

Early Postoperative Fluid Overload Precedes Acute Kidney Injury and Is Associated With Higher Morbidity in Pediatric Cardiac Surgery Patients

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Objective: Fluid overload has been independently associated with increased morbidity and mortality in pediatric patients with renal failure, acute lung injury, and sepsis. Pediatric patients who undergo cardiopulmonary bypass are at risk for poor cardiac, pulmonary, and renal outcomes. They are also at risk of fluid overload from cardiopulmonary bypass, which stimulates inflammation, release of antidiuretic hormone, and capillary leak. This study tested the hypothesis that patients with fluid overload in the early postcardiopulmonary bypass period have worse outcomes than those without fluid overload. We also examined the timing of the association between postcardiopulmonary bypass acute kidney injury and fluid overload.

Design, Setting, and Patients: Secondary analysis of a prospective observational study of 98 pediatric patients after cardiopulmonary bypass at a tertiary care, academic, PICU.

Interventions: None.

Measurements and Main Results: Early postoperative fluid overload, defined as a fluid balance 5% above body weight by the end of postoperative day 1, occurred in 30 patients (31%). Patients with early fluid overload spent 3.5 days longer in the hospital, spent 2 more days on inotropes, and were more likely to require prolonged

mechanical ventilation than those without early fluid overload (all $p < 0.001$). Fluid overload was associated with the development of acute kidney injury and more often preceded it than followed it. Conversely, acute kidney injury was not associated with more fluid accumulation. Patients with fluid overload were administered higher fluid volume over the study period, 395.4 ± 150 mL/kg vs. 193.2 ± 109.1 mL/kg ($p < 0.001$), and had poor urinary response to diuretics. Cumulative fluid administered was an excellent predictor of pediatric-modified Risk, Injury, Failure, Loss, and End-stage "Failure" (area under the receiver-operating characteristic curve, 0.963; 95% CI, 0.916–1.000; $p = 0.002$).

Conclusions: Early postoperative fluid overload is independently associated with worse outcomes in pediatric cardiac surgery patients who are 2 weeks to 18 years old. Patients with fluid overload have higher rates of postcardiopulmonary bypass acute kidney injury, and the occurrence of fluid overload precedes acute kidney injury. However, acute kidney injury is not consistently associated with fluid overload. (*Pediatr Crit Care Med* 2014; 15:131–138)

Key Words: acute kidney injury; cardiac surgery; children; critical illness; fluid balance; mechanical ventilation

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The degree of fluid overload (FO) at initiation of continuous renal replacement therapy (RRT) is an independent predictor of mortality (1–5), and pediatric and adult studies have demonstrated the detrimental effect of an excessive positive fluid balance on a variety of disease outcomes. Retrospective adult studies show that elevated net fluid balance is associated with the development of acute respiratory distress syndrome (6, 7) and, prospectively, that conservative fluid management in acute lung injury can shorten length of mechanical ventilation (LMV) and length of stay (LOS) (8, 9). Similarly, positive fluid balance is associated with worse oxygenation index, fewer ventilator-free days, and difficulty with ventilator weaning in pediatric patients with acute lung injury (10–12). Patients with septic shock or multiple organ failure and FO have higher mortality rates than those without FO (13, 14).

FO is a common occurrence in the early postoperative period in pediatric cardiac surgery patients (15, 16). Low cardiac output syndrome (LCOS), systemic inflammation, release of antidiuretic

hormone, and acute kidney injury (AKI) all lead to fluid accumulation. In turn, FO impacts pulmonary function, renal function, and nutritional status to complicate postoperative recovery. One retrospective study found that infants 72 hours after cardiac surgery with a positive fluid balance had 10 times higher odds of prolonged mechanical ventilation (PMV) than infants without a positive fluid balance (15). These data were supported by a recent prospective observational study that reported greater than 10% FO in 49 infants in the first 3 days after cardiopulmonary bypass (CPB) was associated with poor outcomes including need for RRT, extended LOS, PMV, and death (16).

To our knowledge, no study has investigated the timing of FO and AKI in pediatric cardiac surgery patients (17). Our study tested the hypothesis that pediatric cardiac surgery patients with FO by the end of the first postoperative day (POD) have poorer clinical outcomes than patients without FO in the same time period. We also examined the timing of AKI and FO, to further describe any association between fluid administered, diuretic dose, and AKI in this cohort.

