The Association of Albumin/Creatinine Ratio with Postoperative AKI in Children Undergoing Cardiac Surgery

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Summary

Background and objectives This study determined if preoperative and postoperative urine albumin/creatinine ratios (ACRs) predict postoperative AKI in children undergoing cardiac surgery (CS).

Design, setting, participants, & measurements This was a three-center, prospective study (2007–2009) of 294 children undergoing CS (n=145 aged <2 years). Urine ACR was measured preoperatively and 0–6 hours after intensive care unit arrival. AKI outcomes were based on the Acute Kidney Injury Network serum creatinine (SCr) criteria (stage 1 AKI, ≥50% or 0.3 mg/dl SCr rise from baseline; and stage 2 or worse AKI, ≥SCr doubling or dialysis). AKI was predicted using preoperative and postoperative ACRs and postoperative ACR performance was compared with other AKI biomarkers.

Results Preoperative ACR did not predict AKI in younger or older children. In children aged <2 years, first postoperative ACR ≥908 mg/g (103 mg/mmol) predicted stage 2 AKI development (adjusted relative risk, 3.4; 95% confidence interval, 1.2–9.4). In children aged ≥2 years, postoperative ACR ≥169 mg/g (19.1 mg/mmol) predicted stage 1 AKI (adjusted relative risk, 2.1; 95% confidence interval, 1.1–4.1). In children aged ≥2 years, first postoperative ACR improved AKI prediction from other biomarker and clinical prediction models, estimated by net reclassification improvement (P≤0.03), but only when serum cystatin C was also included in the model.

Conclusions Postoperative ACR is a readily available early diagnostic test for AKI after pediatric CS that performs similarly to other AKI biomarkers; however, its use is enhanced in children aged ≥2 years and in combination with serum cystatin C.

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Introduction

AKI is common in children undergoing cardiac surgery (CS) and is associated with prolonged length of stay (LOS) and mechanical ventilation (1,2). In noncardiac pediatric intensive care unit (ICU) patients, AKI is independently associated with mortality (3–5). Previous AKI therapeutic trials have been negative, in part, due to a delayed rise in serum creatinine (SCr), missing the therapeutic window for mitigating AKI (6). In search of early AKI biomarkers, we found that postoperative urine neutrophil gelatinase-associated lipocalin (NGAL), IL-18, and serum cystatin C (CysC), obtained within hours after CS, predict AKI before SCr rise (7,8).

Postoperative urine albumin is a promising early AKI biomarker, reflecting tubular or glomerular damage (9–12). Preoperative albuminuria predicts AKI in adults (13,14). In children, evaluating albuminuria as an AKI risk factor is complicated by variable protein excretion, which is physiologically higher in younger children (15–17).

Using a multicenter pediatric CS cohort, we determined if the preoperative urine albumin/creatinine ratio (ACR) and/or early postoperative ACR predicts CS-AKI development, and if preoperative and postoperative ACRs provide additional benefit for predicting CS-AKI above what is feasible using other early AKI biomarkers.

Materials and Methods

Study Design, Setting, and Patient Selection

This was a multicenter prospective cohort study of the Translational Research Investigating Biomarker Endpoints in Acute Kidney Injury consortium study (TRIBE-AKI) conducted at Yale New Haven Hospital (New Haven, CT), Cincinnati Children's Hospital Medical Center (Cincinnati, OH), and Montreal Children's Hospital (Montreal, Canada). Children aged ≤18 years undergoing CS between 2007 and 2009 were eligible. Children with a renal transplant or receiving chronic dialysis were excluded. Infants aged <4 weeks were excluded from analysis due to unique characteristics of neonates with regards to proteinuria (16). We enriched our cohort with higher risk patients by favoring enrollment of children

undergoing risk adjustment for congenital heart surgery-1 (RACHS-1) category ≥2 surgeries. Children were recruited preoperatively and followed postoperatively. The original study goal was to validate novel AKI biomarkers such as urine NGAL, IL-18 (7), and serum CysC (8). This study was a secondary analysis of urinary ACR. Each institution's research ethics boards approved the study. Informed consent was obtained from patients or parents/guardians before participation, with assent where appropriate.

Brief Protocol Description

The study protocol has been previously reported (1,7). We recorded demographic data and medical history and collected blood and urine preoperatively for SCr, CysC, and urine ACR measurement. We used the Schwartz equation (18) to estimate preoperative GFR (eGFR) expressed as percentiles for age (8). We recorded surgical procedure details (*e.g.*, anatomy, procedure, bypass time). Within 6 hours of arrival to the ICU (or "first-postoperative") and then daily for 3 days, we collected urine and blood to measure urine AKI biomarkers (NGAL and IL-18), urine ACR, SCr, and CysC. Urine samples were collected fresh from the Foley catheter urimeter, using cotton balls in patients wearing diapers or by clean catch in older children without a bladder catheter. We centrifuged biospecimens (3000×*g* for 10 minutes), aliquoted urine supernatant and plasma, and stored them at −80°C until analyte measurement.

