OBSERVATIONAL STUDY

OPEN

Association of Urine Biomarkers With Acute Kidney Injury and Fluid Overload in Infants After Cardiac Surgery: A Single Center Ancillary Cohort of the Steroids to Reduce Systemic Inflammation After Infant Heart Surgery Trial

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OBJECTIVES: To examine the association between three perioperative urine biomarker concentrations (urine cystatin C [uCysC], urine neutrophil gelatinase-associated lipocalin [uNGAL], and urine kidney injury molecule 1 [uKIM-1]), and cardiac surgery-associated acute kidney injury (CS-AKI) and fluid overload (FO) in infants with congenital heart disease undergoing surgery on cardiopulmonary bypass. To explore how urine biomarkers are associated with distinct CS-AKI phenotypes based on FO status.

DESIGN: Ancillary prospective cohort study.

SETTING: Single U.S. pediatric cardiac ICU.

PATIENTS: Infants less than 1 year old enrolled in the Steroids to Reduce Systemic Inflammation after Infant Heart Surgery trial (NCT03229538) who underwent heart surgery from June 2019 to May 2020 and opted into biomarker collection at a single center. Infants with preoperative CS-AKI were excluded.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Forty infants met inclusion criteria. Median (interquartile) age at surgery was 103 days (5.5–161 d). Modified Kidney Disease Improving Global Outcomes-defined CS-AKI was diagnosed in 22 (55%) infants and 21 (53%) developed FO. UCysC and uNGAL peaked in the early postoperative period and uKIM-1 peaked later. In unadjusted analysis, bypass time was longer, and Vasoactive-Inotropic Score at 24 hours was higher in infants with CS-AKI. On multivariable analysis, higher uCysC (odds ratio [OR], 1.023; 95% CI, 1.004–1.042) and uNGAL (OR, 1.019; 95% CI, 1.004–1.035) at 0–8 hours post-bypass were associated with FO. UCysC, uNGAL, and uKIM-1 did not significantly correlate with CS-AKI. In exploratory analyses of CS-AKI phenotypes, uCysC and uNGAL were highest in CS-AKI+/FO+ infants.

CONCLUSIONS: In this study, uCysC and uNGAL in the early postoperative period were associated with FO at 48 hours. UCysC, uNGAL, and uKIM-1 were not associated with CS-AKI. Further studies should focus on defining expected concentrations of these biomarkers, exploring CS-AKI phenotypes and outcomes, and establishing clinically meaningful endpoints for infants post-cardiac surgery.

KEY WORDS: acute kidney injury; fluid overload; infants; post-cardiac surgery; urine biomarkers

Cardiac surgery-associated acute kidney injury (CS-AKI) occurs in up to two-thirds of children undergoing heart surgery (1–4). CS-AKI causes fluid accumulation, which in turn exacerbates renal injury (5). CS-AKI

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RESEARCH IN CONTEXT

- Cardiac surgery-associated acute kidney injury (CS-AKI) and fluid overload (FO) are both common and associated with poor outcomes, but timely diagnosis is challenging.
- Urine biomarkers may diagnose CS-AKI earlier and more accurately but have not been extensively studied in neonates and infants, and their association with FO is unknown.
- In this study, we evaluate the association of urine biomarkers with CS-AKI and FO in infants after cardiac surgery.

and fluid overload (FO) are independently associated with poor outcomes (6–9). Diagnosing CS-AKI relies on definitions based on serum creatinine (SCr) and urine output. The major limitations of this definition are the difficulty of accurately characterizing urine output after cardiac surgery and a delay between onset of injury and change in SCr level (10, 11). Additionally, SCr levels are affected by gender, muscle mass, maternal levels within the first week of life, and dilution by fluid accumulation (5, 11, 12).