MATERIALS AND METHODS

This study was a secondary analysis of a prospective observational study of pediatric cardiac surgery patients which investigated the diagnostic performance of two biomarkers for post-CPB AKI (18, 19). Of the original 100 subjects, 98 had complete fluid balance data and were included in this study. All patients were enrolled from a single, academic, pediatric tertiary care hospital from August 2009 to July 2010. This study was approved by the Institutional Review Board of Children's Memorial Hospital in Chicago, IL. Care was not impacted by study participation.

Eligible patients were 2 weeks to 18 years old with cardiac disease requiring corrective or palliative cardiac surgery involving CPB. Patients younger than 2 weeks were not included due to the poor clinical utility of serum creatinine (SCr) in the immediate neonatal period. Any patient with preexisting renal failure requiring any type of RRT prior to surgery was also excluded.

Preoperative data collected include age on day of surgery, weight, height, sex, and presence of a cyanotic cardiac lesion. Operative data included Risk Adjustment for Congenital Heart Surgery (RACHS-1) score (20), CPB time, aortic cross-clamp time, blood pressure on CPB, volume removed by ultrafiltration (UF), and modified ultrafiltration (MUF) if performed. Postoperative data included total IV and enteral fluids received each day, urine produced, net daily fluid balance (recorded outputs include fluid removed by any drain or chest tube, urine or stool, and blood for testing or lost from hemorrhage), inotrope score (IS) (21), daily range of renal near-infrared regional spectroscopy (NIRS) readings (Somanetics Corporation, Troy, MI), daily furosemide or furosemide-equivalent dose (if bumetanide used instead of furosemide, the total bumetanide dose was multiplied by a factor of 40) (22), and mean arterial blood pressure range. Blood urea nitrogen, SCr, and cystatin C were obtained at preoperative baseline, immediately postoperatively, and every morning through POD 4. These values were used to calculate a baseline and daily estimated glomerular filtration rate (eGFR) using the updated Schwartz equation (23).

Definitions and Outcomes

Early postoperative FO was defined as a positive fluid balance greater than 5% above body weight starting at PICU admission after surgery up to midnight of POD 1. Percent FO was calculated as $([\text{Volume of fluid in (L)} - \text{Volume of fluid out (L)}] / \text{weight}) \times 100$. Using this equation, 5% FO is equivalent to a positive fluid balance of 50 mL/kg. This threshold was recommended by Basu et al (24) as a cutoff point for higher AKI risk in "very high-risk patients," that is, those requiring mechanical ventilation and one or more vasoactive agents.

Clinical outcomes measured included mortality, LMV, LOS in the ICU (LOS-ICU) and in the hospital, duration of vasoactive medications, and severity of AKI. PMV was defined as requiring mechanical ventilation for longer than 2 days. This threshold was selected after data collection was complete as more than 75% of study patients were ventilator free by POD 2.

Severity of AKI was characterized by the pediatric-modified Risk, Injury, Failure, Loss, and End-stage (pRIFLE) criteria (25). Using urine output and changes in glomerular filtration rate (GFR), the pRIFLE criteria categorize the severity of AKI as Risk, Injury, Failure, Loss, or End stage. Since no patient in this study developed oliguria, we used changes in GFR alone to define AKI. Previous studies have validated this approach (25). "Risk" was defined as greater than 25% decrease in eGFR from baseline to the lowest postoperative value, "Injury" as more than 50% decrease in eGFR, and "Failure" as more than 75% decrease or an absolute eGFR less than 35 mL/min/1.73 m². eGFR was calculated using the updated Schwartz equation (23). All SCr values were adjusted for fluid balance using the equation outlined by Liu et al (26): $\text{Adjusted SCr} = \text{measured SCr} \times (1 + [\text{cumulative net fluid balance}/\text{total body water}])$. Total body water was calculated as $0.6 \times \text{body weight}$, in kilograms. Cumulative fluid balance was reported in liters.

Statistical Methods

Continuous data are presented as medians with interquartile ranges (IQR, 1–3) or as means with \pm SD if normally distributed. Continuous data between groups were compared using Mann-Whitney *U* test or Kruskal-Wallis test as appropriate. Associations between two continuous variables were examined using Spearman rho when nonnormally distributed and Pearson correlation when normally distributed. Receiver-operating characteristic (ROC) curve analysis was performed using the area under the ROC curve (AUC-ROC) to determine predictive value.

Multivariable analysis was performed using a logistic regression model for the presence or absence of PMV and general linear models for the continuous outcomes of LOS in the hospitals and duration of vasoactive medications. No multivariable analysis was performed for LOS-ICU as many nonclinical factors determine time of ICU discharge. Variables found to be significantly associated with FO in the univariate analysis of each outcome were evaluated for inclusion in these models using odds ratio (OR) and variable estimates; as a result, not all outcome models included the same variables.