Urine and Serum Biomarker Measurements

SCr was measured in local laboratories by modified Jaffe or enzymatic assays. Urine biomarkers and CysC were measured at the Cincinnati Children's Hospital Biomarker Laboratory. We measured urine albumin by immunoturbidimetry (Siemens Dimension Plus with HM clinical analyzer) per the manufacturer's instructions and urine creatinine by modified Jaffe reaction. Urine ACR was calculated as milligrams of albumin per grams of creatinine (divided by 8.84 for SI units, mg/mmol). We measured urine NGAL and IL-18 with the ARCHITECT assay (Abbott Diagnostics, Abbott Park, IL), with coefficients of variation (CV) of 5% and 8%, respectively. We measured CysC using a nephelometer (Siemens BN-II, Siemens, AG; www.Siemens.com) (CV=1.1%). Individuals performing measurements were blind to clinical data.

ACR Threshold Definitions

We categorized participants into low-, medium-, or high-risk preoperative ACR threshold groups. Because urine albumin is physiologically higher in children aged <2 years (16), preoperative ACR thresholds differed by age group. Children aged <2 years were classified as low risk (preoperative ACR <30 mg/g [3.4 mg/mmol]), medium risk (ACR ≥30 [3.4 mg/mmol] to <300 mg/g [34 mg/mmol]), and high risk (ACR ≥300 mg/g [34 mg/mmol]) (16). In children aged ≥2 years, we based thresholds on standard microalbuminuria definitions (19,20), with low risk (ACR <10 mg/g [1.1 mg/mmol]), medium risk (ACR ≥10 [1.1 mg/mmol] to <30 mg/g [3.4 mg/mmol]), and high risk (ACR ≥30 mg/g [34 mg/mmol]).

To evaluate first postoperative ACR for early CS-AKI diagnosis, we classified patients into lower, middle, and upper tertile ACR concentrations (for each age group), because there is no standard postoperative albuminuria threshold.

AKI Definition

We based our AKI outcomes on the Acute Kidney Injury Network (AKIN) definition (21); stage 1 AKI was a ≥50% or 0.3 mg/dl (27 μmol/L) SCr rise from preoperative value, stage 2 was doubling of SCr, and stage 3 was a tripling of SCr or receipt of dialysis during hospitalization. This study was not designed to collect hourly urine output required to define AKIN urine output criteria. We did not include the requirement for SCr to rise within 48 hours (stated in the AKIN definition); however, we have shown that most AKI occurred in the first 48 hours of ICU admission in these patients (1).

Statistical Analyses

We performed analyses separately for children aged <2 and ≥2 years. We calculated unadjusted and adjusted relative risks (RRs) of preoperative ACR to predict CS-AKI with Poisson regression (22). In adjusted analyses, we controlled for our previously reported clinical AKI predictors as follows: age (continuous in the group aged <2 years; 2–<6 versus ≥6 years in group aged ≥2 years), sex, white versus nonwhite race, elective versus urgent surgery, RACHS-1 (23) score ≥3 versus <3, preoperative eGFR percentile, and study site. We calculated the area under the receiver operating characteristic curve (AUC; with SEM) to determine the ability of preoperative ACR to discriminate between patients with and without CS-AKI and determined if adding preoperative ACR to the predictive clinical model led to a statistically significant AUC rise (24). We calculated the continuous net reclassification improvement (NRI; with SEM) of adding preoperative ACR to the clinical prediction model for CS-AKI, to determine the added value of preoperative ACR for predicting AKI (25,26). A higher NRI results from individuals with AKI being assigned to having a higher AKI risk and from individuals without AKI being assigned a lower AKI risk, when the new biomarker is added to the model.

We used similar analyses to determine if tertiles of first postoperative ACR predicted CS-AKI. For these analyses, we included cardiopulmonary bypass time (CPB; <120 versus ≥120 minutes) in the clinical prediction model. We calculated diagnostic characteristics for different first postoperative ACR threshold values for AKI prediction. Because of our previous findings that first postoperative urine NGAL (7), urine IL-18 (7), and serum CysC (8) were predictive of CS-AKI, we additionally determined the extent to which adding first postoperative ACR to CS-AKI prediction models led to significant increase in the AUC for AKI prediction and to statistically significant NRI. The previously reported biomarkers were collected at the same time points as urine ACR. To evaluate if preoperative ACR affected the postoperative ACR-AKI relation, we repeated the above AUC and NRI analyses expressing postoperative ACR as the raw difference and as the percentage change in postoperative ACR relative to preoperative ACR and by including preoperative ACR in clinical prediction models.

