipients are hypercoagulable for the first 30 days following transplant.[27] Hypercoagulability may contribute to sluggish arterial and venous blood flow through the transplanted allograft anastomoses. Strategies to maintain a positive FB have been historically used to potentially mitigate the risk of thromboses; however, wide variability exists between pediatric LT programs in postoperative management, and there are no universally adopted guidelines for antithrombotic or postoperative fluid management.[28,29] In this retrospective study,

TABLE 2 Pediatric liver transplant recipient bivariate analyses of outcomes by cumulative fluid balance strata.

Outcome	Total ($n = 129$)	<10% FB ($n = 66$)	10–20% FB ($n = 37$)	>20% FB ($n = 26$)	*p*-Value
PICU LOS, in days, *median* (*IQR*)	8 (5–15)	6 (3–10)	10 (5–16)	12 (9–27)	<.001
Hospital LOS, in days, *median* (*IQR*)	15.0 (11.1–22.5)	13.5 (10.0–18.0)	14.7 (12.8–25)	20.3 (16–33)	<.001
Ventilator-free days at 28 days, *median* (*IQR*)	25 (19–27)	27 (24–27)	22 (16–27)	20 (12–24)	<.001
In-hospital mortality, *n* (%)	1 (0.8)	0 (0)	0 (0)	1 (3.9)	.1
Day 3 severe AKI (stage 2 or 3), *n* (%)	17 (13.2)	3 (4.6)	7 (18.9)	7 (26.9)	.008
Day 3 AKI					
Stage 1, *n* (%)	15 (11.6)	5 (7.6)	6 (16.2)	4 (15.4)	.02
Stage 2	10 (7.8)	3 (4.6)	4 (10.8)	3 (11.5)	
Stage 3	7 (5.4)	0	3 (8.1)	4 (15.4)	
Day 3 fluid-corrected severe AKI (stage 2 or 3), *n* (%)	23 (17.8)	1 (1.5)	11 (29.7)	11 (42.3)	<.001
New postoperative RRT, *n* (%)	2 (1.6%)	0	0	2 (7.7%)	.02

Note: Cumulative fluid balance was measured in the first 72 h postoperatively. Kruskal-Wallis and chi-square were used to generate *p*-Value, as appropriate. PICU length of stay is number of days in hospital following transplant, hospital length of stay is time between post-transplant admission timestamp and discharge timestamp. AKI staging is based on KDIGO creatinine-based criteria. Fluid-corrected severe AKI was determined using a fluid-corrected creatinine equation and KDIGO creatinine-based criteria.

Abbreviations: AKI, acute kidney injury; FB, fluid balance; LOS, length of stay; RRT, renal replacement therapy.

TABLE 3 Pediatric liver transplant recipient multivariate analyses of outcomes by cumulative fluid balance strata.

Outcome	Cumulative fluid balance	Unadjusted IRR	Adjusted IRR
PICU LOS, in days	<10%	Reference	Reference
	10–20%	1.63 (1.22–2.17)	1.37 (1.04–1.81)
	>20%	2.22 (1.61–3.06)	1.62 (1.18–2.24)
Hospital LOS, in days	<10%	Reference	Reference
	10–20%	1.30 (1.06–1.60)	1.17 (0.95–1.43)
	>20%	1.70 (1.35–2.14)	1.39 (1.10–1.77)
Ventilator-free days at 28 days	<10%	Reference	Reference
	10–20%	0.84 (0.74–0.96)	0.94 (0.84–1.05)
	>20%	0.71 (0.61–0.83)	0.85 (0.74–0.97)
Outcome	Cumulative fluid balance	Unadjusted RR	Adjusted RR
Day 3 severe AKI (stage 2 or 3)	<10%	Reference	Reference
	10–20%	4.16 (1.13–15.21)	2.75 (0.67–11.25)
	>20%	5.92 (1.65–21.28)	3.17 (0.78–12.90)
Day 3 fluid-corrected severe AKI (stage 2 or 3)	< 10%	Reference	Reference
	10–20%	19.62 (2.62–147.17)	16.76 (1.95–144.19)
	>20%	27.92 (3.76–207.14)	22.16 (2.40–204.43)

