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Urinary Cystatin C and Acute Kidney Injury After Cardiac Surgery

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Abstract

Background—Acute Kidney Injury (AKI) is common following cardiac surgery and is associated with adverse patient outcomes. Urinary cystatin C (CysC) is a biomarker of proximal tubule function and may rise earlier in AKI than serum creatinine.

Study Design—Prospective cohort study

Settings & Participants—The TRIBE AKI (Translational Research Investigating Biomarker Endpoints in AKI) Consortium prospectively enrolled 1,203 adults and 299 children at 8 institutions from 2007–2009.

Index Test—Urinary CysC (mg/L) within the first 12 hours after surgery

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Outcome—Serum Creatinine based AKI was defined as AKI Network stage 1 (Mild AKI) as well as a doubling of serum creatinine from the pre-operative value or the need for dialysis during hospitalization (Severe AKI).

Other Measurements—Analyses were adjusted for characteristics used clinically for AKI risk stratification including age, sex, race, eGFR, diabetes, hypertension, heart failure, non-elective surgery, cardiac catheterization within 72 hours, type of surgery, myocardial infarction, and cardiopulmonary bypass time greater than 120 minutes.

Results—Urinary CysC measured in the early post-operative period (0–6 and 6–12 hours postoperatively) correlated with both mild and severe AKI in adults and children. However after analyses were adjusted for other factors the effect was attenuated for both forms of AKI in both cohorts.

Limitations—Limited numbers of patients with severe AKI and short-term dialysis

Conclusions—Urinary CysC values are not significantly associated with the development of AKI following cardiac surgery in adults and children.

Keywords

Acute kidney injury Biomarkers; Cystatin C; Dialysis; Peri-operative

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A common and serious complication of cardiac surgery, acute kidney injury (AKI) has been associated with several adverse patient outcomes. (1, 2) Validation of consensus definitions of AKI have aided in the ascertainment of the real incidence of AKI after cardiac surgery and have demonstrated that, regardless of severity or stage, AKI is associated with adverse patient outcomes including longer length of intensive care unit (ICU) and hospital stay, increased cost of hospitalization and increased patient mortality. (3–6) In the past several years, a number of studies have demonstrated that biomarkers can uncover acute tubular injury before serum creatinine in the setting of AKI. (7–11) However large scale prospective multi-center validation of these biomarkers have only recently begun. (12, 13)

Urinary Cystatin C (UCysC) has demonstrated mixed results when investigated for its ability to detect AKI, in a variety of clinical settings including cardiac surgery. (8, 14–20) In the physiological steady-state, CysC is excreted by glomerular filtration; it then goes through essentially complete tubular reabsorption and catabolism, without secretion. (16, 21, 22) Thus the presence of an increased concentration of cystatin C in the urine may signify renal tubular damage and this dysfunction is likely to occur instantaneously at the time of cellular injury. We conducted a large, prospective, multicenter cohort study of adults and children undergoing cardiac surgery and present the first large scale validation study of UCysC as a biomarker of AKI after cardiac surgery.

METHODS

Patient Cohorts and Samples

The detailed methods of the Translational Research Investigating Biomarker Endpoints in AKI (TRIBE AKI) cardiac surgery cohort have been previously described. (12, 13) Adults deemed high risk for AKI following cardiac surgery (coronary artery bypass graft and/or valve) were prospectively enrolled at six academic medical centers in North America between July 2007 and December 2009. Children undergoing surgery for congenital cardiac disorders from three academic centers were enrolled during the same period. All participants or their caregivers provided written informed consent and the study was approved by each institution’s research ethics board. We collected urine and plasma specimens preoperatively and daily for up to 5 postoperative days. All patients were admitted to the ICU immediately

after their surgery. The first postoperative samples were collected within 6 hours of admission to the ICU, at a mean of 0.8 ± 1.2 (standard deviation [SD]) hours, while the second postoperative samples were collected between hours 6–12 of the ICU stay (mean7.0± 2.4 hours). For the first 24 hours postoperatively, urine samples were collected every 6 hours. The remaining daily blood and urine samples were obtained at the time of routine morning blood collection done for clinical care. Specimen collection was stopped on postoperative day 3 in patients who did not demonstrate any AKI in the 3 days following surgery. Details on sample collection and processing have been previously described. (12, 13)