We evaluated if first postoperative ACR (natural logarithm-transformed, not in tertiles) predicted longer hospital and ICU LOS independent of other clinical variables described above, using negative binomial multiple regression. All analyses were performed using SAS (version 9.1; SAS Institute, Cary, NC) and R software (version 2.12.1; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Characteristics

Figure 1 displays the study flow. In the group aged <2 years, younger age was associated with higher ACR and ACR differed by study site (Table 1); in the group aged ≥2 years, participants in the high ACR category had higher RACHS-1 scores and longer ICU and hospital stays (Table 1). AKI (stage 1 or worse) first occurred on mean postoperative day 1.6 (SD 0.5) and day 1.5 (SD 1.3) in the groups aged <2 years and ≥2 years, respectively.

Association of Preoperative ACR and CS-AKI

There was little difference in CS-AKI incidence across the preoperative ACR categories in the group aged <2 years; in the group aged ≥2 years, CS-AKI was most common in the highest ACR category, but the difference was not statistically significant (Table 1). There was no statistically significant association between preoperative ACR and postoperative development of mild (stage 1 or worse) or moderate (stage 2 or worse) AKI (Table 2).

A preoperative clinical model predicted CS-AKI with AUCs of 0.68 for the group aged <2 years (SEM 0.04) and 0.77 for the group aged ≥2 years (SEM 0.04). Adding preoperative ACR to the clinical model had no statistically significant effect on AUC, with AUCs of 0.72 for the group aged <2 years (SEM 0.05) and 0.80 for the group aged ≥2 years (SEM 0.04) ($P>0.05$ compared with clinical model alone). The NRI of adding preoperative ACR to the clinical model was not statistically significant, being 0.21 (SEM 0.19; $P=0.26$) in the group aged <2 years and 0.03 (SEM 0.18; $P=0.86$) in the group aged ≥2 years.

Association of First Postoperative ACR and CS-AKI

In patients with and without CS-AKI, first postoperative ACR was statistically significantly higher than preoperative ACR ($P<0.001$, both age groups). Figure 2 displays the dramatic rise in first postoperative ACR in both age groups and in AKI and non-AKI patients, with a rapid drop in ACR by the second and third postoperative days.

In the group aged ≥2 years, the highest first postoperative ACR tertile (≥169 mg/g, 19.1 mg/mmol) predicted postoperative stage 1 or worse AKI after adjusting for clinical variables (unadjusted RR, 2.29; 95% confidence interval [95% CI], 1.17–4.49) (adjusted RR, 2.10; 95% CI, 1.08–4.08) (Table 3). For both age groups, the highest postoperative ACR tertile predicted development of stage 2 AKI or worse in unadjusted analyses (Table 3). In adjusted analyses, for the group aged <2 years, first postoperative ACR in the third tertile predicted stage 2 AKI development (adjusted RR, 3.41; 95% CI, 1.24–9.37) (Table 3). It was not possible to calculate adjusted risk for postoperative ACR to predict stage 2 AKI in the group aged ≥2 years due to low event numbers. Table 4 displays the diagnostic characteristics of first postoperative ACR thresholds for early AKI diagnosis. The ACR threshold value with maximal sensitivity and specificity in the group aged ≥2 years was almost half of the similar value in the group aged <2 years. In general, negative predictive values were high with low positive predictive values (Table 4).

Added Benefit of Postoperative ACR to Predict CS-AKI above Known Clinical and Biomarker Predictors

Table 5 displays postoperative ACR performance for predicting AKI over and above clinical data, urine (NGAL, IL-18), and serum (CysC) biomarkers. Results on stage 2 AKI or worse for the group aged ≥2 years were

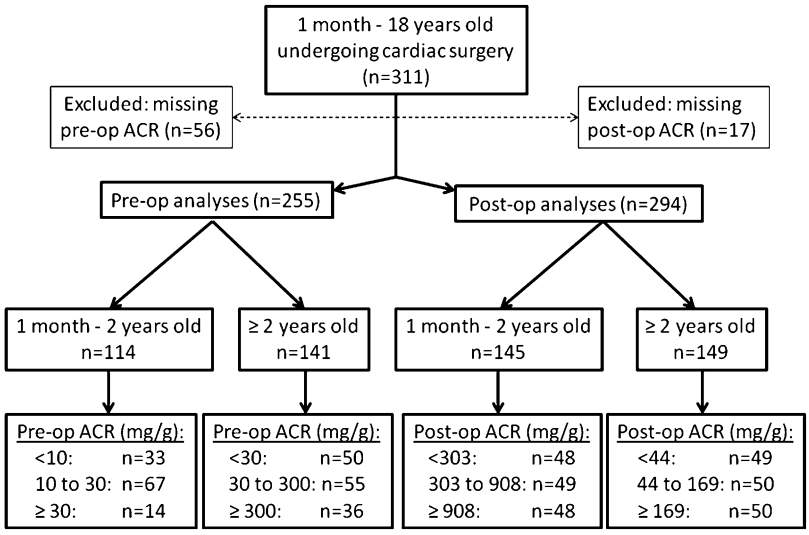

Figure 1. | **Study flow leading to the analysis population**. The top of the figure displays the total study population. The diagram flows downward demonstrating the final patient numbers leading to the preoperative and postoperative analysis groups in the groups aged <2 years and ≥2 years, with respective ACR thresholds. To convert albumin to creatinine ratio to SI units, divide by 8.84. ACR, albumin/creatinine ratio.