TABLE 1. Characteristics of Patients With and Without Fluid Overload

Variable	Early FO (<i>n</i> = 30)	No Early FO (<i>n</i> = 68)	<i>p</i>
Age (mo)	6.5 (4–29.5)	60.5 (6.3–143.5)	< 0.001 ^a
Male, <i>n</i> (%)	19 (63.3)	34 (50)	0.222 ^b
Weight (kg)	6.8 (5.2–12.7)	16.5 (6.9–40.4)	< 0.001 ^a
Baseline estimated glomerular filtration rate (mL/min/1.73 m ²)	73 (63–93)	97 (81–109)	< 0.001 ^a
Cyanotic lesion, <i>n</i> (%)	19 (63.3)	25 (36.8)	0.015 ^b
Risk Adjustment for Congenital Heart Surgery-1 score			0.020 ^b
1–2, <i>n</i> (%)	10 (23.3)	40 (58.8)	
3–6, <i>n</i> (%)	20 (66.7)	28 (41.2)	
Cardiopulmonary bypass time (min)	132.5 (76.5–175.5)	94.5 (69.3–137.3)	0.028 ^a
Aortic cross-clamp time (min)	77 (49–115.5)	56.5 (26.3–82)	0.058 ^a
Ultrafiltration and modified ultrafiltration removal volume (mL/kg)	155.3 (81.9–209.3)	79.5 (45.8–115.8)	0.001 ^a
Peak inotrope score	10.5 (10.5–17.5)	10.5 (7.5–11.5)	< 0.001 ^a
Lowest daily urine output (mL/kg/hr)	1.57 (1.31–2.14)	1.35 (1.01–2.03)	0.050 ^a
Maximum furosemide dose (mg/kg/d)	3.7 (3.14–5.46)	2.63 (1.16–3.73)	< 0.001 ^a
Peak weight gain (%)	9.2 (3.6–13.9)	2.45 (0.0–4.9)	< 0.001 ^a
Cumulative POD 1 fluid balance (mL/kg)	80.2 (68.5–99.5)	24.5 (6.0–34.5)	< 0.001 ^a
Cumulative POD 2 fluid balance (mL/kg)	75.1 (43–90.6)	17.2 (1.9–34.0)	< 0.001 ^a
Cumulative POD 3 fluid balance (mL/kg)	56.6 (25.1–95.1)	10.2 (–6.5 to 33.3)	< 0.001 ^a
Cumulative POD 4 fluid balance (mL/kg)	44.9 (1.8–91.1)	22.7 (–16.2 to 53)	0.043 ^a

FO = fluid overload, POD = postoperative day.

^a*p* values obtained using Mann-Whitney *U* test.

^b*p* values obtained using chi-square comparisons.

Values are reported as medians with interquartile range or absolute values with percentage.

Variables were included in the model in a forward stepwise approach. Logistic regression results are presented as adjusted ORs with 95% CIs. For the general linear models evaluating the association between FO and LOS in the hospitals and FO and duration of vasoactive medications, variables with a parameter estimate *p* value of less than 0.15 were included. Effect modification or confounding was examined using Cochran-Mantel-Haenszel test.

Significance was set at a *p* value of less than 0.05. All univariable statistical calculations were performed using SPSS software, version 12.0 (SPSS, Chicago, IL). Multivariable models were built using SAS (SAS Institute, Cary, NC).

RESULTS

Early postoperative FO developed in 30 patients (31%). **Table 1** shows the characteristics of those with and without early FO. Patients with early FO were younger, had a lower baseline eGFR, and were more likely to have a cyanotic heart lesion. Early FO patients were also more likely to have surgery with a higher RACHS-1 score, longer CPB time, and more fluid removed by UF and MUF than those without early FO.

FO and Clinical Outcomes

Patients with early FO did worse in every clinical outcome measured (**Table 2**). No patients died nor were placed on any form of RRT. Median LOSs in the ICU and hospital were 3.5 days longer for those with early FO when compared with those without early FO (*p* < 0.001). After adjusting for CPB time, presence of a cyanotic lesion, and maximum daily furosemide dose, early FO remained a significant predictor for LOS in the hospital (*F* = 9.60, *r*² = 0.2252, *p* = 0.0026).