Outcomes: Study Variables

Mild AKI was defined as developing a 50% increase or absolute increase of 0.3 mg/dL in serum creatinine from pre-operative baseline during the hospital stay (AKI Network [AKIN] stage 1) while severe AKI was defined as receipt of short-term dialysis or a doubling in serum creatinine from the pre-operative baseline value (RIFLE [Risk, Injury, Failure, Loss, End-Stage Disease] stage “I” or AKIN stage 2 AKI) during the hospital stay (3, 6) The outcome of progression of AKI was defined by worsening of AKIN Stage (Stage 1 to either Stage 2 or 3; or, from Stage 2 to 3) according to the first AKI stage observed after surgery. (23) Patients treated with dialysis at any point during hospitalization were classified as Stage 3.

All pre-operative creatinine and biomarker values were measured within two months prior to surgery. Pre- and post-operative serum creatinine concentrations were measured in the same clinical laboratory for each patient at all sites. Serum creatinine values were recorded for every patient throughout the hospital stay. For adults we estimated GFR (eGFR) preoperatively using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation. (24) For children we estimated preoperative eGFR using the updated Schwartz equation and determined eGFR percentiles using published normal kidney function data for 651 children. (25) (26) As previously described we collected preoperative characteristics, operative details, and post-operative complications using definitions of the Society of Thoracic Surgeons (11a, 12, 13)

Biomarker Assays

Urine Cystatin C was measured using the Sekisui Diagnostics Cystatin C Reagent on a Daytona Analyzer (Randox, Co. Antrim, UK). The reagent contains colloidal gold particles coated with polyclonal anti cystatin C antibodies. The reaction between particles and any cystatin C in the sample results in the formation of agglutinates and an associated change in absorbance signal. The intra-assay coefficient of variation is ≤ 5% with an assay range of 0.05 – 8 mg/L. Personnel measuring the biomarkers were blinded to clinical outcomes.

Statistical Analysis

All analyses were conducted separate for adults and children. Continuous variables were compared with a two-sample t-test or Wilcoxon rank sum test and dichotomous variables with the chi-square test or fisher’s exact test. Each population (adults and children separately) was divided into quintiles using the first post-operative value of urine Cystatin C. Unadjusted trends across biomarker quintiles were assessed by Cochran-Armitage test for dichotomous outcomes and Jonckheere-Terpstra test for continuous outcomes. Adjusted trends were assessed using contrasts in linear or logistic regression depending on the outcome (Wald chi square test). To evaluate the association between biomarkers and AKI, mixed logistic regression models were used with random intercept for site. For adult patients, we adjusted for age (per year), gender, white race, CPB time > 120 minutes, non-elective surgery, preoperative CKD-EPI eGFR, diabetes and hypertension. For pediatric

patients we adjusted for age (per year), gender, white race, CPB time > 120 minutes, non-elective surgery, Risk Adjustment in Congenital Heart Surgery (RACHS-1) score ≥ 3 and pre-operative eGFR percentile. To determine the ability of the biomarkers to discriminate between patients with and without AKI we calculated the AUC and compared AUCs using the DeLong Test. We quantified the improvement in risk prediction after the addition of biomarkers to the clinical model with the categorical Net Reclassification Index (NRI) and Integrated Discrimination Improvement (IDI). For NRI analyses, risk category definitions were based on clinical utility and the incidence of the outcomes in the study. All analyses were performed in SAS version 9.2 (SAS Institute Inc, Cary, NC) and R 2.12.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Characteristics

We studied 1,203 adults and 299 children. Baseline and operative characteristics of these cohorts, stratified by early post-operative UCysC concentration, can be found in Tables 1 (Adult) and 2 (children). 416 (35%) of adults and 124 (41%) of children developed Mild AKI (AKIN Stage 1). Doubling of serum creatinine from pre-operative baseline or need for dialysis (Severe AKI) occurred in 56 (4.7%) adults and 49 (16.4%) children after surgery. Sixteen adult patients (1.3%) and four child patients (1.3%) received dialysis in the post-operative period. Adult patients who developed AKI were more likely to have a higher preoperative serum creatinine, a history of congestive heart failure, combined coronary artery bypass graft and valve surgery, longer cardiopulmonary bypass and cross-clamp times and an increased need for postoperative intra-aortic balloon pump.(12) Children with AKI were younger, had higher pre-operative eGFRs, longer cardiopulmonary bypass time and cross-clamp times, and were more likely to undergo an urgent procedure. (13)

