Fluid Overload Is Associated With Higher Mortality and Morbidity in Pediatric Patients Undergoing Cardiac Surgery*

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Objectives: Fluid overload after pediatric cardiac surgery is common and has been shown to increase both mortality and morbidity. This study explores the risk factors of early postoperative fluid overload and its relationship with adverse outcomes.

Design: Secondary analysis of the prospectively collected data of children undergoing open-heart surgery between 2004 and 2008.

Setting: Tertiary national cardiac center.

Patients: One thousand five hundred twenty consecutive pediatric patients (<18 years old) were included in the analyses.

Interventions: None.

Measurements and Main Results: In the first 72 hours of the postoperative period, the daily fluid balance was calculated as milliliter per kilogram and the daily fluid overload was calculated as fluid balance (L)/weight (kg) × 100. The primary endpoint was in-hospital mortality; the secondary outcomes were low cardiac output syndrome and prolonged mechanical ventilation. One thousand three hundred and sixty-seven patients (89.9%) had a cumulative fluid overload below 5%; 120 patients (7.8%), between 5% and 10%; and 33 patients (2.1%), above 10%. After multivariable analysis, higher fluid overload on the day of the surgery was independently associated with mortality (adjusted odds ratio, 1.14; 95% CI, 1.008–1.303; $p = 0.041$) and low cardiac output syndrome (adjusted odds ratio, 1.21; 95% CI, 1.12–1.30; $p = 0.001$). Higher maximum serum creatinine levels (adjusted odds ratio, 1.01; 95% CI, 1.003–1.021; $p = 0.009$), maximum vasoactive-inotropic scores (adjusted odds ratio, 1.01; 95% CI, 1.005–1.029; $p = 0.042$), and higher blood loss on the day of the surgery (adjusted odds ratio, 1.01; 95% CI, 1.004–1.025; $p = 0.015$) were associated with a higher risk of fluid overload that was greater than 5%.

Conclusions: Fluid overload in the early postoperative period was associated with higher mortality and morbidity. Risk factors for fluid overload include underlying kidney dysfunction, hemodynamic instability, and higher blood loss on the day of the surgery.
(*Pediatr Crit Care Med* 2016; 17:307–314)

Key Words: cardiopulmonary bypass; congenital heart disease; fluid overload; fluid therapy; mortality

Fluid overload (FO) both during and after pediatric cardiac surgery is common. Intraoperative FO is associated with factors such as lower tolerability and reserve capacity in children, excessive exogenous fluid used for the cardiopulmonary bypass (CPB) priming, cardioplegia, medication administration, and hypotension management. Children undergoing cardiac surgery often arrive in the operating room already overloaded due to a degree of heart failure, complex congenital abnormalities, and diminished baseline renal function (1). Recently, FO has been shown to be associated with poor outcomes, including increased mortality, acute kidney injury (AKI), acute lung injury, sepsis, and low cardiac output syndrome (LCOS) (2–5). The assessment of the severity of FO suggests that a cutoff value of 10% is associated with increased mortality in children (3). Furthermore, intraoperative CPB and surgical stress cause ischemia, reperfusion injury, and systemic inflammatory response, and these processes also augment edema formation and damaged microcirculation (6). We have previously shown that AKI is associated with increases in both morbidity and resource utilization regardless

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***See also p. 367.**

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Dr. Lex is employed by Semmelweis University (National scholarship for postgraduate education). Dr. Tóth is employed by the national scholarship fund. Dr. Breuer is employed by Gottsegen Institute of Cardiology. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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DOI: 10.1097/PCC.0000000000000659

of differences in severity scoring systems (7, 8). We hypothesized that AKI and/or LCOS might be exacerbated by FO, and if so, the exploration of risk factors for FO is crucial in reducing acute and long-term adverse outcomes.

The aim of this study was to investigate the relationship between FO and adverse outcomes in a large and heterogeneous cohort of pediatric patients undergoing open-heart surgery in a single center. As a novel approach, we also aimed at exploring the risk factors of developing early FO.