Table 1. Patient characteristics by age group and by preoperative ACR category

Characteristic	Aged 1 mo–2 yr			Aged ≥2 yr		
	ACR <30 mg/g (*n*=33)[a]	ACR 30–<300 mg/g (*n*=67)	ACR ≥300 mg/g (*n*=14)	ACR <10 mg/g (*n*=50)	ACR 10–<30 mg/g (*n*=55)	ACR ≥30 mg/g (*n*=36)
Age at surgery (yr)[b]	0.69±0.45	0.50±0.35	0.49±0.38[c]	7.4±3.8	6.8±4.4	6.9±4.7
Male sex	18 (55)	42 (63)	6 (43)	28 (56)	25 (45)	24 (67)
White race[b]	31 (94)	53 (79)	12 (86)	37 (74)	51 (93)	27 (75)
Study site						
Cincinnati	27 (82)	39 (58)	10 (71)[c]	35 (70)	33 (60)	24 (67)
Montreal	5 (15)	18 (27)	0 (0)	13 (26)	14 (25)	7 (19)
Yale	1 (3)	10 (15)	4 (29)	2 (4)	8 (15)	5 (14)
Preoperative eGFR[d]	87.2±26.4	78.7±24.3	82.4±28.5	96.9±20.6	102.0±20.1	103.6±26.5
Preoperative eGFR percentile[d]	66.2±33.4	59.2±34.9	67.5±30.8	39.2±31.2	46.9±31.0	45.8±34.8
RACHS-1 score	2.4±0.7	2.5±0.7	2.3±0.5	2.2±0.7	2.5±0.7	2.6±0.7[d]
CPB time (min)	114±82	113±51	102±46	94±55	108±73	118±73
Cross-clamp time (min)	61±46	65±44	51±40	34±37	36±49	44±51
Outcomes						
Stage 1 or higher AKI	19 (58)	34 (51)	8 (57)	12 (24)	17 (31)	14 (39)
Stage 2 or 3 AKI	10 (30)	15 (22)	2 (14)	3 (6)	7 (13)	6 (17)
ICU stay (d)	3 (2–5)	3 (2–6)	3 (2–13)	1 (1–2)	2 (1–4)	2 (1–4)[e]
Hospital stay (d)	6 (4–9.5)	6 (5–12)	6 (4–19)	4 (3–5)	5 (3–7)	5.5 (3–9.5)[c]
Dialysis	0 (0)	1 (1)	0 (0)	0 (0)	1 (2)	2 (6)
Mortality	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	2 (6)

Data are mean ± SD, *n* (%), or median (interquartile range). ACR, albumin/creatinine ratio; eGFR, estimated GFR; RACHS-1, risk adjustment for congenital heart surgery; CPB, cardiopulmonary bypass; ICU, intensive care unit.
[a]ACR cutoffs evaluated differed for the two age groups based on the known association of higher ACR in children aged <2 years. To convert to SI units (mg albumin per mmol creatinine), divide ACR by 8.84.
[b]Interval variables presented as mean ± SD and categorical variables presented as *n* (% of column total).
[c]Denotes a statistically significant difference between the three ACR categories with $P<0.05$.
[d]GFR was estimated using the Schwartz equation (18); eGFR percentile was calculated using normative-based values from a previous study (8).
[e]Denotes a statistically significant difference between the three ACR categories with $P<0.01$.

omitted due to low event rates. In both age groups, AUCs from the clinical predictive model and first postoperative ACR were extremely similar to the models including clinical risk factors and other biomarkers (shown in Table 5). Adding first postoperative ACR to other predictive models (clinical, clinical plus biomarkers) did not improve AUC for predicting stage 1 AKI or worse in either age group. When urine biomarkers were normalized to creatinine, adding ACR to the model including clinical and urine biomarker data were associated with a significant NRI in the group aged <2 years; however, this effect disappeared once CysC was in the model (all shown in Table 5). In the group aged ≥2 years, adding first postoperative ACR to the predictive models only led to significant NRIs for predicting stage 1 AKI or worse, when CysC was also in the model and urine biomarkers were not normalized to urine creatinine (shown in Table 5). First postoperative ACR performance for predicting AKI was not improved by incorporating preoperative ACR in any of the models (data not shown).