Peri-operative urinary CysC concentrations

There was no statistically significant difference in pre-operative UCysC values in those adults with (median, 0.18 [interquartile range (IQR), 0.10–0.25] mg/L) and without Severe AKI (median, 0.17 [IQR, 0.07–0.26] mg/L; p = 0.8). UCysC values continued to rise until Day 4 in adults with Mild AKI and Day 5 in those with Severe AKI. (Figures 1A and 1C) At the first post-operative time point (0–6 hour ICU), UCysC concentrations were higher in those who developed Severe AKI (median, 0.21 [IQR, 0.10–0.35] mg/L) compared to those without AKI (median, 0.16 [IQR, 0.05–0.26] mg/L; p=0.02), however this effect was not sustained over subsequent early post-operative timepoints (Figure 1C).

There was no statistically significant difference in the pre-operative UCysC values between those children with (median, 0.13 [IQR, 0.07 –0.19] mg/L) and without AKI (median, 0.13 [IQR, 0.08–0.19] mg/L); p=0.9. Urine CysC values peaked, for those with and without AKI, at the 6–12 hours post-operative time point. At this timepoint there was a statistical difference between UCysC values between those children with and without AKI (p=0.02) however this effect was not sustained over subsequent timepoints (Figure 1D).

Urinary CysC Biomarker of Postoperative AKI in Adults

In adults, several quintiles of UCysC at both the 0–6 and 6–12 hour timepoints, had a significant association with mild AKI in unadjusted analysis, displaying a nearly two fold greater AKI risk. (Table 3) At the 0–6 hour timepoint this effect was attenuated following adjustment, however quintiles 3,4 and 5 remained significant at the 6–12 hour timepoint with the highest quintile (>0.3 mg/L) displaying a 1.8 fold greater risk of mild AKI (95% confidence interval [CI], 1.17–2.81). For Severe AKI, only the highest quintile at the 0–6 hour timepoint (>0.28 mg/L) was significant in the unadjusted analysis however this effect

was not statistically significant after adjustment (odds ratio [OR], 2.38; 95% CI, 0.97–5.89). No quintile for the 6–12 hour timepoint displayed statistical significance for severe AKI in the adjusted or unadjusted analyses. (Table 3)

In adults, the addition of urine Cystatin C to the clinical model did not significantly increase the area under the curve (AUC) for any receiver operating characteristic (ROC) curves regardless of the endpoint (Mild or Severe AKI) or timepoint (0–6 hours or 6–12 hours). (Table 5) The Net Reclassification Index (NRI) and Integrated Discrimination Improvement (IDI) data for urine Cystatin C can be found in Table S1 (provided as online supplementary material).

Urinary CysC Biomarker of Postoperative AKI in Children

There was no increased risk of mild AKI across the quintiles for children of UCysC at either of the first 2 post-operative timepoints (Table 4). The highest quintile for children (>0.22 mg/L) was significantly associated with severe AKI in the unadjusted analyses at the 6–12 hour timepoint however this effect was attenuated in the adjusted analyses (Table 4).

In children, the AUC's for urine Cystatin C were higher than those of the clinical model alone for all combinations of AKI and timepoints. However the addition of urine Cystatin C to the clinical model did not significantly increase the AUC regardless of the AKI endpoint or timepoint. (Table 5) The NRI and IDI data for urine Cystatin C in the cohort of children can be found in Table S2.

Urinary CysC for prediction of Short-Term Dialysis in Adults

For this secondary analysis, there were no adult subjects in the first 6 hour postoperative Quintile 1 UCysC concentrations who required dialysis; therefore Quintiles 1 and 2 were combined to form the referent cohort. UCysC concentrations within the first 6 post-operative period hours, in adults, were associated with subsequent receipt of dialysis during hospitalization; the 5th quintile (>0.28 mg/L) had a 7.1 fold increased unadjusted odds compared with Quintiles 1 & 2 (<0.12 mg/L) (OR, 7.10; 95% CI, 1.46–34.5). Given the limited number of adults receiving dialysis we did not perform an adjusted analysis controlling for factors known to affect AKI. Similarly, there were too few dialysis events to undertake this same analysis in the cohort of children.