PATIENTS AND METHODS

Institutional review board approval (189/2008) was given for the retrospective use of the selected data collated from a prospectively collected database of consecutive pediatric patients undergoing cardiac surgery and who were admitted to our cardiac ICU at Gottsegen Hungarian Institute of Cardiology in Budapest, Hungary, between January 1, 2004 and December 31, 2008, including waiving the requirement for informed consent from the parents. During the study period, 1,665 cardiac surgeries were performed. Only patients undergoing open-heart surgery and less than 18 years old were considered for the study. One thousand two hundred and sixteen patients (80%) were on CPB during surgery. One hundred forty-five patients were excluded in the case of preoperative renal replacement therapy (RRT) administration, and where the fluid balance for the study period could not be calculated due to missing data. Only the first operation was considered for the present analysis. The surgical and medical management of the patients, and institutional policies were identical during the study period (9).

Outcome Assessment

The fluid intake and output were recorded perioperatively up to 72 hours after the surgery. The urine output (UO) was recorded and analyzed as milliliter per kilogram per hour. The daily fluid balance was calculated from the difference between the intake (crystalloids, colloids, parenteral nutrition, oral intake, and transfusion) and the output (recorded fluid loss included any fluid removed by a drain or chest tube, urine or stool, and blood for testing or lost from bleeding). The fluid intake and output were recorded hourly, and the daily data were analyzed as milliliter per kilogram. As a general guideline, patients were treated with dextrose containing (D5) 0.45% normal saline as much as 750 mL/m^2 and 1,000 mL/m^2 body surface area on the day of surgery (DOS) and postoperative day (POD)1, respectively. Serum creatinine (SCr) values were adjusted to the patient's fluid balance as proposed by Liu et al (10) by using total body water estimation as per Wells et al (11).

Using the patient's fluid balance in milliliter per kilogram, the percentage of FO was calculated for each patient by the following formula: (total fluid intake – total fluid output) (L)/body weight (kg) × 100. The body weight was based on the patient's weight at hospital admission or on the most recent available patient weight measured in the ICU. The cumulative FO (cFO) was calculated by summarizing the respective %FO of the PODs (e.g., cFO POD1 = %FO DOS + %FO POD1); also, for DOS, the cFO includes intraoperative fluid status. Based on this calculation, 5% FO is the equivalent of 50 mL/kg positive balance.

RRT was defined as the implementation of either peritoneal dialysis or hemodialysis for indications such as metabolic/electrolyte imbalance, ascites, pulmonary edema, and excess fluid removal as per the attending physician's preference (12). Furosemide was used as 1 mg/kg bolus administration without an institutional protocol.

LCOS during the study period was defined by using clinical signs (tachycardia, hepatomegaly, cardiac arrest), with a base excess lower than –4 mmol/L or a lactate level higher than 2 mmol/L in two consecutive arterial blood samples, a UO lower than 1 mL/kg/hr, a maximum vasoactive-inotropic score (VIS) higher than 20, or the need for mechanical circulatory support (13, 14). An intensivist and a cardiologist determined separately all of the patient outcomes included in the database during the discharge of the patient from the hospital.

Prolonged mechanical ventilation (PMV) was defined as longer than 72 hours, as 75% of our patients were extubated by POD2 and previous studies showed a median duration of 3 days (15, 16).

VIS was calculated as dopamine (μg/kg/min) + dobutamine (μg/kg/min) + 100 × epinephrine (μg/kg/min) + 10 × milrinone (μg/kg/min) + 10,000 × vasopressin (U/kg/min) + 100 × norepinephrine (μg/kg/min) (17).

Statistical Analysis

The continuous variables were expressed as medians and interquartile ranges. For continuous variables, the *p* values are based on a Mann-Whitney *U* test comparing patients with and without adverse outcomes.