Changes in SCr or urine output that are transient and of little clinical significance versus those that identify true tissue injury impacting clinical outcomes are unclear; therefore, identifying urine biomarkers that permit earlier and more accurate diagnosis of clinically significant CS-AKI, or are reflective of deleterious CS-AKI phenotypes, would be beneficial (13). Several urine biomarkers, including urine neutrophil gelatinase-associated lipocalin (uNGAL) (12, 14–18), urine kidney injury molecule 1 (uKIM-1) (12, 17), and urine cystatin C (uCysC) seem promising in predicting CS-AKI in adult and neonatal populations but have not been studied extensively in children post-cardiac surgery (19, 20). No studies have evaluated the relationship between urine biomarkers and FO in any population post-cardiac surgery. We examined the association of uNGAL, uCysC, and uKIM-1 concentrations with CS-AKI and FO at various perioperative timepoints in infants with congenital heart disease undergoing cardiac surgery and explore how these biomarkers are associated with CS-AKI phenotypes.

MATERIALS AND METHODS

We performed a single-institution ancillary prospective cohort study of infants less than 1 year old enrolled in the Steroids to Reduce Systemic Inflammation after Infant Heart Surgery trial (NCT03229538), which was a multisite, randomized, double-blind, placebo-controlled trial to evaluate perioperative steroids in infants undergoing heart surgery on cardiopulmonary bypass (21, 22). All infants enrolled at Duke between June 2019 and May 2020 could opt-in to additional urine biomarker sampling. We excluded infants with preoperative CS-AKI or renal failure.

Our primary outcome was CS-AKI development. CS-AKI was defined using the modified Kidney Disease Improving Global Outcomes (KDIGO) criteria (23). We evaluated CS-AKI as a: 1) binary variable and 2) categorical variable by CS-AKI stage. Baseline creatinine was the last creatinine obtained prior to undergoing cardiopulmonary bypass. Maximum creatinine in the first 48 postoperative hours was used to determine CS-AKI (23).

Our secondary outcome was development of FO, defined as greater than or equal to 10% positive cumulative fluid balance at 48 hours (6–9). Fluid balance was calculated using the cumulative fluid input and output methodology in equation 1 (24):

$$\text{Percent fluid balance} = \frac{\text{Total Intake (mL)} - \text{Total Output (mL)}}{\text{Anchor Weight (kg)}} \times 100 \quad (1)$$

where anchor weight was the dosing weight at time of surgery. Fluid balance was evaluated continuously and categorically in 24-hour increments.

We conducted several sensitivity analyses, including evaluating CS-AKI and FO in neonates (surgery < 28 d old), correcting SCr levels for degree of FO (SCr_{CORR}), and classifying CS-AKI as severe (stage 2/3) versus nonsevere (stage 0/1) (25). SCr_{CORR} was calculated using equation 2 (13, 26):

$$SCr_{CORR} = \text{maximum postoperative SCr} \times \left[1 + \frac{\text{Net Fluid Balance}}{0.8 \times \text{Anchor Weight}}\right] \quad (2)$$

where net fluid balance was the cumulative fluid balance on the day the maximum SCr was documented.

In an exploratory analysis, we evaluated the association between urine biomarker concentrations and CS-AKI phenotype, defined as a combination of CS-AKI

and FO (e.g., CS-AKI–/FO–, CS-AKI+/FO–, CS-AKI–/FO+, CS-AKI+/FO+) (14). Informed consent was obtained from all parents or legal guardians. The study, titled "Steroids to Reduce Inflammation after Infant Heart Surgery," was approved by the Duke Institutional Review Board and performed in accordance with the ethical standards in the 1964 Declaration of Helsinki and its later amendments (Institutional Review Board number: Pro00086082; approval date: July 31, 2017).

Sample Collection

Spot urine samples were collected from the metered column of the Foley catheter at three perioperative timepoints: 1) preoperative; 2) early postoperative 0 to less than 8 hours post-bypass; and 3) late postoperative 8–24 hours post-bypass. Urine samples were centrifuged at room temperature at 2,000 × *g* for 10 minutes and the supernatants were stored in cryovials at –80°C. Urine samples were shipped to the Institute of Drug Safety Sciences at the University of North Carolina Eshelman School of Pharmacy and run through the Meso Scale Discovery Human Kidney Injury Multiplexed enzyme-linked immunosorbent assay panels (**eFig. 1**, http://links.lww.com/CCX/B188) (27). Control samples with high, medium, and low levels of each analyte were measured using a minimum of two replicates on 11 runs over 5 days. All samples were run in duplicate.