Note: Cumulative fluid balance was measured in the first 72 postoperative hours. Negative binomial regression analyses were done to evaluate incident rate ratio in continuous variables, modified Poisson regression analyses were done to evaluate relative risk in categorical variables. PICU length of stay is number of days in hospital following transplant, hospital length of stay is time between post-transplant admission timestamp and discharge timestamp. AKI staging is based on KDIGO creatinine-based criteria. Fluid-corrected severe AKI was determined using a fluid-corrected creatinine equation and KDIGO creatinine-based criteria. Adjusted analyses accounted for a-priori-defined variables of age, Pediatric Risk of Mortality (PRISM)-III score, preoperative location.

Abbreviations: AKI, acute kidney injury; IRR, incident rate ratio; LOS, length of stay; RR, relative risk.

we found no association between postoperative FB and postoperative vascular complications (Table S1, $p = .5$).

Growing evidence of the deleterious effects of positive FB in critically ill children, including the findings of this study, suggest that close monitoring of postoperative FB is important and that intervention in postoperative fluid management with attention to potential associations with postoperative complications should be evaluated.[16] A single-center feasibility randomized controlled trial currently ongoing is investigating goal-directed fluid therapy in adult LT recipients using stroke volume optimization.[30] Goal-directed fluid therapy and advanced coagulation monitoring tools such as thromboelastography may allow for precise management of FB, hemodynamics, and hypercoagulable state in pediatric LT recipients. Further study in this area has the potential to lead to evidence-based postoperative management.[30]

Limitations of our study include that it was a retrospective review at a single center. Our cohort of donor types may be different than other pediatric centers and, therefore, not as generalizable to these institutions. We chose the first 3 PODs as the data collection timepoint to reflect completion of the initial resuscitation period following transplant; however it is possible that this does not represent the peak cumulative FB or peak serum creatinine, and we may have missed a postoperative time point where FB was more strongly associated with outcomes.[31] We used KDIGO creatinine-based criteria to diagnose AKI. Although creatinine is the best widely available biomarker currently, measurements of creatinine have a number of limitations in patients with acute or chronic liver failure. Creatine is produced by the liver and stored in muscle; children with liver disease may have decreased production of creatine, protein-malnutrition, and decreased muscle use from chronic illness, potentially making creatinine a less accurate measure of renal function in this population.[32–34] The multivariate analyses of FB and day 3 fluid-corrected severe AKI (Table 3) had wide confidence intervals, which may be due to our relatively small sample size and suggests less precision in these particular findings. Intraoperative fluid administration was not included in our model in order to isolate postoperative fluid management. One potential minor limitation of this approach is that intraoperative fluid administration may have impacted fluid management and clinical decision making postoperatively, and this potential impact was not able to be accounted for. Finally, we adjusted for severity of illness by including PRISM-III score in our adjusted multivariate analyses, which is a highly validated and commonly used severity of illness score in general PICU populations, but it is possible that other variables may better predict disease severity in pediatric LT recipients.[35]

5 | CONCLUSIONS

Our study reports that positive FB in the first 72 h postoperatively is common and associated with poor in-hospital clinical outcomes in pediatric LT recipients. This is consistent with other critically ill pediatric populations and cohorts of adult LT recipients. Prospective studies are needed to confirm our findings, determine the long-term impact of positive FB in this population, and investigate postoperative LT fluid management strategies.

ACKNOWLEDGMENTS

Thank you to Jacob Schauer for his review of statistical methods.