The adjusted risk of FO and mortality, LCOS, and PMV were calculated by using multivariable logistic regression. Model selection and fitting was based on Akaike Information Criterion by using the backward stepwise selection method. For the mortality and PMV model, the variables added in the first step of the stepwise process were as follows: CPB time (minute), operation time (minute), preoperative inotrope administration, delayed chest closure, Risk Adjustment for Congenital Heart Surgery (RACHS) score, acute operation, logarithmic transformation of age, deep hypothermic cardiac arrest (DHCA), body weight (kg), intraoperative RBC use (mL/kg), intraoperative fresh frozen plasma (FFP) use (mL/kg), intraoperative aprotinin use, maximum VIS score, gender (male), aorta cross-clamp time (min), nitric oxide administration, blood loss on DOS (mL/kg), RRT, LCOS, and postoperative infection. For the LCOS model, the variables added in the first step of the stepwise process were as indicated earlier and also intraoperative ultrafiltration (UF) administration and maximum SCr (μmol/L), with the exclusion of intraoperative aprotinin use, aorta cross-clamp time (min), and postoperative infection. cFO variables were added to the final models. Deaths prior to the investigated cFO day were excluded.

A separate multivariable model was constructed for the analysis of the predictors for a cFO greater than 5%, and also a linear regression model was constructed for the analysis of cFO on the POD2. The variables added in the first step of the stepwise process were as follows: gender (male), logarithmic transformation of age, body weight (kilogram), preoperative inotrope administration, preoperative SCr (micromole per liter), RACHS score, acute operation, CPB time (minute), DHCA, intraoperative RBC use (milliliter per kilogram), intraoperative FFP use (milliliter per kilogram), intraoperative UF administration, delayed chest closure, maximum VIS score, maximum SCr (micromole per liter), NO administration, blood loss on DOS (milliliter per kilogram), RRT, and LCOS.

For survival analysis, Kaplan-Meier log-rank pairwise comparison was used.

SPSS 21 statistical software (SPSS, Chicago, IL) was used. A p value of less than 0.05 was considered statistically significant.

RESULTS

Of the 1,520 patients, 90 patients (5.9%) died, 370 patients (25.4%) had postoperative LCOS, and 102 patients (6.7%) required RRT. Twenty-two patients (1.3%) died on the DOS, 21 patients (1.3%) died on the POD1, and 6 patients (0.4%) died on the POD2; thus, 54% of all deaths occurred during the study period. Patients requiring RRT on the DOS ($n = 75$) had higher intraoperative fluid balances (milliliter per kilogram, 20.3 ± 25.3 vs 24.16 ± 41.1; $p = 0.004$). One hundred twenty-one patients (7.3%) reached Kidney Disease Improving Global Outcomes stage I, 29 (1.7%) reached stage II, and 114 (6.8%) reached stage III. Of the 153 patients with a cFO greater than 5% at the end of POD2, 30 patients (20%) were newborns, 35 (23%) underwent an acute or urgent operation, 20 (13%) had univentricular physiology, 9 (6%) underwent arterial switch, 21 (14%) had modified Blalock-Taussig Shunt, and 10 (7%) underwent Norwood procedure.

We found that during the first 72 hours of the postoperative period, 1,367 patients (89.9%) had a cFO below 5%, 120 patients (7.8%) had a cFO between 5% and 10%, and 33 patients (2.1%) had a cFO above 10%. Patients with a cFO greater than 5% were younger, had lower body weight, and underwent more complex surgeries with higher occurrence of cyanotic lesions, longer CPB, and aortic cross-clamp time (**Table 1**).

When comparing unadjusted and adjusted SCr values, we found that the adjusted SCr levels were significantly higher on all 3 PODs ($p = 0.028$, $p < 0.001$, $p < 0.001$, respectively), although no difference was observed between them regarding patients with or without a cFO greater than 5% on POD2.

The nonsurvivors had higher fluid balances and cFOs on DOS and POD1 compared with the patients without complications (**Table 2** and **Fig. 1**). After adjusting for confounding variables, cFO by DOS remained an independent predictor of mortality, as for every %FO by the end of DOS, the risk of mortality increased by 14% (**Table 3**). As the strongest predictor, the occurrence of LCOS increased the risk for mortality by 14 times. Mean survival times for patients with a cFO less than 5%, greater than 5%, and greater than 10% on POD2 were 67.7 (95% CI, 62.1–73.4), 39.9 (95% CI, 35.6–44.3; $p = 0.03$), and 35.6 days (95% CI, 23.2–48.1; $p < 0.001$), respectively (**Fig. 2**).

Patients requiring RRT had higher intraoperative, DOS, POD1 and lower POD2 fluid balances and cFO compared with those without complications (Table 2).