Association of Postoperative Urine ACR with LOS

In the group aged <2 years, first postoperative ACR predicted longer hospital LOS (adjusted $P=0.02$), independent of other clinical variables, but not longer ICU LOS. In children aged ≥2 years, first postoperative ACR was independently associated with longer hospital LOS (adjusted $P=0.02$) and ICU LOS (adjusted $P=0.01$).

Discussion

Early postoperative, but not preoperative, ACR predicted CS-AKI in children. The utility of postoperative ACR to predict AKI and other outcomes was greater in children aged ≥2 years.

Animal and human studies have demonstrated that urine albumin rises dramatically with AKI (9–11). Albumin is normally filtered by the glomerulus, transported, and degraded in the proximal tubule. With AKI, albumin excretion may rise due to glomerular and/or renal tubular damage or albumin gene upregulation in the renal cortex or tubules (12). Albuminuria may also occur due to CPB-associated inflammation causing increased glomerular permeability (27). Although we could not evaluate inflammatory markers, when we controlled for CPB, postoperative ACR remained predictive of AKI.

The utility of postoperative ACR for AKI prediction was discrepant between the two age groups. In children aged <2 years, postoperative ACR only predicted more severe (stage 2) AKI and was less strongly associated with the LOS

Table 2. Unadjusted and adjusted RRs for preoperative ACR to predict development of postoperative stage 1 or stage 2 AKI, by age group

Preoperative ACR	Stage 1 or Higher AKI[a]			Stage 2 or 3 AKI[a]		
	Stage 1 AKI	Unadjusted RR	Adjusted RR[b]	Stage 2 AKI	Unadjusted RR	Adjusted RR[b]
	n (% of Group)	95% CI	95% CI	n (% of Group)	95% CI	95% CI
Participants aged 1 mo–<2 yr at surgery						
No. of events	61			27		
<30 mg/g (*n*=33)	19 (58)	1	1	10 (30)	1	1
30–<300 mg/g (*n*=67)	34 (51)	0.88 (0.61, 1.28)	0.84 (0.57, 1.24)	15 (22)	0.74 (0.37, 1.46)	0.73 (0.37, 1.45)
≥300 mg/g (*n*=14)	8 (57)	0.99 (0.58, 1.7)	1.06 (0.62, 1.82)	2 (14)	0.47 (0.12, 1.88)	0.53 (0.13, 2.1)
Participants aged ≥2 yr at surgery[c]						
Number of events	43			16		
<10 mg/g (*n*=50)	12 (24)	1	1	3 (6)	1	1
10–<30 mg/g (*n*=55)	17 (31)	1.29 (0.68, 2.42)	1.03 (0.55, 1.92)	7 (13)	2.12 (0.58, 7.76)	1.8 (0.43, 7.55)
≥30 mg/g (*n*=36)	14 (39)	1.62 (0.85, 3.08)	1.2 (0.66, 2.15)	6 (17)	2.78 (0.74, 10.38)	2.82 (0.82 ,9.71)

RR, relative risk; ACR, albumin/creatinine ratio; CI, confidence interval; AKIN, Acute Kidney Injury Network; RACHS-1, risk adjustment for congenital heart surgery-1; eGFR, estimated GFR.

[a]The outcomes were the presence of stage 1 AKI or worse (based on AKIN staging; includes participants with stages 2 or 3 AKI) or of stage 2 AKI or worse. To convert to SI units (mg albumin per mmol creatinine), divide ACR by 8.84.

[b]In the group aged <2 years, RRs are adjusted for age, sex, white (versus nonwhite), elective versus urgent surgery, RACHS-1 score ≥3 versus <3, preoperative eGFR percentile, and study site.

[c]In the group aged ≥2 years, RRs are adjusted for age (2–<6 years versus ≥6 years), sex, white versus nonwhite, elective versus urgent surgery, RACHS-1 score ≥3 versus <3, preoperative eGFR percentile, and study site.