Urinary CysC Normalized to Urinary Creatinine in Adults and Children

The ratio of urine CysC to urine Creatinine was analyzed for both children and adult cohorts for both definitions of AKI as well as both time points. There was no statistically significant difference between the results for the adjusted and unadjusted UCysC values (Tables S3 and S4)

Urianry CysC for the prediction of AKI progression

UCysC measured on the day the serum creatinine met criteria for AKI in those adults and children who developed at least AKIN Stage 1 was not able to predict the progression of AKI (e.g Stage 1 to Stage 2) in either cohort (Table S5).

Discussion

The role of UCysC as a biomarker of cardiac surgery-associated AKI is controversial with small studies demonstrating mixed results.(8, 15, 18, 19) The results from this large prospective observational international investigation of biomarkers of AKI following cardiac surgery does not demonstrate urine Cystatin C to be a reliable predictor of the future development of AKI.

UCysC demonstrated a significant increase in adjusted odds at the second postoperative timepoint for the development of mild AKI. However the adjusted results for severe AKI in adults as well as both mild and severe AKI in children remained insignificant. It deserves noting that UCysC performed on par with our clinical model, often displaying AUCs that were equal to or greater than our clinical model in both adults and children. Thus, UCysC was able to detect AKI, but unable to improve upon factors already known to correlate with the development of post cardiac surgery AKI. Although these findings suggest that future studies of post-cardiac surgery investigations should not include UCysC, this should not imply that all investigations of UCysC in the setting of AKI should be abandoned. There is data that support the utility of UCysC in a variety of other clinical settings including critical illness and nephrotoxin-associated AKI. (14, 16, 17, 20, 27) The discrepancy in results between cardiac surgery and other clinical settings may be due, in part, to the timing of the AKI in relation to the biomarker performance. In the setting of sepsis and nephrotoxin (e.g non-steroidal drugs or cisplatin) the time course of AKI is very different compared to cardiac surgery AKI. Patients often have several days of systemic inflammatory response syndrome (SIRS) prior to developing septic shock or have received several doses of a nephro-toxic drug and develop AKI within several days. UCysC, a functional marker of the renal tubules, is not ideally suited to detect AKI within hours of the inciting event and may have a role in settings with protracted AKI.

As a marker of renal tubular functional, UCysC did not perform as well, in the TRIBE AKI cohort, as several biomarkers of renal tubular injury (e.g Neutrophil Gelatinase–Associated Lipocalin (NGAL) or urinary Interleukin 18 [IL-18]). In the adult cohort the highest quintiles of urine IL-18 (6.8 fold greater adjusted odds) and plasma NGAL (5-fold greater adjusted odds) were strongly associated with the development of AKI, defined as a post-operative doubling of serum creatinine or the receipt of dialysis. (12) In the cohort of children, after multivariable adjustment, the highest quintiles of urine IL-18 and urine NGAL were associated with 6.9- and 4.1-fold higher odds of AKI. (13) Biomarkers of direct tubular injury elevated more rapidly and appear to be more specific to our definition of AKI. This is in contrast to UCysC which increased progressively over the first 4 to 5 post-operative days in adults with and without AKI. This continuous rise in post-operative UCysC potentially signals the loss of function in the days following a tubular insult rather than direct tubular injury.

Despite UCysC's inconsistent results in predicting mild and severe AKI in adults, its utility in determining those adults who go on to receive dialysis during hospitalization warrants further study. The unadjusted odds of 7.10 for the highest adult quintile (> 0.28 mg/L) to predict the receipt of dialysis during hospitalization may be potentially usefully but must be viewed with a large degree of caution given the low number of dialysis events. The number of adult events (n= 16) did not permit an adjusted analysis using our clinical model as it would have problems with over-fitting and unreliable risk estimates. While not ideally suited for detecting individuals with less severe forms of AKI, UCysC could potentially help in the selection/randomization of individuals in trials that seek to investigate the timing of RRT or other therapeutic trials for the most severe forms of AKI.