Data Collection

We prospectively collected the following demographic and clinical data from the electronic health record: postnatal age at surgery; weight at surgery; sex; race; ethnicity; cardiac diagnosis; surgery performed, including Society of Thoracic Surgeons - European Association for Cardio-Thoracic Surgery Congenital Heart Surgery Mortality Categories, cardiopulmonary bypass time, cross-clamp time, use of sustained all-region perfusion (28); need for extracorporeal membrane oxygenation or repeat surgery; laboratory values; and total intake, output, and overall fluid balance.

Definitions

Vasoactive-Inotropic Score (VIS) was calculated based on inotrope and vasoactive dose, where moderate support equals a VIS of 15 (29). The low cardiac output syndrome definition was derived from the Prophylactic IV Use of Milrinone After Cardiac Operation in Pediatrics study and was limited to laboratory criteria of greater than 30% difference in arterial and mixed venous saturation or metabolic acidosis with lactate greater than 5 in the first 24 hours post-surgery or increase in lactate of greater than 2 on successive blood gases (30).

Statistical Analysis

Distribution of continuous and categorical variables were described using medians (25–75th percentiles) and frequencies (percentages), respectively. Summary statistics described infants in the cohort, categorized by CS-AKI and FO. Continuous variables were compared with Wilcoxon rank-sum tests or univariable regressions. Categorical variables were compared with chi-square tests. Due to the lack of available data for the predictive ability of urine biomarkers in this population and the nature of this pilot study, no formal sample size calculations were performed.

The association between urine biomarker concentrations and CS-AKI and categorical FO were examined using separate multivariable logistic regressions for each biomarker, controlling for factors that were found to be significant on univariable analysis or clinically relevant. Concentrations for uCysC and uNGAL were divided by 10 to aid in interpretation of odds ratios (ORs). Variables were centered when collinearity was detected by a variance inflation factor greater than 5. The association between urine biomarker concentrations and continuous FO was examined using linear regression, controlling for the same factors. Changes in uCysC, uNGAL, and uKIM-1 over time and associations with CS-AKI and FO were graphically explored. A p value of less than 0.05 was considered significant. All analyses were conducted in STATA SE (Version 16.1; Stata Corps, College Station, TX).

RESULTS

Overall, 40 infants met inclusion/exclusion criteria and were enrolled in this study. All three urine samples were collected in 13 of 40 infants (32.5%), with a mean of two urine samples per infant. Gestational age at birth was a median (25–75th percentile) of 38 weeks (38–39 wk). At surgery, postnatal age was 103 days (5.5–161 d) and weight was 4.83 kg (3.6–5.88 kg).