Patients with early FO had a median of 2 days longer on vasoactive medications than those without early FO: first inotrope-free day was POD 5 (IQR, 4–5) vs. POD 3 (IQR, 3–4) (*p* < 0.001). After adjusting for age, presence of a cyanotic lesion, RACHS-1 score more than 3, CPB time, aortic cross-clamp time, baseline eGFR, and pRIFLE category, early FO remained a significant predictor for duration of vasoactive medications (*F* = 27.67, *r*² = 0.2237, *p* < 0.001).

Median LMV was statistically higher in those with early FO when compared with those without (*p* = 0.003). The total range for LMV in early FO patients was 0–24 days compared with 0–4 days for those without early FO. Patients with early FO had a higher prevalence of PMV than patients without early FO

TABLE 2. Clinical Outcomes in Patients With and Without Fluid Overload Early After Cardiac Surgery

Variable	Early FO (n = 30)	No Early FO (n = 68)	p
Length of mechanical ventilation (d)	1 (1–5.25)	1 (1–1)	0.003 ^a
Total range	0–24	0–4	
Prolonged mechanical ventilation (> 2 d)	13 (43.3)	6 (8.8)	< 0.001 ^b
LOS-ICU (d)	9 (5.75–12.3)	5.5 (4–8)	< 0.001 ^a
LOS in the hospital (d)	10 (7.8–15.8)	6.5 (5–8)	< 0.001 ^a
First inotrope-free postoperative day	5 (4–5)	3 (3–4)	< 0.001 ^a
Pediatric-modified Risk, Injury, Failure, Loss, and End-stage criteria			
None	17 (56.7)	45 (66.2)	0.023 ^c
Risk	8 (26.7)	21 (30.9)	
Injury	1 (3.3)	2 (2.9)	
Failure	4 (13.3)	0	

FO = fluid overload, LOS = length of stay.

^ap values were obtained using Mann-Whitney U test.

^bp values were obtained using chi-square test.

^cp values were obtained using Kruskal-Wallis comparisons.

Values are presented as median (interquartile range) or absolute number (%).

(43% vs 8.8%) ($p < 0.001$). Fluid balance by POD 1 was a fair predictor of PMV (AUC-ROC, 0.775; 95% CI, 0.665–0.886; $p < 0.001$). After adjusting for age, CPB time, presence of a cyanotic lesion, baseline eGFR, and pRIFLE category in a logistic regression model, only CPB time and age remained as significant predictors of PMV (Table 3).

CPB was an effect modifier of the association between early FO and PMV. Pediatric cardiac surgery patients with longer CPB times (> 100 min) and FO had double the risk of PMV (relative risk [RR], 6.86; 95% CI, 1.88–24.97; $p = 0.002$) than those with shorter CPB times (< 100 min) and FO (RR, 3.70; nonsignificant).

FO and Hemodynamic Variables

Patients with early FO had a statistically higher peak IS (10.5 [10.5–17.5] vs 10.5 [7.5–11.5]; $p = 0.002$) than those without early FO. During every POD, those with early FO had a higher median IS than those without: POD 0, 10.5 (10.5–15.5)

vs. 10.5 (7.5–11.3) ($p < 0.001$); POD 1, 10.5 (8.4–15.4) vs. 7.7 (5.3–10.5) ($p < 0.001$); POD 2, 10.2 (4.5–14.2) vs. 4.5 (1.2–7.5) ($p < 0.001$); POD 3, 9.4 (2–12.6) vs. 0 ($p < 0.001$); and POD 4 6.2 (0–12) vs. 0 ($p < 0.001$). Patients with early FO were more likely to need an escalation in inotropic support from POD 0 to POD 1 than those without FO (20% vs 4.4%) ($p = 0.014$).

Median systemic ventricular ejection fraction (EF) did not differ between those with and without early FO (62.5% [56.3–69] vs 64% [58–67]; $p = 0.908$). Over the entire study period, median Svo₂ was lower in patients with early FO than in those without (Svo₂, 66.4% [IQR, 61.9–71.4] vs 72% [IQR, 66–80.2]; $p = 0.003$). Lowest daily Svo₂ only reached statistical difference on POD 0 when those with early FO had a median Svo₂ of 69.5% (IQR, 59.4–74.7) and those without early FO had a median Svo₂ of 74.6% (IQR, 58.8–83.5; $p = 0.015$). As Svo₂ was not routinely obtained, there were no other significant differences between those with and without early FO on any other study day.

Lowest daily renal NIRS values did not differ in those with and without early FO. There was no significant correlation between IS and fluid balance, NIRS and fluid balance, NIRS and IS, nor NIRS and EF.