Recent years have seen a flurry of publications reporting on biomarkers of AKI in a variety of clinical settings. (8, 9, 12–16, 18–21, 23, 28) However the overwhelming majority of these studies have been single-center investigations with a great deal of variation in the number of major adverse kidney events. As previously discussed data from the TRIBE-AKI consortium demonstrated that several other biomarkers (NGAL and IL-18) measured in the first 6 post-operative hours can forecast AKI as well as adverse patient outcomes (increased length of ICU and hospital stay, mortality). (12, 13) These data validated and improved upon previously published biomarker studies. The successes and failures of these previously

published findings remind nephrologists, intensivists, and other clinicians the importance of validating results from single center studies. (8, 18, 29, 30) The failure to replicate findings in larger multicenter investigations is not specific to the AKI biomarker literature and highlights, in part, the inherent publication bias of biomarker work; as negative single center biomarker studies are unlikely to be published.

Strengths of our study include that our data, samples, and measurements were all performed as part of a large prospective, multicenter international investigation. Furthermore, we relied on standardized modern AKI staging criteria (AKIN); these are currently used by the international community and are easily duplicated in follow up investigations. Of note, our reliance on a serum creatinine-based definition of AKI may have limited UCysC's performance as serum creatinine's imprecision as a marker of tubular injury may have led to the misclassification of several cases and controls thus diminishing UCysC's power. (31) Additionally, while we did not measure UCysC via nephelometry; we did utilize a standardized, valid, commercially available turbidity method that provided accurate and readily reproducible results with an intra-assay coefficient of variation of ≤ 5%. We would also note that there are increasingly more methods for reliable UCysC measurement besides nephelometry. (16, 18, 32)

In summary, UCysC values measured in the early post-operative period do not serve as a clinically meaningful biomarker to predict less severe forms of AKI following cardiac surgery in adults and children. Thus, routine measurement of UCysC should not be performed for the detection of early AKI following cardiac surgery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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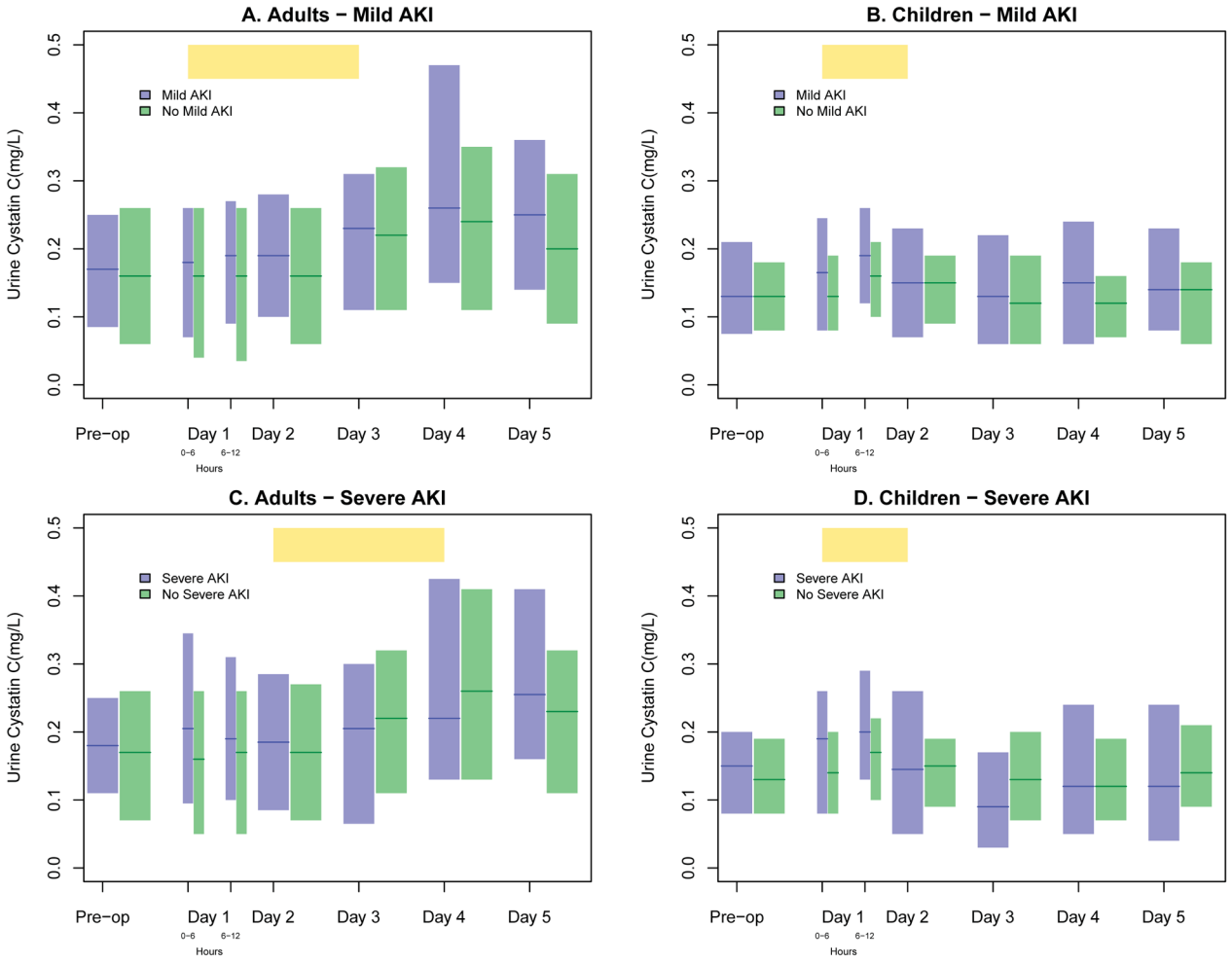