Patients with LCOS had higher intraoperative, DOS and lower POD2 fluid balances and cFO compared with those without complications. After adjusting for confounding variables, cFO by DOS remained an independent predictor of LCOS, as

TABLE 1. Demographic Variables by 5% Fluid Overload at the End of the Second Postoperative Day

	cFO < 5%	cFO > 5%	
Variables	***n* = 1,367 (90%)**	***n* = 153 (10%)**	***p***
Age (d)	448 (169–2,037)	151 (47–453)	< 0.001
Male, *n* (%)	868 (55)	59 (67.8)	0.019
Weight (kg)	8.4 (4.9–17)	4.3 (3.1–9.1)	< 0.001
Baseline estimated creatinine clearance (mL/min/1.73 m^2)	87 (61–111)	64 (45–88)	< 0.001
Cyanotic lesion, *n* (%)	508 (32.2)	43 (49.4)	0.001
RACHS score			
RACHS score 1–2	955 (60.6)	24 (27.6)	< 0.001
RACHS score 3–6	620 (39.4)	63 (72.4)	< 0.001
Cardiopulmonary bypass time (min)	78 (54.5–129)	131 (107–191)	< 0.001
Aortic cross-clamp time (min)	39 (25–71)	69 (49–84)	< 0.001
Maximum vasoactive-inotropic score	6 (0–18)	26 (13–46.5)	< 0.001
Lowest urine output (mL/kg/hr)	2.6 (1.9–3.4)	1.69 (0.6–2.6)	< 0.001

cFO = cumulative fluid overload, RACHS = Risk Adjustment for Congenital Heart Surgery.
Data are presented as median and interquartile range and number of patients and percentage.

TABLE 2. Daily Fluid Data and Urine Output According to Adverse Outcomes

	Nonsurvivors	Low Cardiac Output Syndrome	Renal Replacement Therapy	Kidney Disease Improving Global Outcomes Stage II + III	Prolonged Mechanical Ventilation	No Complications
Variables	*n* = 90 (5.9%)	*n* = 370 (24.3%)	*n* = 102 (6.7%)	*n* = 143 (9.4%)	*n* = 427 (28%)	*n* = 729 (47.9%)
Fluid balance, intraoperative (mL/kg)	22.58 (4.30 to 39.25)	**21.7 (9.75 to 40.75)**	**32.20 (10.50 to 49.20)**	**25.00 (10.50 to 39.60)**	21.4 (8.9 to 39.5)	16.94 (7.94 to 27.67)
Fluid balance, DOS (mL/kg)	**16.90 (−12.50 to 48.00)**	**16 (−12.95 to 43.2)**	**12.35 (−17.50 to 39.33)**	**21.91 (−8.72 to 48.54)**	**0.5 (−23.88 to 28.88)**	−10.35 (−23.50 to 0.10)
Fluid balance, POD1 (mL/kg)	**7.60 (−18.85 to 65.30)**	−3.1 (−24.4 to 16.3)	**5.20 (−16.10 to 35.50)**	0.23 (−15.31 to 31.66)	−5.55 (−25.3 to 12.73)	−1.30 (−17.80 to 11.40)
Fluid balance, POD2 (mL/kg)	−9.00 (−26.68 to 17.13)	**−13.4 (−44.7 to 6.15)**	**−14.80 (−48.30 to 4.80)**	**−20.32 (−52.65 to 2.34)**	−19.75 (−39.6 to 0.78)	−0.05 (−15.30 to 15.13)
cFO, DOS (%)	**2.24 (−1.31 to 5.02)**	**1.6 (−1.29 to 4.32)**	**1.22 (−1.78 to 4.28)**	**2.18 (−0.87 to 4.85)**	**0.24 (−1.38 to 2.89)**	−1.03 (−2.35 to 0.01)
cFO, POD1 (%)	**0.76 (−1.88 to 6.53)**	−0.31 (−2.43 to 1.63)	**0.52 (−1.61 to 3.55)**	0.02 (−1.52 to 3.15)	0.56 (−1.53 to 2.27)	−0.13 (−1.78 to 1.14)
cFO, POD2 (%)	−0.56 (−5.57 to 2.13)	**−1.34 (−4.47 to 0.61)**	**−1.48 (−4.83 to 0.48)**	**−2.02 (−5.25 to 0.23)**	**0.12 (−1.96 to 1.07)**	0.01 (−1.53 to 1.51)
Urine output, DOS (mL/kg/hr)	**3.03 (1.46 to 3.77)**	2.57 (1.49 to 3.62)	**1.7 (0.79 to 3.12)**	1.9 (1.06 to 2.77)	**3 (1.94 to 4)**	3.12 (2.14 to 3.91)
Urine output, POD1 (mL/kg/hr)	**3.74 (0.22 to 7.06)**	**3.94 (2.51 to 5.29)**	**1.95 (0.73 to 4.00)**	**2.45 (0.95 to 4.05)**	**4.57 (3.17 to 5.87)**	3.90 (2.76 to 5.45)
Urine output, POD2 (mL/kg/hr)	6.5 (0.29 to 10.16)	**4.45 (2.64 to 5.81)**	**2.66 (0.91 to 5.50)**	**3.37 (1.66 to 5.45)**	**5.17 (3.66 to 6.41)**	4.04 (2.95 to 5.70)