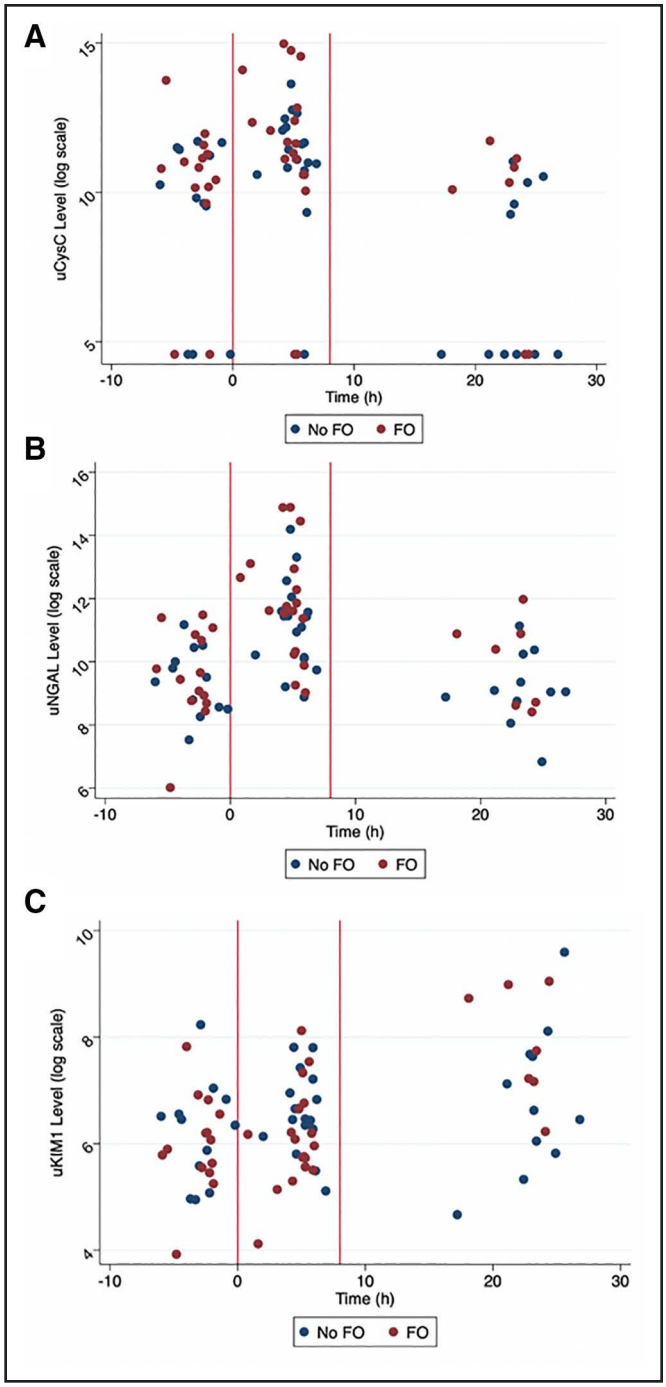

Figure 1. Changes in urine cystatin C (uCysC), urine neutrophil gelatinase-associated lipocalin (uNGAL), and urine kidney injury molecule 1 (uKIM-1) levels over time in relation to fluid overload (FO). Changes in: (**A**) uCysC; (**B**) uNGAL; and (**C**) uKIM-1 levels over time in relation to FO. Biomarker concentrations are plotted on log axis with time displayed in hours relative to separation from cardiopulmonary bypass (time = 0). *Vertical lines* denote perioperative time categories.