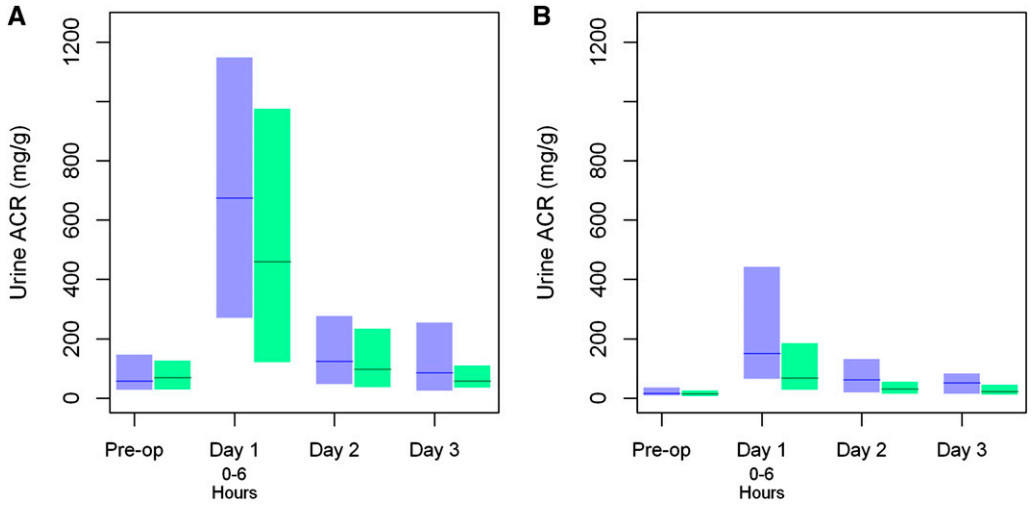

Figure 2. | Preoperative and postoperative ACR in children aged <2 versus ≥2 years, by AKI status. Box plots of urine ACR from four time points (left to right: preoperative, first postoperative or day 1, the day after surgery or day 2, and 2 days after surgery or day 3) in patients with AKI (in blue) and patients who did not develop AKI (in green). The middle bar represents the median ACR value and the upper and lower box borders represent the 75th and 25th percentile values, respectively. The left panel includes children aged 1 month to <2 years; the right panel includes children aged ≥2 years. ACR, albumin/creatinine ratio; day 1, obtained the day of surgery, within 6 hours of arrival to intensive care unit; day 2, the day after surgery; day 3, 2 days after surgery.

Table 3. Unadjusted and adjusted RR for first postoperative ACR to predict postoperative stage 1 or stage 2 AKI, by age group

Tertile of First Postoperative ACR[a]	Stage 1 AKI	Unadjusted RR	Adjusted RR[b]	Stage 2 AKI	Unadjusted RR	Adjusted RR[b]
	n (% of group)	95% CI	95% CI	*n* (% of group)	95% CI	95% CI
Aged 1 mo–<2 yr at surgery						
Events (*n*)	78			34		
Tertile						
1 (*n*=48) (<303 mg/g)	21 (44)	1	1	5 (10)	1	1
2 (*n*=49) (303–908 mg/g)	28 (57)	1.31 (0.87,1.95)	1.23 (0.82,1.85)	14 (29)	2.74 (1.07,7.02)[c]	2.5 (0.97,6.45)
3 (*n*=48) (>908 mg/g)	29 (60)	1.38 (0.93,2.05)	1.39 (0.92,2.09)	15 (31)	3.00 (1.18,7.60)[c]	3.41 (1.24,9.37)
Aged ≥2 yr at surgery						
Events (*n*)	43			15		
Tertile						
1 (*n*=49) (<44 mg/g)	9 (18)	1	1	1 (2)	1	1
2 (*n*=50) (44–169 mg/g)	13 (26)	1.42 (0.67,3.01)	1.38 (0.69,2.78)	5 (10)	4.9 (0.59,40.44)	. . .
3 (*n*=50) (>169 mg/g)	21 (42)	2.29 (1.17,4.49)	2.1 (1.08,4.08)	9 (18)	8.82 (1.16,67.03)	. . .

RR, relative risk; ACR, albumin/creatinine ratio; CI, confidence interval; AKIN, Acute Kidney Injury Network; RACHS-1, risk adjustment for congenital heart surgery-1; eGFR, estimated GFR.

[a]The outcomes of Poisson regression analyses were the presence of stage 1 AKI or worse (based on the AKIN staging; includes participants with stages 2 or 3 AKI) or of stage 2 AKI or worse. Note that AKI event numbers differ slightly from what is presented in Table 2 due to differential missing urine specimens. To convert to SI units (mg albumin per mmol creatinine), divide ACR by 8.84.

[b]In the group aged <2 years, RRs from multivariable Poisson regression analysis are adjusted for age, sex, white (versus nonwhite), elective versus urgent surgery, RACHS-1 score≥3 versus <3, preoperative eGFR percentile, study site, and cardiopulmonary bypass time (< versus ≥120 minutes).

[c]In the group aged ≥2 years, RRs from multivariable Poisson regression analysis are adjusted for age (aged 2–<6 years versus ≥6 years), sex, white (versus nonwhite), elective versus urgent surgery, RACHS-1 score ≥3 versus <3, preoperative eGFR percentile, study site, and cardiopulmonary bypass time (< versus ≥120 minutes).