Figure 1.

Figure 1A, 1B, 1C and 1D: Urine Cystatin C levels over time after surgery in adults and children

Figure 1A and 1B displays the UCyCs concentrations in adults (1A) and children (1B) over time for those who did and did not develop Mild AKI. Mild AKI defined as AKIN Stage 1 or higher. Figure 1C and 1D displays the UCyCs concentrations in adults (1C) and children (1D) over time for those who did and did not develop Severe AKI. Severe AKI defined as 100% increase from preoperative baseline or the receipt of short-term dialysis. For each timepoint, the line indicates the median and the bottom and top of the box indicates the 25th and 75th percentile of urine cystatin C among patients with AKI (blue) and without AKI (green) patients. Yellow bars indicate the 25th to 75th percentile day of the initial creatinine-based diagnosis of AKI

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Table 1

Baseline Characteristics by Early Postoperative Urinary CysC among 1,203 Adults Undergoing Cardiac Surgery

	Urinary CysC Category (mg/L)					P
	Q1: <0.02 (n=244)	Q2: 0.02–0.12 (n=241)	Q3: 0.13–0.20 (n=242)	Q4: 0.21–0.28 (n=231)	Q5: >0.28 (n=245)	
Demographics						
Age at time of surgery (y)	72.1 (11.1)	71.2 (10.4)	71.7 (9.1)	71.5 (9.8)	70.9 (10.2)	0.4
Male sex	159 (65)	158 (66)	165 (68)	167 (72)	165 (67)	0.5
White Race	227 (93)	225 (93)	230 (95)	219 (95)	225 (92)	0.6
Diabetes	97 (40)	105 (44)	98 (41)	97 (42)	105 (43)	0.9
Hypertension	188 (77)	189 (78)	189 (78)	182 (79)	201 (82)	0.8
Congestive Heart Failure	58 (25)	72 (31)	55 (24)	63 (28)	58 (25)	0.3
Status of procedure						
Elective	200 (82)	190 (79)	180 (74)	175 (76)	108 (85)	0.03
Urgent or Emergent	44 (19)	51 (22)	62 (27)	55 (25)	36 (16)	
Cardiac catheterization in past 72 h	32 (14)	34 (15)	19 (8)	19 (8)	17 (7)	0.03
Preoperative Kidney Function						
Serum Creatinine (mg/dL)	1.10 (0.32)	1.11 (0.36)	1.08 (0.34)	1.09 (0.33)	1.07 (0.35)	0.4
eGFR (mL/min/1.73 m2)†	65.8 (18.9)	66.0 (19.7)	67.9 (19.3)	67.5 (19.3)	69.4 (19.8)	0.2
Characteristics of Surgery						
Incidence						
1st CV Surgery	204 (84)	210 (87)	219 (91)	201 (87)	219 (89)	0.2
Re-op CV Surgery	40 (17)	31 (14)	23 (10)	30 (14)	26 (12)	
Surgery						
CABG	97 (40)	117 (49)	129 (53)	128 (55)	108 (44)	0.02
Valve	89 (36)	71 (30)	60 (26)	53 (24)	77 (32)	
CABG & Valve	58 (25)	53 (23)	53 (23)	50 (23)	60 (25)	
CPB Use	220 (90)	211 (88)	218 (90)	203 (88)	228 (93)	0.3
Perfusion Time (min)¶	114.6 (47.0)	111.5 (59.7)	107.1 (52.2)	107.8 (59.1)	126.4 (69.8)	0.04
Cross-Clamp time (min)	84.6 (40.6)	77.7 (45.8)	72.3 (40.0)	69.8 (40.1)	83.3 (50.3)	0.002