DOS = day of surgery, POD = postoperative day, cFO = cumulative fluid overload.

Data are presented as median and interquartile range. All comparisons were made with patients without any complications by using Mann-Whitney *U* test. Significant values are represented in bold at $p < 0.05$.

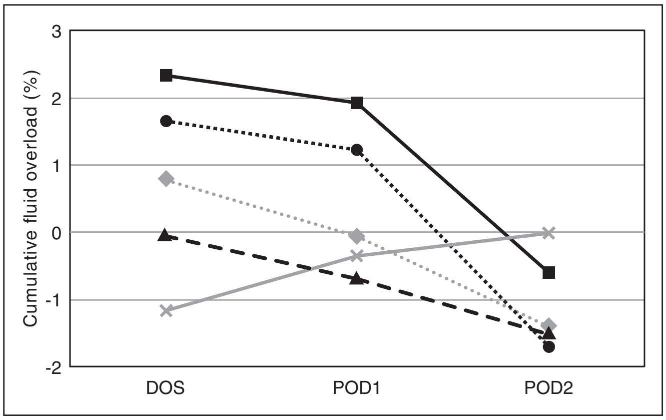

Figure 1. Cumulative fluid overload (FO) and complications. Data are presented as cumulative median FO in percentage according to the different outcomes on the postoperative days (PODs). DOS = day of surgery, POD1 = first postoperative day, POD2 = second postoperative day. *Black squares* = nonsurvivors, *gray diamonds* = low cardiac output syndrome, *black circles* = renal replacement therapy, *black triangles* = prolonged mechanical ventilation, *gray crosses* = no complications.

for every %FO by the end of DOS, the risk of LCOS increased by 15% (**Table 4**). As the strongest predictor, the need for RRT increased the risk for LCOS by five times.

Patients requiring PMV had higher fluid balance and cFO on DOS compared with those without complications. After adjusting for confounding variables, cFO by POD2 remained an independent predictor of PMV, as for every % FO by the end of POD2 the risk of PMV increased by 1.2% (**Table 5**). As the strongest predictor, the occurrence of LCOS increased the risk for PMV by seven times.

The nonsurvivors had a lower UO on the DOS and POD1 compared with the patients without complications, and the patients with LCOS had a higher UO on POD1 and POD2 compared with those without complications (Table 2). Patients requiring RRT had a lower UO on all 3 PODs compared with those without complications.

Independent risk factors of a cFO greater than 5% by the end of POD2 include maximum SCr level, blood loss on DOS,

TABLE 3. Multivariable Logistic Regression Model for In-Hospital Mortality

Predictors	Adjusted OR (95% CI)	*p*
Age (log)	0.520 (0.282–0.958)	0.036
Acute operation	4.682 (1.341–16.34)	0.016
Cardiopulmonary bypass time (min)	1.005 (1.001–1.012)	0.031
Renal replacement therapy	2.937 (1.027–8.401)	0.045
Low cardiac output syndrome	14.08 (2.951–67.199)	0.001
Cumulative fluid overload on the day of the surgery (%)	1.142 (1.008–1.303)	0.041

OR = odds ratio.