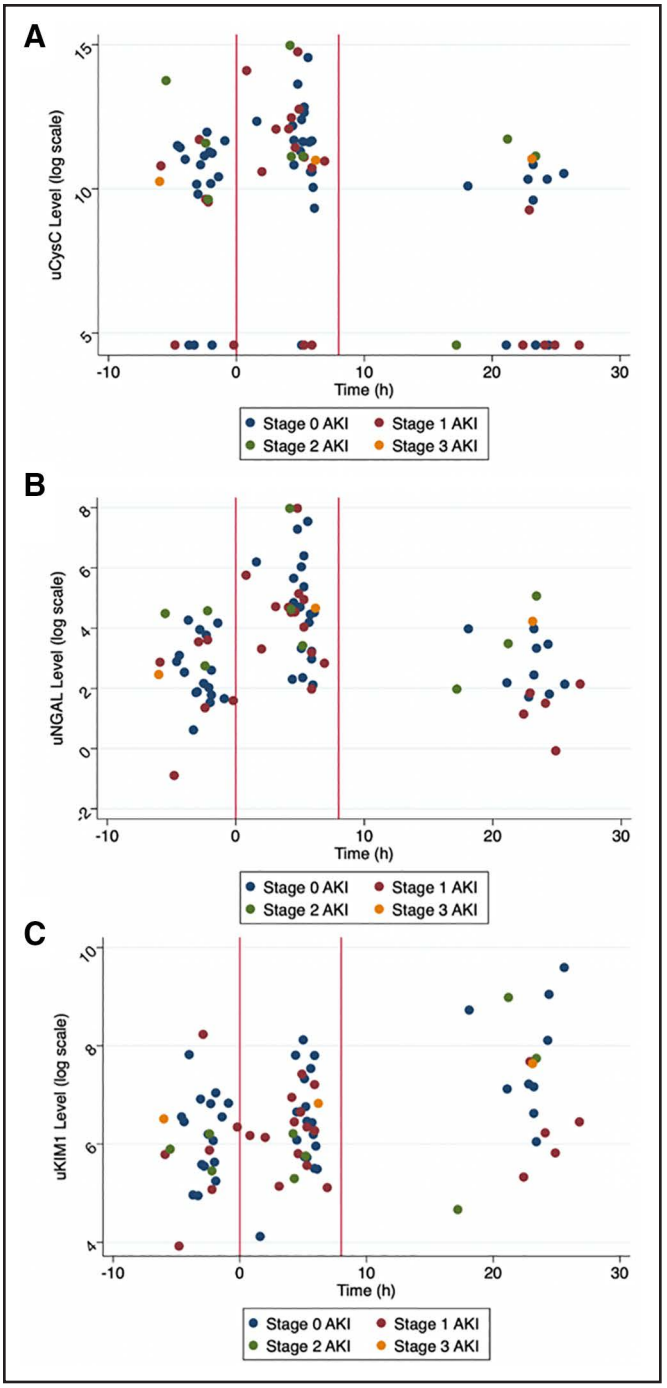

Figure 2. Changes in urine cystatin C (uCysC), urine neutrophil gelatinase-associated lipocalin (uNGAL), and urine kidney injury molecule 1 (uKIM-1) levels over time in relation to acute kidney injury (AKI) stage. Changes in: (**A**) uCysC; (**B**) uNGAL; and (**C**) uKIM-1 levels over time in relation to AKI stage. Biomarker concentrations are plotted on log axis with time displayed in hours relative to separation from cardiopulmonary bypass (time = 0). *Vertical lines* denote perioperative time categories.

No infants received prophylactic peritoneal dialysis or other kidney-supportive therapies, and no infants died. When examining trends over time, all biomarkers peaked post-bypass. Both uCysC and uNGAL peaked in the early postoperative period, whereas uKIM-1 peaked later (**Figs. 1** and **2**).

Cardiac Surgery-Associated Acute Kidney Injury

Twenty-two infants (55%) were diagnosed with CS-AKI: 15 (37.5%) had stage 1, six (15%) had stage 2, and one (2.5%) had stage 3. Median time to peak creatinine was postoperative day 1 with no difference by presence of CS-AKI (p = 0.5). Infant characteristics are shown stratified by CS-AKI in **Table 1** and CS-AKI stage in **eTable 1** (http://links.lww.com/CCX/B188).

In unadjusted analyses, bypass time was longer, and VIS was higher in infants with CS-AKI (p = 0.01 and p = 0.02, respectively). CS-AKI was not associated with fluid balance or cumulative FO. Urine biomarker concentrations stratified by CS-AKI stage are summarized in **eTable 2** (http://links.lww.com/CCX/B188).

In multivariable analyses controlling for bypass time, VIS, and need for arch repair as a surrogate marker of preoperative obstruction to systemic blood flow, there were no significant correlations between CS-AKI and uCysC, uNGAL, and uKIM-1 (**Table 2**).

FO at 48 Hours

At 48 hours, 21 infants (52.5%) developed FO. **eTable 3** (http://links.lww.com/CCX/B188) displays urine biomarker concentrations stratified by FO. In multivariable analyses controlling for bypass time, VIS, and need for arch repair, higher concentrations of early postoperative uCysC (OR, 1.023; 95% CI, 1.004–1.042) and uNGAL (OR, 1.019; 95% CI, 1.004–1.035) were associated with categorical FO at 48 hours (Table 2). Similarly, higher levels of early postoperative uCysC (β = 0.045; p = 0.003) and uNGAL (β = 0.047; p = 0.003) were associated with FO when evaluated continuously. Please refer to the **Supplemental Results** and **eTable 4** (http://links.lww.com/CCX/B188) for information on a subanalysis we performed in 13 neonates. Please refer to Supplemental Results and **eTables 5–7** (http://links.lww.com/CCX/B188) for our examination of fluid accumulation-corrected SCr.

AT THE BEDSIDE

- Early postoperative urine neutrophil gelatinase-associated lipocalin and urine cystatin C were associated with FO in infants at 48 hours after cardiac surgery, but no urine biomarkers were associated with CS-AKI.
- Exploratory analyses suggest urine biomarkers may be able to differentiate CS-AKI and FO phenotypes.
- Further studies should definitively evaluate the association between urine biomarkers, CS-AKI and FO phenotypes, and clinical outcomes in this population.