To assess the independent effects of FO and indicators of low cardiac output or hemodynamic instability on morbidity, multivariable analyses including Svo₂, peak IS, low NIRS on POD 1, LCOS, and FO were performed. LCOS was defined as an EF of less than 50% with a normal preoperative EF. Only Svo₂ remained an independent predictor of PMV. Peak IS, low NIRS on POD 1, and LCOS were all independent predictors of LOS in the hospital. FO remained an independent predictor of length of inotrope need after accounting for these indicators of hemodynamic status.

TABLE 3. Multivariable Analysis of the Predictors of Prolonged Mechanical Ventilation

Variable	Adjusted OR (95% CI)	p
Early fluid overload	3.15 (0.58–17.12)	0.1835
Cardiopulmonary bypass time	1.04 (1.02–1.07)	0.0001
Age (mo)	0.98 (0.96–0.99)	0.0277

OR = odds ratio.

p values obtained by logistic regression controlling for presence of a cyanotic lesion, cardiopulmonary bypass time, baseline estimated glomerular filtration rate, and pediatric-modified Risk, Injury, Failure, Loss, and End-stage category.

FO and Timing of AKI

In all patients with AKI at any time point, FO preceded the development of AKI. Fifty percent of patients with FO on POD 0 developed AKI in the morning of POD 1, whereas only 14.4% of patients without FO on POD 0 developed AKI on POD 1 ($p = 0.023$). Patients with FO on POD 0 thus had almost six times higher odds of developing AKI on POD 1 than those without FO on POD 0 (OR, 5.92; 95% CI, 1.31–26.67; $p = 0.021$). FO on POD 1 was associated with over three times higher odds of developing AKI on POD 2 (OR, 3.2; 95% CI, 1.03–9.76; $p = 0.045$). FO on POD 2 increased the odds of AKI on POD 3 four-fold (OR, 4.26; 95% CI, 1.40–12.98; $p = 0.011$).

There was a less consistent relationship between AKI and FO by midnight the same day. Patients with AKI immediately after surgery were more likely to develop FO on POD 0 than those without AKI (21.1% vs 5.1%, $p = 0.002$). Likewise, patients with AKI on the morning of POD 1 had an increased prevalence of FO by midnight on POD 1 as compared with those patients without AKI (58.8% vs 24.7%, $p = 0.014$). This association did not hold true on POD 2, 3, or 4.

Patients with early FO, more than 5% FO by the end of POD 1, were more likely to develop AKI at some point in the study period than those without early FO (43.3% vs 33.8%, $p = 0.023$). Patients with early FO had almost seven times the odds of developing either Injury or Failure at any point in the

study period when compared with those without early FO (OR, 6.6; 95% CI, 1.2–36.2; $p = 0.015$). Percent early FO had good predictability for pRIFLE Injury or Failure (AUC-ROC, 0.829; 95% CI, 0.679–0.979; $p = 0.004$). On this ROC curve, greater than 8% FO, or 80 mL/kg, had 71% sensitivity and 90% specificity for predicting Injury or Failure.

Patients with AKI did not have significantly higher rates of FO on every study day. Although those with “Failure” ($n = 4$) had absolute cumulative balances higher than patients in every other pRIFLE category (Fig. 1), when compared across categories of AKI, cumulative fluid balance was only statistically different on POD 1. There was no difference between groups on any other study date.

Relationship Between Fluid Volume Administration, FO, and AKI

Patients with early FO were administered higher mean fluid volumes on every POD (Fig. 2). The mean cumulative fluid volume through POD 4 given to those with early FO was 105% higher than that given to those without early FO (395.4 ± 150 mL/kg vs 193.2 ± 109.1 mL/kg; $p < 0.001$).

The volume of fluid administered on POD 0 and 1 had good predictability for the development of early FO (AUC-ROC, 0.826; 95% CI, 0.732–0.921; $p < 0.001$ and AUC-ROC, 0.814; 95% CI, 0.730–0.899; $p < 0.001$). An ideal point on the ROC curve showed that a total fluid volume given of 51 mL/kg on POD 0 had 80% sensitivity and 76% specificity for FO by POD 1, one day later.

The cumulative fluid volume administered through POD 4 had excellent predictability for pRIFLE Failure (AUC-ROC, 0.963; 95% CI, 0.916–1.000; $p = 0.002$). A total cumulative fluid dose of greater than 500 mL/kg had 100% sensitivity and 91% specificity for pRIFLE Failure. There was a positive correlation between fluid volume administered and decrease in eGFR over the study period ($r = 0.225$; $p = 0.030$).