Data are presented as adjusted OR (95% CI) of the predictors according to the risk of in-hospital mortality. Nonsignificant variables in the final model were maximum vasoactive-inotropic score, gender (male), and postoperative infection.

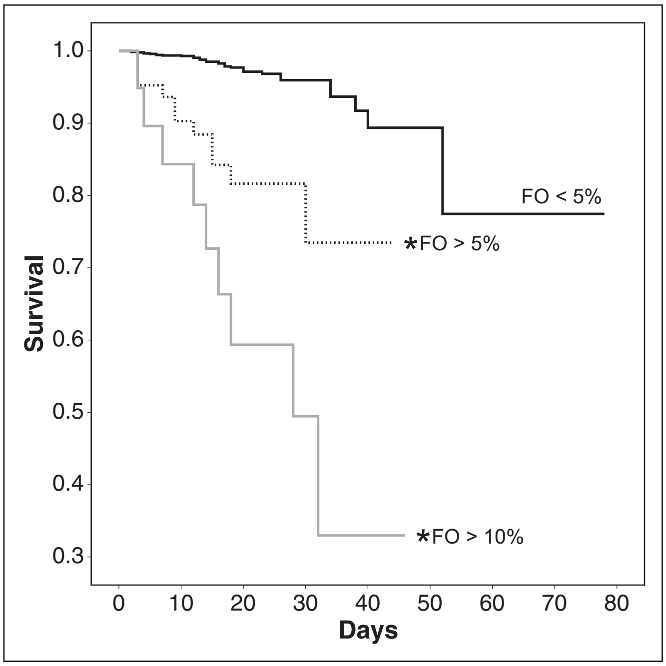

Figure 2. Survival according to different severities of cumulative fluid overload (FO). Data are presented as cumulative survival according to the severity of cumulative FO by the end of the second postoperative day. *Asterisks* represent significant comparisons as obtained by using Kaplan-Meier survival analysis.

maximum VIS point, and the occurrence of LCOS, whereas higher body weight shows a protective association (**Table 6**). Every point increase in the maximum VIS, every µmol/L elevation in the maximum SCr level, and every 1 mL/kg blood loss on DOS increased our patient's risk for a cFO greater than 5% by 1.3%, 1.2%, and 1.4%, respectively. As the strongest predictor, the occurrence of LCOS increased the risk for an FO greater than 5% by three times.

After multivariable linear regression analysis, risk factors of cFO by the end of POD2 include preoperative inotrope administration, intraoperative RBC use (milliliter per kilogram), blood loss on DOS (milliliter per kilogram), maximum VIS point, maximum SCr level, delayed chest closure, occurrence of LCOS, and the need for RRT (**Table 7**). The final model was statistically significant ($F = 21.164$, adjusted $R^2 = 0.347$; $p < 0.001$). There was no first-order linear auto-correlation in the final model ($d = 1.967$). There was no multicollinearity present in the final model (highest variance inflation factor = 3).

TABLE 4. Multivariable Logistic Regression Model for Low Cardiac Output Syndrome

Predictors	Adjusted OR (95% CI)	*p*
Body weight (kg)	0.971 (0.946–0.996)	0.025
Cardiopulmonary bypass time (min)	1.014 (1.006–1.021)	0.001
Delayed chest closure	2.314 (1.259–4.254)	0.007
Renal replacement therapy	5.303 (1.725–15.815)	0.004
Blood loss DOS (mL/kg)	1.011 (1.004–1.029)	0.042
Maximum vasoactive-inotropic score	1.016 (1.003–1.029)	0.015
Cumulative fluid overload DOS (%)	1.211 (1.126–1.303)	0.001

OR = odds ratio, DOS = day of surgery.

Data are presented as adjusted OR (95% CI) of the predictors according to the risk of low cardiac output syndrome. Nonsignificant variables in the final model: intraoperative RBC use (milliliter per kilogram), intraoperative fresh frozen plasma use (mL/kg), intraoperative nitric oxide use, and intraoperative ultrafiltration.