CONFLICT OF INTEREST STATEMENT

None to report.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Jessica M. Winters https://orcid.org/0000-0003-4437-0890
Catherine A. Chapin https://orcid.org/0000-0003-3339-9372
Caroline P. Lemoine https://orcid.org/0000-0002-3422-6740
Riccardo Superina https://orcid.org/0000-0003-3076-2244
Katherine A. Brandt https://orcid.org/0000-0002-5790-1972
L. Nelson Sanchez-Pinto https://orcid.org/0000-0002-7434-6747
Matthew F. Barhight https://orcid.org/0000-0002-1954-5823

REFERENCES

1. Aggarwal S, Kang Y, Freeman JA, Fortunato FL Jr, Pinsky MR. Postreperfusion syndrome: hypotension after reperfusion of the transplanted liver. *J Crit Care*. 1993;8(3):154-160.
2. Bellamy MC, Galley HF, Webster NR. Changes in inflammatory mediators during orthotopic liver transplantation. *Br J Anaesth*. 1997;79(3):338-341.
3. Siniscalchi A, Gamberini L, Laici C, et al. Post reperfusion syndrome during liver transplantation: from pathophysiology to therapy and preventive strategies. *World J Gastroenterol*. 2016;22(4):1551-1569.
4. Hilmi I, Horton CN, Planinsic RM, et al. The impact of postreperfusion syndrome on short-term patient and liver allograft outcome in patients undergoing orthotopic liver transplantation. *Liver Transplant*. 2008;14:504-508.
5. Reich DL, Wood RK, Emre S, et al. Association of Intraoperative Hypotension and Pulmonary Hypertension with adverse outcomes after orthotopic liver transplantation. *J Cardiothorac Vasc Anesth*. 2003;17(6):699-702.
6. Bhaskar P, Dhar AV, Thompson M, Quigley R, Modem V. Early fluid accumulation in children with shock and ICU mortality: a matched case–control study. *Intensive Care Med*. 2015;41(8):1445-1453.
7. Valentine SL, Sapru A, Higgerson RA, et al. Fluid balance in critically ill children with acute lung injury. *Crit Care Med*. 2012;40(10):2883-2889.
8. Willson DF, Thomas NJ, Tamburro R, et al. The relationship of fluid administration to outcome in the pediatric calfactant in acute respiratory distress syndrome trial. *Pediatr Crit Care Med*. 2013;14(7):666-672.
9. Hassinger AB, Wald EL, Goodman DM. Early postoperative fluid overload precedes acute kidney injury and is associated with higher morbidity in pediatric cardiac surgery patients. *Pediatr Crit Care Med*. 2014;15(2):131-138.
10. Seguin J, Albright B, Vertullo L, et al. Extent, risk factors, and outcome of fluid overload after pediatric heart surgery. *Crit Care Med*. 2014;42(12):2591-2599.