Diuretic Responsiveness in FO

As reported in Table 1, patients with early FO received a higher maximum daily furosemide dose (3.7 mg/kg [3.1–5.5 mg/kg]) than those without early FO (2.6 mg/kg [1.2–3.7] mg/kg) ($p < 0.001$). Daily diuretic dose was significantly higher in patients with

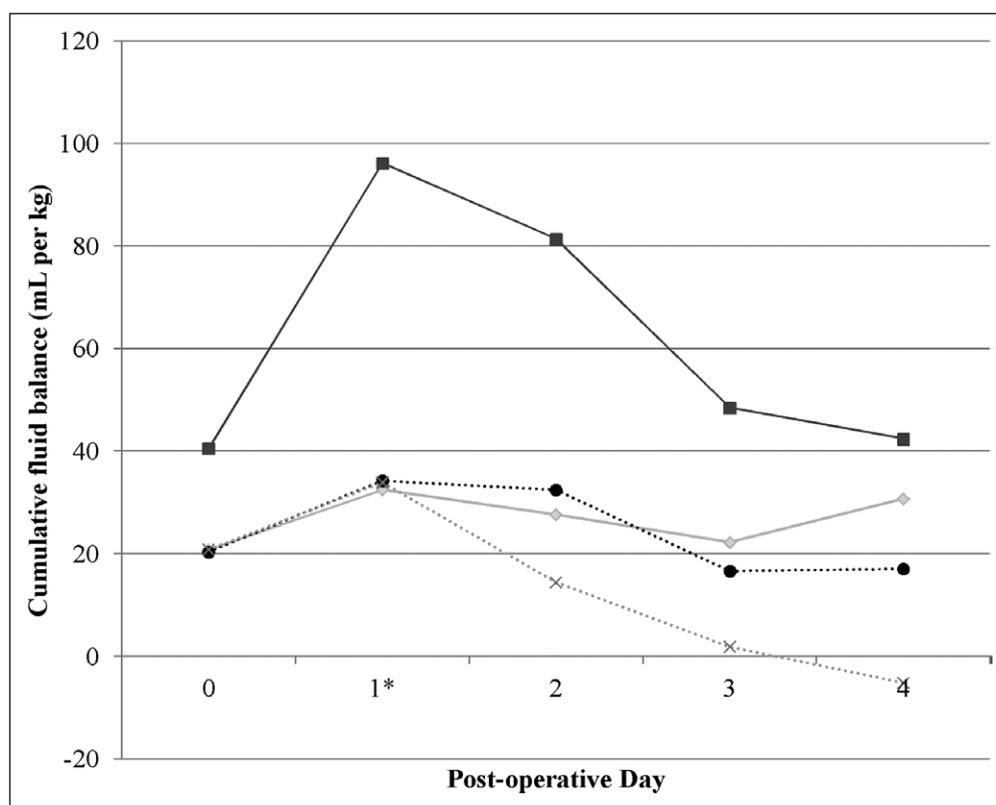


Figure 1. Median cumulative fluid balance in milliliters per kilogram body weight in patients in each category of acute kidney injury using pediatric-modified Risk, Injury, Failure, Loss, and End-stage criteria over the study period. Risk = more than 25% loss of renal function, Injury = more than 50%, Failure = more than 75% loss or an absolute function less than 35 mL/min/1.73 m². *Significant comparisons as obtained using Kruskal-Wallis comparison between all groups. None = gray diamond, Risk = closed circle, Injury = “x” mark, Failure = closed square.