Table 4. Diagnostic characteristics of various first postoperative urine ACR threshold values to predict postoperative stage 1 or higher AKI

First Postoperative ACR Threshold Values	Sensitivity	Specificity	Likelihood Ratio +	Likelihood Ratio −	PPV	NPV
Aged <2 yr						
>303 mg/g (2nd tertile or higher)	0.85	0.39	1.40	0.38	0.30	0.90
>908 mg/g (3rd tertile of higher)	0.44	0.69	1.40	0.81	0.31	0.80
Maximal sensitivity and specificity value: >618 mg/g	0.71	0.60	1.80	0.49	0.34	0.87
Aged ≥2 yr						
>44 mg/g (2nd tertile or higher)	0.93	0.36	1.50	0.19	0.14	0.98
>169 mg/g (3rd tertile of higher)	0.60	0.69	2.0	0.58	0.18	0.94
Maximal sensitivity and specificity value: >289 mg/g	0.60	0.79	2.90	0.51	0.22	0.95

ACR, albumin/creatinine ratio; PPV, positive predictive value; NPV, negative predictive value.

outcomes compared with older children. A possible explanation is that albumin excretion changes dramatically in the first 2 years of life, with renal tubular maturation (16,20). This leads to variable urine albumin excretion, making it difficult to distinguish non-AKI from mild AKI patients. These results highlight the need to consider age when studying novel urine AKI biomarkers in children.

We previously showed that early postoperative serum CysC was a good predictor of postoperative AKI development in this cohort (8); this is evidenced in Table 5, in which of all three biomarker methods evaluated (serum CysC, urine AKI biomarkers, and ACR), adding CysC to the clinical model led to the highest point-estimate rise in AUC. In children aged ≥2 years, we found a consistent

Table 5. Improvement in AUC and NRI as a result of adding first postoperative ACR to different clinical and biomarker predictive models

Model	Aged 1 mo–<2 yr at Surgery				Aged ≥2 yr at Surgery	
	Stage 1 or Higher AKI[a]		Stage 2 or 3 AKI[a]		Stage 1 or Higher AKI[a]	
	AUC (SEM)	NRI (SEM)	AUC (SEM)	NRI (SEM)	AUC (SEM)	NRI (SEM)
	P Value by Adding ACR[b]	*P* Value	*P* Value by Adding ACR	*P* Value	*P* Value by Adding ACR	*P* Value
Clinical model alone[c]	0.71 (0.04)	—	0.75 (0.04)	—	0.79 (0.04)	—
ACR alone	0.57 (0.05)	—	0.63 (0.05)	—	0.63 (0.05)	—
Clinical model + ACR	0.72 (0.04)	0.26 (0.17)	0.79 (0.04)	0.34 (0.20)	0.82 (0.04)	0.30 (0.18)
	0.31	0.12	0.13	0.08	0.17	0.10
Clinical model + CysC	0.77 (0.04)	—	0.81 (0.04)	—	0.84 (0.03)	—
Clinical model + CysC + ACR	0.78 (0.04)	0.24 (0.17)	0.83 (0.04)	0.33 (0.20)	0.87 (0.03)	0.48 (0.19)
	0.67	0.16	0.50	0.09	0.14	0.01
Clinical model + biomarkers	0.72 (0.04)	—	0.78 (0.04)	—	0.81 (0.04)	—
Clinical model + biomarkers + ACR	0.73 (0.04)	0.18 (0.17)	0.80 (0.04)	0.10 (0.20)	0.84 (0.04)	0.22 (0.18)
	0.42	0.27	0.26	0.61	0.36	0.22
Clinical model + biomarkers/ creatinine[d]	0.72 (0.04)	—	0.78 (0.04)	—	0.83 (0.04)	—
Clinical model + biomarkers/ creatinine + ACR[d]	0.73 (0.04)	0.27 (0.17)	0.80 (0.04)	0.41 (0.20)	0.84 (0.04)	0.20 (0.18)
	0.36	0.11	0.42	0.04	0.45	0.27
Clinical model + CysC + biomarkers	0.79 (0.04)	—	0.82 (0.04)	—	0.86 (0.03)	—
Clinical model + CysC + biomarkers + ACR	0.80 (0.04)	0.22 (0.17)	0.84 (0.04)	0.22 (0.20)	0.88 (0.03)	0.39 (0.19)
	0.46	0.21	0.41	0.28	0.46	0.03
Clinical model + CysC + biomarkers/ creatinine[d]	0.77 (0.04)	—	0.82 (0.04)	—	0.87 (0.03)	—
Clinical model + CysC + biomarkers/ creatinine + ACR[d]	0.79 (0.04)	0.26 (0.17)	0.84 (0.04)	0.22 (0.20)	0.88 (0.03)	0.28 (0.19)
	0.27	0.13	0.34	0.28	0.64	0.13

AUC, area under the curve; NRI, net reclassification improvement; ACR, albumin/creatinine ratio; CysC, serum cystatin C; urine biomarkers, urinary neutrophil gelatinase-associated lipocalin and urine IL-18; RACHS-1, risk adjustment for congenital heart surgery-1; eGFR, estimated GFR.