TABLE 5. Multivariable Logistic Regression Model for Prolonged Mechanical Ventilation (> 72 Hours)

Predictors	Adjusted OR (95% CI)	*p*
Age (log)	0.545 (0.352–0.845)	0.007
Delayed chest closure	3.402 (1.542–7.504)	0.002
Postoperative infection	8.792 (3.926–19.686)	< 0.001
Maximum vasoactive-inotropic score	1.005 (1.005–1.045)	0.016
Low cardiac output syndrome	7.363 (4.035–13.434)	< 0.001
Cumulative fluid overload on second postoperative day (%)	1.012 (1.005–1.032)	0.025

OR = odds ratio, DOS = day of surgery.

Data are presented as adjusted OR (95% CI) of the predictors according to the risk of prolonged mechanical ventilation > 72 hr. Nonsignificant variables in the final model: intraoperative fresh frozen plasma use (milliliter per kilogram) and blood loss on the day of the surgery (milliliter per kilogram).

DISCUSSION

Based on our results, we show that early postoperative FO was independently associated with adverse outcomes. Although a

TABLE 6. Multivariable Logistic Regression Model for Cumulative Fluid Overload Greater Than 5% at the Second Postoperative Day

Predictors	Adjusted OR (95% CI)	*p*
Body weight (kg)	0.942 (0.894–993)	0.026
Maximum serum creatinine (μmol/L)	1.012 (1.003–1.021)	0.009
Low cardiac output syndrome	3.179 (1.298–7.451)	0.009
Blood loss on day of surgery (mL/kg)	1.014 (1.004–1.025)	0.015
Maximum vasoactive-inotropic score	1.013 (1.005–1.029)	0.042

OR = odds ratio.

Data are presented as adjusted OR (95% CI) of the predictors.
Nonsignificant variables in the final model were cardiopulmonary bypass time (min) and renal replacement therapy.

positive postoperative fluid balance on the DOS was associated with higher risks of mortality and adverse outcomes, this association decreased on POD1, and no relationships with mortality were observed on POD2. Early positive FO on DOS was associated with a higher risk of LCOS, whereas cFO by the end of POD2 was associated with a higher risk of PMV. After analyzing the potential predictors of FO, we found a higher risk in the case of higher maximum creatinine levels and inotrope requirements, early postoperative blood loss, and the occurrence of LCOS.

FO in pediatric cardiac patients continues to be a challenging problem in the perioperative period despite a growing body of evidence and advancement in therapeutic goals (18). Studies of adult critically ill patients have shown that an FO above 10% is associated with a higher long-term mortality and a higher occurrence of AKI, thus indicating this threshold as a potential indicator of adverse outcomes (19, 20). Studies of pediatric patients requiring RRT showed a correlation of the degree of FO with poor outcomes and mortality, hinting at a dynamic FO value for predicting adverse outcomes, with the 10% cutoff value proving to be clinically significant (3, 5, 21). However, little is known about the specifics of FO in the pediatric cardiac population with regard to the degree of FO, the circumstances, and its relationship between adverse events. In a recent study of infants undergoing congenital heart surgery, early FO was associated with a composite poor outcome (with a mean maximum FO of 12%) but not with mortality when using fluid balance and daily weight methods (22). We used the 5% cutoff, as our results show an even lower value; 75% of the nonsurviving infants had a maximum %FO of only 6.03 on the DOS. Basu et al (23) proposed a higher risk of AKI if an FO criterion greater than 5% is met in very-high-risk patients (requiring inotropes and mechanical ventilation). By using a 5% cutoff, Hassinger et al (24) showed an association between FO and the development of AKI.

Several risk factors of FO overlap with the predictors of other adverse outcomes, pointing at possible additive effects. Preoperative poor status requiring inotrope administration possibly carries an existing volume load that poses a difficult assessment later. Intraoperative RBC use and early postoperative blood loss are markers of operational complexity and surgical success. High postoperative SCr values correlate with kidney dysfunction, and high postoperative inotropic requirement and delayed chest closure are possibly surrogate markers of LCOS and hemodynamic instability, leading to diminished UO and FO. Identification of high-risk patients for FO by calculation of fluid balance has its limitations, and here, we present additional markers that are available for use as early as POD1. Early intervention in the management of FO appears to be the key factor for reducing mortality and morbidity, although the correct timing of RRT initiation is still unclear because of the lack of clinical definitions and thresholds and unconfirmed biomarker values (25, 26). A detailed analysis of the fluid balance, UO, and cFO has also confirmed the renal angina phenomenon in the pediatric cardiac population; that