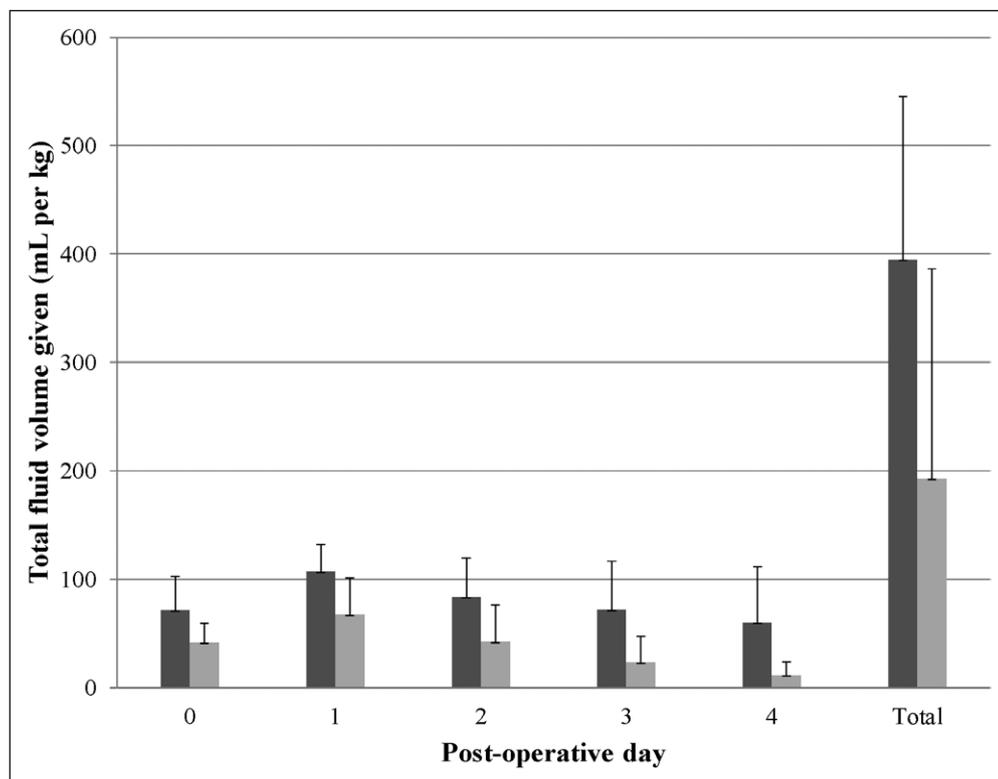


Figure 2. Mean daily and total fluid volume received in milliliters per kilogram of body weight in patients with and without fluid overload (FO). The error bars represent the sd. All comparisons are significant using the Student *t* test ($p < 0.001$). Early FO = black bar, no early FO = gray bar.

early FO than in those without early FO from POD 1 through POD 4: 2.4 mg/kg (1.6–3.7 mg/kg) vs. 1.3 mg/kg (0.6–2.3 mg/kg); 3.4 mg/kg (2.8–4.7 mg/kg) vs. 1.8 mg/kg (0.9–3.2 mg/kg); 3.5 mg/kg (2.6–4.6 mg/kg) vs. 2.0 mg/kg (1–3.3 mg/kg); and 3.1 mg/kg (2.7–4.1 mg/kg) vs. 1.4 mg/kg (0.7–3.1 mg/kg) (all $p < 0.001$).

In patients without FO on any study day, there was a positive strong correlation between total daily diuretic dose and urine output on the same day (r_s , 0.663–0.856; all $p < 0.001$). In those with FO on any study day, there was no significant correlation between diuretic dose and urinary output (r_s , -0.133 to 0.266; all $p > 0.05$).

DISCUSSION

By examining the outcomes in pediatric patients with FO early after cardiac surgery, our study adds to the growing body of evidence that FO is independently associated with increased morbidity (1–16, 27). We found that early FO is common after cardiac surgery in children, occurring 31% of the time, and is associated with a protracted recovery from surgery as evidenced by 3.5 more days in the hospital, two more days on inotropes, and increased prevalence of PMV.

Our data show that patients with early FO were more likely to develop AKI. However, not all patients with AKI developed FO at any point. Patients with pRIFLE Risk and Injury did not have noticeably different fluid balances than those without AKI. In fact, by POD 3, patients with Injury had improved balances over those patients without AKI. It was not until Failure

that fluid balances were statistically different at any point in the study period. Therefore, it was not until 75% of renal function was lost or the GFR fell below 35 mL/min/1.73 m² that fluid balances noticeably increased. These data support that fluid balance is an insensitive indicator of mild degrees of AKI and that fluid accumulation is not entirely explained by loss of GFR. Importantly for the clinician, once FO has developed, significant renal function may have already been lost.

If FO is not simply a secondary consequence of AKI, could it be a contributor to AKI development? In this cohort of pediatric cardiac surgery patients with AKI, FO more consistently occurred before the detection of AKI. One plausible explanation is that with current clinical diagnostics, AKI may have

occurred before it was detected by serum laboratory tests. The limitations and delays in rises in SCr after AKI has occurred are well documented (28). Although this study attempted to mitigate these effects by using an estimation for renal function not solely dependent on SCr, we did not use a gold standard. Additionally, the mathematical inclusion of FO and SCr in the calculation for eGFR could account for some of the association detected here.

Assuming our detection to be timely, our findings are consistent with previous evidence that FO can precede and contribute to AKI. Fluid retention has been shown to initiate or worsen the renal injury in different causes of AKI, including nephrotic syndrome (29), systemic inflammatory response syndrome (30), and intra-abdominal hypertension (31). The degree of FO being described in our study is unlikely to lead to intra-abdominal hypertension. The poor diuretic response in patients with FO in our study may support the concept that FO is a component of capillary dysfunction at the glomerulus; whether this is simply a consequence of AKI or a contributor to AKI is yet to be determined.