Severe CS-AKI

When evaluating CS-AKI as nonsevere or severe using SCR_{CORR}, seven infants (17.5%) in our cohort developed severe CS-AKI. Cumulative fluid balance at 24 and 48 hours were associated with severe CS-AKI (p = 0.04 and p = 0.01, respectively) (**eTable 8**, http://links.lww.com/CCX/B188). In unadjusted analyses, early and late postoperative uCysC and late postoperative uNGAL were significantly associated with severe CS-AKI. In multivariable analyses controlling for VIS, bypass time, and need for arch repair, only uNGAL in the early postoperative period was associated with severe CS-AKI (OR, 1.02; 95% CI, 1.00–1.04; **eTable 9**, http://links.lww.com/CCX/B188).

CS-AKI Phenotypes

In analysis of CS-AKI phenotypes, 18 infants (45%) were FO-/CS-AKI-, one infant (3%) was FO–/CS-AKI+, 14 infants (35%) were FO+/CS-AKI-, and seven infants (18%) were FO+/CS-AKI+ (**eTable 10**, http://links.lww.com/CCX/B188). In unadjusted analyses, postoperative uCysC and uNGAL were significantly higher in FO+/CS-AKI+ infants (**eTable 11**, http://links.lww.com/CCX/B188). In multivariable analyses controlling for bypass time, VIS, and need for arch repair, early postoperative uNGAL and uCysC remained significantly higher in FO+/CS-AKI+ infants (**eTable 12**, http://links.lww.com/CCX/B188).

TABLE 1.
Infant Demographic and Clinical Characteristics of the Entire Cohort, and of Those With and Without Acute Kidney Injury

Characteristics	All, *n* = 40 (%)	No AKI, *n* = 18 (%)	Any AKI, *n* = 22 (%)	*p*
Gestational age at birth (wk)[a]	38 (38–39)	38.5 (38–39)	38 (38–39)	0.97
Age at surgery (d)[a]	103 (5.5–161)	118 (6–188)	96 (5–154)	0.65
Weight at surgery (kg)[a]	4.83 (3.6–5.88)	5.13 (3.66–5.95)	4.13 (3.3–5.8)	0.17
Male	19 (48)	10 (56)	9 (41)	0.36
Race				0.12
White	24 (60)	14 (78)	10 (45)	
Black	11 (28)	2 (11)	9 (41)	
Asian	1 (3)	0 (0)	1 (5)	
Other	4 (10)	2 (11)	2 (9)	
Ethnicity				0.19
Hispanic	2 (5)	0 (0)	2 (9)	
Arch repair	7 (17.5)	3 (17)	4 (18)	0.9
Baseline creatinine[a]	0.35 (0.3–0.5)	0.3 (0.3–0.6)	0.4 (0.3–0.4)	0.81
Creatinine peak (postoperative day)[a]	1 (1–1)	1 (1–1)	1 (1–1)	0.78
STAT category				0.16
1	8 (20)	6 (33)	2 (9)	
2	7 (18)	3 (17)	4 (18)	
3	11 (28)	6 (33)	5 (23)	
4	9 (23)	2 (11)	7 (32)	
5	5 (13)	1 (6)	4 (18)	
Cardiopulmonary bypass time[a]	139 (99–192)	111 (75–155)	171 (106–222)	***0.01***
Cross-clamp time[a]	61 (36–100)	58 (32–84)	71.5 (37–117)	0.35
Sustained all region perfusion	4 (10)	1 (6)	3 (14)	0.40
Lowest intraoperative temperature (°C)[a]	28 (28–32)	32 (28–33.8)	28 (27.8–31.4)	0.08
Diuretic in first 24 hr after surgery	34 (94)	17 (100)	17 (89)	0.17
Low cardiac output syndrome	9 (24)	3 (19)	6 (29)	0.5
Vasoactive-Inotropic Score[a]	8 (4–11)	5 (2–9.5)	9.5 (6–11.5)	***0.02***
Cumulative fluid balance (mL/kg)[a]				
24 hr	37 (7.8–64)	33 (–6.2 to 65)	50 (15–62)	0.29
48 hr	20 (–23 to 55)	34 (–4.3 to 56)	–1 (–34 to 48)	0.34
72 hr	–7.5 (–60 to 43)	8.3 (–39 to 45)	–12 (–87 to 29)	0.39
Cumulative fluid overload (%)				
24 hr	30 (75)	13 (72)	17 (77)	0.71
48 hr	21 (53)	11 (61)	10 (45)	0.32
72 hr	18 (45)	9 (50)	9 (41)	0.57

AKI = acute kidney injury.