11. Zhang S, Ma J, An R, et al. Effect of cumulative fluid balance on acute kidney injury and patient outcomes after orthotopic liver transplantation: a retrospective cohort study. *Nephrol Ther*. 2020;25(9):700-707.
12. Jeong HW, Jung KW, Kim SO, et al. Early postoperative weight gain is associated with increased risk of graft failure in living donor liver transplant recipients. *Sci Rep*. 2019;9(1):1-9. doi:10.1038/s41598-019-56543-3
13. Codes L, de Souza YG, D Oliveira RAC, et al. Cumulative positive fluid balance is a risk factor for acute kidney injury and requirement for renal replacement therapy after liver transplantation. *World J Transplant*. 2018;8(2):44-51.
14. Liver - OPTN. Organ Procurement and Transplantation Network. Available: https://optn.transplant.hrsa.gov/patients/by-organ/liver/. [Accessed: 10-Nov-2022]
15. Goldstein SL, Currier H, Graf JM, Cosio CC, Brewer ED, Sachdeva R. Outcome in children receiving continuous venovenous hemofiltration. *Pediatrics*. 2001;107(6):1309-1312.
16. Alobaidi R, Morgan C, Basu RK, et al. Association between fluid balance and outcomes in critically ill children: a systematic review and meta-analysis. *JAMA Pediatr*. 2018;172(3):257-268.
17. Gist KM, Selewski DT, Brinton J, Menon S, Goldstein SL, Basu RK. Assessment of the independent and synergistic effects of fluid overload and acute kidney injury on outcomes of critically ill children. *Pediatr Crit Care Med*. 2020;21(2):170-177.
18. Hoste L, Dubourg L, Selistre L, et al. A new equation to estimate the glomerular filtration rate in children, adolescents and young adults. *Nephrol Dial Transplant*. 2014;29(5):1082-1091.
19. Liu KD, Thompson BT, Ancukiewicz M, et al. Acute kidney injury in patients with acute lung injury: impact of fluid accumulation on classification of acute kidney injury and associated outcomes. *Crit Care Med*. 2011;39(12):2665-2671.
20. Basu RK, Andrews A, Krawczeski C, Manning P, Wheeler DS, Goldstein SL. Acute kidney injury based on corrected serum creatinine is associated with increased morbidity in children following the arterial switch operation. *Pediatr Crit Care Med*. 2013;14(5):e218-e224.
21. Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159(7):702-706.
22. Venick RS, Farmer DG, McDiarmid SV, et al. Predictors of survival following liver transplantation in infants: a single-center analysis of more than 200 cases. *Transplantation*. 2010;89(5):600-605.
23. Arikan AA, Zappitelli M, Goldstein SL, Naipaul A, Jefferson LS, Loftis LL. Fluid overload is associated with impaired oxygenation and morbidity in critically ill children. *Pediatr Crit Care Med*. 2012;13(3):253-258.
24. Claure-Del Granado R, Mehta RL. Fluid overload in the ICU: evaluation and management. *BMC Nephrol*. 2016;17(1):1-9.
25. Ebel NH, Hsu EK, Dick AAS, Shaffer ML, Carlin K, Horslen SP. Decreased incidence of hepatic artery thrombosis in pediatric liver transplantation using technical variant grafts: report of the Society of Pediatric Liver Transplantation Experience. *J Pediatr*. 2020;226:195-201.e1.
26. Stevens JP, Xiang Y, Leong T, Naik K, Gupta NA. Portal vein complications and outcomes following pediatric liver transplant: data from the Society of Pediatric Liver Transplantation. *Liver Transpl*. 2022;0–3:1196-1206.
27. Werner MJM, de Meijer VE, Adelmeijer J, et al. Evidence for a rebalanced hemostatic system in pediatric liver transplantation: a prospective cohort study. *Am J Transplant*. 2020;20(5):1384-1392.
28. Calinescu AM, Karam O, Wilde JCH, Ansari M, McLin VA, Wildhaber BE. International survey on anticoagulation and antiplatelet strategies after pediatric liver transplantation. *Pediatr Transplant*. 2019;23(1):1-9.
29. Maue DK, Mangus RS, Lutfi R, et al. Practice variation in the immediate postoperative care of pediatric liver transplant patients: framework for a national consensus. *Pediatr Transplant*. 2021;25(5):1-7.
30. Froghi F, Koti R, Gurusamy K, et al. Cardiac output optimisation following liver transplant (COLT) trial: study protocol for a feasibility randomised controlled trial. *Trials*. 2018;19(1):1-9.
31. Lima L, Menon S, Goldstein SL, Basu RK. Timing of fluid overload and association with patient outcome. *Pediatr Crit Care Med*. 2021;22(1):114-124.
32. Slack A, Yeoman A, Wendon J. Renal dysfunction in chronic liver disease. *Crit Care*. 2010;14(2):214.
33. Borrows R, Cockwell P. Measuring renal function in solid organ transplant recipients. *Transplantation*. 2007;83(5):529-531.
34. Lacquaniti A, Campo S, Casuscelli Di Tocco T, et al. Acute and chronic kidney disease after pediatric liver transplantation: An underestimated problem. *Clin Transplant*. 2020;34(11):1-11.
35. Ferah O, Akbulut A, Açık ME, et al. Scoring systems and postoperative outcomes in pediatric liver transplantation. *Transplant Proc*. 2019;51(7):2430-2433.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Winters JM, Brocks R, Chapin CA, et al. Fluid balance in pediatric postoperative liver transplant recipients. *Pediatric Transplantation*. 2023;27:e14499. doi:10.1111/petr.14499