Regardless of causal inference, the observation that FO precedes clinically apparent AKI supports the need for heightened vigilance. This is of imperative clinical utility as FO continues to emerge as a warning sign, a true “renal angina” as coined by Goldstein and Chawla (32). Adjusting SCr values for fluid balance, as proposed by Liu et al (26), is essential in detecting early subtle signs of AKI. In our analysis, 8% FO, the equivalent of 80 mL/kg, was 90% specific for subsequent Injury or Failure.

These values are far less than those proposed in the continuous RRT literature and are easy to overlook in daily totals and ignoring net cumulative balance.

Although the relationship between administered fluid and fluid balance we report may seem obvious, we present these data to highlight potential practice patterns that may perpetuate or exacerbate FO. A recent retrospective cohort study by Valentine et al (12) showed that pediatric patients with acute lung injury accumulate more fluid than the liberal arm of the Fluid and Catheter Treatment Trial, a multicenter randomized trial of adult acute lung injury investigating conservative and liberal fluid management on survival and LMV (8). We report comparable fluid balances as those in Valentine et al (12), and our data confirm that this fluid balance could be due to the volumes of fluid being administered. For the bedside clinician, knowing that reaching a cumulative IV fluid dose of 500 mL/kg carries 100% sensitivity for the development of AKI may direct care away from fluid administration and toward vasoactive medications.

The second explanation for the measured association between FO and worse pulmonary and renal outcomes could be confounding by the indication for the large fluid administration: hemodynamic instability. If this is the case, the higher morbidity observed for patients with FO could be largely due to impaired cardiac output or systemic vascular function rather than FO itself. Higher RACHS-1 score, IS, and bypass time all suggest that patients with FO had more complicated surgeries and had the potential to be sicker in the postoperative period. We present the data that those patients with FO had higher IS and were more likely to need an escalation in inotropic support from POD 0 to POD 1 than those without FO, suggesting a need for increased hemodynamic support. Mixed venous oxygen saturation was on average 6% lower in patients with FO compared with those without FO; however, this S_{vo_2} difference could be partially explained by the larger proportion of cyanotic lesions in those with early FO (63.3%) vs. those without early FO (36.8%) ($p = 0.015$). Additionally, renal NIRS values and systemic ventricular EFs did not differ consistently across the groups. No invasive measurements of cardiac index or output were performed; however, IS has been shown as a more reliable marker of hemodynamic status (17) than NIRS (15) or EF. Mixed venous saturation has shown utility in indicating oxygen extraction when it is a true “mixed” sample at the level of the right atrium with a concomitant arterial saturation (18). Those data were not available for this study.

Furthermore, the results of the multivariable analysis confirm that we cannot rule out confounding by hemodynamic instability in the association between FO and extended LOS and LMV.

It is unclear whether diuretics can improve renal outcomes and if they are safe or deleterious in critically ill children. There is some evidence in adult studies that use of diuretics after cardiac surgery worsens renal function (33). Other adult studies have shown no effect on renal function but improved diuresis and a decreased need for RRT after cardiac surgery (34, 35). These are consistent with large meta-analyses concluding that

loop diuretics improve urine output but may not improve mortality or need for RRT in adult patients (36, 37). It is of clinical utility to note that patients with FO did not respond as well to diuretics and higher doses are needed for effect in these patients.

This study is limited as a secondary analysis of data originally collected with a different intent, by its observational nature, small sample size, and homogenous patient population. As a single-center study, external validity is also limited. Although the timing we report of the association between AKI and FO is intriguing, we cannot infer causality. We also cannot determine if the fluid administration was preventable especially without randomizing patients to each fluid group to avoid any confounding. Additionally, the wide CI reported in **Table 3** reflects a small sample size and potentially imprecise estimate of the association between FO and PMV.

CONCLUSION

If our findings are confirmed, this study offers vital information to the clinician regarding FO in the early post-CPB period. Younger patients with longer CPB times and more fluid removed via UF and MUF are at higher risk for FO. FO can be associated with higher rates of AKI, extended LOS, and PMV. Whether prognostic or causative, FO should raise suspicion for significant renal dysfunction. Avoiding aggressive fluid administration in the first few days after surgery in these high-risk patients could potentially mitigate poorer outcomes. The amount of fluid administered is an excellent predictor of AKI. Patients with FO are also likely to need higher doses of diuretics to achieve a desired clinical effect.

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