[a]Median (25–75th percentile).

Data presented at counts (percentages). Significant findings are bolded/italicized.

TABLE 2.

Multivariable Logistic Analyses Evaluating the Association Between Perioperative Urine Biomarkers and Acute Kidney Injury and Fluid Overload at 48 Hours, Controlling for Vasoactive-Inotropic Score, Cardiopulmonary Bypass Time, and Need for Arch Repair (Presented As Odds Ratio [95% CI])

Biomarkers	Acute Kidney Injury	Fluid Overload at 48 hr
Preoperative		
Cystatin C	1.01 (0.94–1.09)	1.06 (0.97–1.17)
NGAL	1.25 (0.86–1.83)	1.18 (0.83–1.68)
KIM-1	1.10 (0.38–3.14)	0.80 (0.28–2.31)
0 to < 8 hr after cardiopulmonary bypass		
Cystatin C	1.00 (0.98–1.01)	***1.02 (1.00–1.04)***
NGAL	0.99 (0.98–1.00)	***1.02 (1.00–1.04)***
KIM-1	0.30 (0.07–1.33)	0.46 (0.14–1.46)
≥ 8 hr after cardiopulmonary bypass		
Cystatin C	1.18 (0.82–1.71)	1.78 (0.71–4.44)
NGAL	1.05 (0.77–1.42)	1.48 (0.70–3.13)
KIM-1	0.81 (0.52–1.28)	5.55 (0.18–173.3)

KIM-1 = kidney injury molecule-1, NGAL = neutrophil gelatinase-associated lipocalin.

Odds ratios (ORs) for cystatin C and NGAL are for 0.1 ng/mL increments, while ORs for KIM-1 are for 1 ng/mL increments. Significant findings are bolded/italicized.

DISCUSSION

We evaluated the association of uNGAL, uCysC, and uKIM-1 with CS-AKI and FO in infants post-cardiopulmonary bypass. While prior studies focused on the association between urine biomarkers and CS-AKI, our study evaluated the interplay of urine biomarkers, CS-AKI, and FO. Both CS-AKI and FO were common, occurring in more than half of infants, and most CS-AKI was stage 1, consistent with prior literature (3, 5–11). Higher uNGAL and uCysC concentrations in the first 8 postoperative hours were associated with FO at 48 hours, suggesting the possibility these biomarkers could facilitate early identification of infants at risk for FO.

FO has been strongly associated with adverse outcomes (5, 8, 31). In a secondary analysis of prospectively collected data of children less than 18 years old undergoing cardiac surgery, positive fluid balance on the first postoperative day was associated with higher morbidity and mortality (6). A prospective observational study in infants less than 6 months after cardiac surgery showed that infants with a maximal cumulative fluid balance of 12–24% in the first three postoperative days had increased odds of requiring continuous renal replacement therapy, longer time to extubation, longer ICU stay, and death (9). Two additional studies of neonates after cardiac surgery showed that fluid accumulation peaked on postoperative day 2 and was independently associated with worse outcomes when controlling for CS-AKI (2, 32). Early identification of infants likely to develop FO may allow for risk stratification and optimization of medical management through limiting fluid intake, increasing diuresis, improving renal perfusion pressure, and avoiding nephrotoxic medications.

Our study did not show an association between urine biomarker concentrations and KDIGO-defined CS-AKI in infants. Prior studies in adults and children after cardiac surgery show a strong association between urine biomarker concentrations and CS-AKI, but studies in neonates and infants have mixed results (9–11, 16, 33). In a prospective cohort analysis of 59 infants undergoing cardiac surgery, perioperative uNGAL was not associated with CS-AKI (16) but was associated with bypass time and perioperative plasma interleukin-6 concentrations as an inflammation marker. In another prospective cohort of 53 neonates, uCysC at 24–48 hours and preoperative uNGAL were associated with CS-AKI (33), but uKIM-1 was not. Conversely, a multicenter pilot study of 98 infants undergoing cardiac surgery found that uKIM-1 at 6 hours was associated with CS-AKI (34). The inconsistent association between urine biomarker concentrations and CS-AKI in infants is likely multifactorial but may be due to heterogeneous mechanisms of injury in CS-AKI or limitations of current CS-AKI definitions that fail to account for age- and disease-related renal changes in this population (35–37).