TABLE 7. Multivariable Linear Regression Model for Cumulative Fluid Overload at the Second Postoperative Day

Predictors	β	95% CI	*p*
Preoperative inotrope administration	1.172	0.094–2.250	0.033
Intraoperative RBC use (mL/kg)	0.025	0.014–0.036	0.007
Blood loss on day of surgery (mL/kg)	0.017	0.004–0.030	0.011
Maximum vasoactive-inotropic score	0.021	0.006–0.037	0.008
Maximum serum creatinine (μmol/L)	0.010	0.002–0.019	0.022
Delayed chest closure	1.120	0.460–1.954	0.003
Low cardiac output syndrome	1.420	0.554–2.434	< 0.001
Renal replacement therapy	1.387	0.249–2.525	0.017

Data are presented as adjusted regression coefficient and 95% CI of the predictors. Nonsignificant variables in the final model: logarithmic transformation of age, gender (male), cardiopulmonary bypass time (min), and deep hypothermic cardiac arrest.

is, a large proportion of the patients (most likely those with a pediatric Risk, Injury, Failure, Loss, and End-stage renal disease-Risk category) are unable to fulfill the higher demand for fluid excretion in the intraoperative and early postoperative period. This inability may be due to both prerenal and renal causes. These patients will have a positive fluid balance, which will be eliminated at the end of the POD2 (27). This may be exacerbated in cases where normal creatinine and poor UO are ascribed to prerenal factors, including volume depletion, and it is treated with additional fluids. In these cases, the renal injury may have already occurred and not been recognized, leading to an imbalance in fluids, which is later recognized and dealt with on POD1 and POD2 (10).

Similar to Seguin et al (28), we also showed POD2 cFO and younger age as risk factors for PMV. In contrast with Sampaio et al (29), we observed higher inotrope requirements and LCOS to be significant predictors of PMV. This might be due to differences in the patient population, as we had more cyanotic children with higher RACHS scores. Also, in contrast to Hassinger et al, we showed that early FO is a predictor of PMV and we did not observe CPB time as a significant risk factor. However, our patients had shorter CPB durations and lower RACHS scores. The comparability of the studies might be undermined by differences in center performance, patient numbers, and heterogeneity. Consistent with our other results, postoperative LCOS and high inotrope requirements proved to be the most important predictors for every adverse outcome, including PMV.

Limitations of this study include its retrospective nature and the lack of randomization. Although these results come from a single center, we aimed at overcoming this by using large patient number and a heterogeneous population. Also, our methods do not allow us to define the preoperative characteristics that may influence the outcomes, as we used the preoperative weight as the baseline even if FO was present. The use of clinical parameters for the definition of LCOS is subjective, although two independent experts defined the outcomes prospectively, which were later validated by using variables recorded in the database, in an attempt to minimize bias. Also, the study design is limited in its ability to ascertain direct causal relationships between LCOS, renal dysfunction, and FO, as detailed timing information of outcomes in relationship to FO during the study period is unavailable and volume therapy in the more severely ill patients as a valid therapeutic intervention is also considered in the analyses.

CONCLUSIONS

Using an exceptionally large cohort of pediatric patients undergoing cardiac surgery, we found that FO was independently associated with an increased risk for mortality, LCOS, and PMV, after adjustment for covariates such as age, weight, acute operation, RACHS score 1, CPB time, intraoperative RBC use, RRT, delayed chest closure, maximum VIS score, early postoperative blood loss, and postoperative infection. Our data also indicate that the degree of FO that is dangerous appears to be lower than 10%. Our study adds to the growing body of evidence regarding risk factors of postoperative FO, and it aims at helping in the early identification of high-risk patients. Avoidance of aggressive fluid therapy and early intervention with fluid removal or institution of RRT appear to be the key therapeutic concepts. Furthermore, the uncertain methodology of assessing fluid balance, the lack of a universal definition for FO, and the need to better evaluate preoperative fluid status in the pediatric cardiac population call for further studies on this subject.

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