[a]The outcomes were stage 1 AKI and stage 2 AKI in the group aged ≤2 years, and stage 1 AKI in the group aged >2 years (too few events for analysis of stage 2 AKI as the outcome). "Stage 1 or higher AKI" includes participants with AKI stages 2 or 3.

[b]*P* values are only included in cells with ACR added to the previous model. For example, AUC or NRI for the clinical model + CysC does not include a *P* value; the model with clinical model + CysC + ACR includes a *P* value, which denotes whether addition of ACR led to a significant increase in AUC and NRI, relative to the previous model.

[c]The clinical predictive model includes age (continuous in the group aged ≤2 years; categorized as 2–<6 versus ≥6 years in the group aged >2 years), sex, white (versus nonwhite), elective versus urgent surgery, RACHS-1 score ≥3 versus <3, preoperative eGFR percentile, study site, and cardiopulmonary bypass time (< versus ≥120 minutes).

[d]These prediction models utilize urine biomarkers normalized to urine creatinine concentrations. The other models including urine biomarkers utilize nonurine creatinine normalized values (*i.e.*, concentration values).

tendency for urine ACR to provide added usefulness for predicting AKI (based on NRI and not AUC rise, Table 5) only when CysC was also in the predictive model. This may represent interaction between CysC and ACR, which we were unable to evaluate due to sample size limitations. Moreover, although discrepancy between results from the use of the NRI metric versus the AUC rise is known (25,26), with the NRI being more sensitive to capturing improvement in risk classification than AUC does, it must be acknowledged that at present the clinical significance of a high NRI is still somewhat unclear. Ultimately, only clinical trials that incorporate novel biomarkers in clinical care and evaluate the effects of such measures on clinical (*e.g.*, mortality) and morbidity or cost (*e.g.*, LOS, hospital costs) outcomes, will the added benefit of AKI biomarker measurement be known. When urine biomarkers (NGAL, IL-18) were in AKI predictive models, adding ACR provided no additional benefit. It is possible that because ACR rise occurs due to tubular injury, similar to urine biomarkers, it may not provide substantial additional predictive information. The finding that AUC for AKI prediction using the model of clinical factors and ACR was extremely similar to the model including clinical factors and urine biomarkers supports this hypothesis. Overall, our results suggest that in future trials with stage 2 AKI or worse as a study outcome, early postoperative ACR may be used to predict AKI risk in all children, but that postoperative ACR will likely only be beneficial for predicting all AKI (mild to severe)

in older children. Our results reported in Table 4 provide reasonable ACR threshold values for screening patients eligible for future AKI trials or for patients in whom AKI preventive measures (*e.g.*, fluid overload or nephrotoxin avoidance) may help. Because urine ACR is a routinely available test and ACR values already have clinical meaning to clinicians, early AKI diagnosis may be a clinically feasible goal sooner than would be with other novel biomarkers, which may require more time for acceptance by clinicians and institutions.

Preoperative ACR did not predict postoperative AKI in our cohort, which contradicts previous findings in adults (13,14). In adults, microalbuminuria is common and considered a manifestation of CKD (28). In children, CKD and thus clinically significant microalbuminuria, is uncommon, as shown in our cohort. This may explain why preoperative ACR may not distinguish patients who are at higher risk for AKI. It is possible that in children with underlying known renal disease, urine albumin may provide similar utility for AKI prediction as found in adults.

Our study had limitations. Our sample size was not large enough to effectively evaluate prediction of more severe AKI in older children. Our findings cannot be generalized to noncardiac children admitted to the ICU. It must also be acknowledged that the analysis may not have adequately accounted for residual confounding such as effects of CPB-associated inflammation on both ACR elevations and AKI. Our study also had several unique strengths. Because this was a multicenter conducted in the United States and Canada, generalizability to other populations was enhanced. We evaluated two clinically reproducible time points for urine ACR measurement: during preoperative assessment and upon arrival to the ICU from surgery. Unlike most previously published AKI biomarker studies, we provide data on the extent to which adding ACR to other known AKI predictors (clinical and biomarker risk factors) improves current AKI prediction. Finally, because urine ACR is a routine test, timely application is potentially feasible.

Early AKI diagnosis after CS will allow for future trials of AKI to be performed in children and may help to reduce complications of AKI by early avoidance of fluid overload or nephrotoxic medication in high-risk individuals. Although benefit for postoperative AKI prediction may be limited to combination with serum CysC, urine ACR provides an easy postoperative diagnostic test for AKI, particularly in older children.

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Disclosures

P.D. is a coinventor on patents regarding NGAL as a biomarker of AKI and is a consultant to Abbott Diagnostics and Biosite Inc. These associations had no effect on the research performed in this manuscript.

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