Our sensitivity analyses highlight areas where further research can be directed to clarify CS-AKI definitions, incorporate FO, determine clinically meaningful endpoints, and establish normal values for urine biomarker concentrations. For neonates, those without CS-AKI had higher baseline SCr than those with CS-AKI, likely

reflective of maternal creatinine, potentially leading to CS-AKI underdiagnosis (5, 11). Neonatal urine biomarker concentrations may be higher than those in infants: UCysC and uNGAL trended higher, and uKIM-1 was significantly higher in neonates. Establishing "normal" biomarker concentrations based on age and disease process will allow easier identification of infants with abnormal values. When correcting SCr for FO, differences between biomarker concentrations and CS-AKI seen on unadjusted analyses did not persist in multivariable analysis. Using SCr_{CORR} may control for degree of FO and more accurately diagnose CS-AKI, but our data suggest there remains no association between urine biomarker concentrations and CS-AKI as currently defined. Last, when evaluating urine biomarker concentrations and severe CS-AKI, early postoperative uNGAL was associated with severe CS-AKI—a finding consistent with literature where urine biomarkers have been shown to better predict severe CS-AKI (36, 38). While any renal injury can be detrimental, predicting which infants are most likely to develop severe CS-AKI and facilitating intervention may have a positive effect on outcomes.

CS-AKI represents a heterogeneous disease process that both contributes to and is a consequence of FO (35). Capillary leak after bypass results in generalized fluid retention, which increases renal subcapsular pressure resulting in renal injury. Similarly, lower renal blood flow and tubular dysfunction lead to lower urine output and fluid accumulation. Emerging literature suggests that CS-AKI has distinct phenotypes in relation to FO, reflecting different pathophysiologic mechanisms of injury (13, 35). Categorizing infants by CS-AKI phenotype may allow for improved prognostic and therapeutic stratification. In our exploratory analysis, we found that early postoperative uNGAL and uCysC were significantly different between CS-AKI phenotypes, with the highest concentrations in FO+/CS-AKI+ infants. Future studies exploring the relationship between urine biomarkers, mechanism of renal injury, CS-AKI phenotypes, and outcomes may provide the best guidance on interpreting these findings.

Our study has important limitations. Biomarker concentrations were not adjusted for urine output or urine creatinine concentrations given the absence of literary consensus on whether absolute concentrations, those normalized to urine creatinine, or normalized to urine output most effectively aid urine biomarker concentration interpretations (39, 40). Therefore, we used absolute biomarker concentrations as these are used in clinical practice. Only one infant developed stage 3 CS-AKI, which limited our ability to determine associations between urine biomarkers and severe CS-AKI. We attempted to control for important covariables, although they may not account for all confounders in our small cohort. We calculated fluid balance by intake and output, which does not account for insensible losses, but is recommended by the Pediatric Acute Disease Quality Initiative group and is more feasible than using weight change in the immediate postoperative setting (24). As with most pediatric studies, our sample size was small and from a single center, yet our data may inform future studies that interpret urine biomarker concentrations based on age and disease process in the context of CS-AKI and FO. Finally, the study group was heterogeneous in its cardiac diagnosis and repair, representing a subgroup from a larger randomized controlled trial in which receipt of preoperative steroids was blinded and uncontrolled in this study.

CONCLUSIONS

In this single-center, prospective cohort study in infants undergoing cardiac surgery, early postoperative uCysC and uNGAL were associated with FO at 48 hours. Stage 1 CS-AKI, uCysC, uNGAL, and uKIM-1 were not associated with CS-AKI, but uCysC and uNGAL may be associated with CS-AKI phenotypes. UCysC and uNGAL peaked in the early postoperative period, and uKIM-1 peaked later. In neonates, early postoperative uNGAL was higher in those who developed FO. Further studies should focus on defining expected concentrations of these biomarkers, exploring CS-AKI phenotypes and outcomes, and establishing clinically meaningful endpoints for infants post-cardiac surgery.

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