	Urinary CysC Category (mg/L)					P
	Q1: <0.02 (n=244)	**Q2: 0.02–0.12 (n=241)**	**Q3: 0.13–0.20 (n=242)**	**Q4: 0.21–0.28 (n=231)**	**Q5: >0.28 (n=245)**	
Cardioplegia	220 (90)	204 (85)	214 (88)	202 (87)	223 (91)	0.2
Postoperative IABP	18 (7)	10 (4)	10 (4)	7 (3)	9 (4)	0.2

Note: Values for categorical variables are given as number (percentage); values for continuous variables are given as median [interquartile range] or mean +/− standard deviation. Conversion factor for Serum Creatinine in mg/dL to μmol/L, x88.4.

¶ Perfusion time is reported for the patients who had CPB and cross clamping

† eGFR calculated with the Chronic Kidney Disease Epidemiology Collaboration creatinine equation

eGFR = estimated glomerular filtration rate

CABG = coronary artery bypass grafting

CPB= cardiopulmonary bypass; CysC, cystatin C; IABP, intra-aortic balloon pump; CV, cardiovascular; Q, quintile

Table 2

Baseline Characteristics by Early Postoperative Urinary CysC among 299 Children Undergoing Cardiac Surgery

	Urinary CysC Category (mg/L)					
	Q1: <0.07 (n=56)	**Q2: 0.07–0.12 (n=67)**	**Q3: 0.13–0.16 (n=60)**	**Q4: 0.17–0.22 (n=53)**	**Q5: >0.22 (n=63)**	**P**
Demographics						
Age at time of surgery	4.4 (5.1)	4.6 (4.7)	4.1 (4.7)	3.2 (3.75)	2.6 (3.2)	0.04
Male sex	29 (52)	38 (57)	32 (53)	27 (51)	40 (63)	0.7
White Race	43 (77)	57 (85)	49 (82)	44 (83)	51 (81)	0.9
Status of procedure						
Elective	52 (93)	61 (91)	56 (93)	50 (94)	56 (89)	0.9
Urgent or Emergent	4 (7)	6 (9)	4 (7)	3 (6)	7 (12)	
Preoperative Kidney Function						
Serum Creatinine (mg/dL)	0.46 (0.21)	0.45 (0.15)	0.43 (0.15)	0.40 (0.14)	0.38 (0.11)	0.2
eGFR (mL/min/1.73 m2)	90.1 (28.1)	93.0 (21.5)	90.6 (25.7)	91.8 (25.2)	89.0 (27.4)	0.8
eGFR percentile	47.1 (37.3)	50.0 (31.7)	51.9 (34.1)	58.6 (32.6)	57.2 (34.7)	0.4
Characteristics of Surgery						
CPB Use	55 (98)	66 (99)	60 (100)	53 (100)	62 (98)	0.8
Perfusion Time (min)[¶]	88.2 (44.1)	93.0 (49.3)	99.5 (51.7)	113.4 (51.8)	138.3 (84.7)	< 0.001
Cross-Clamp time (min)	36.8 (32.7)	42.6 (46.2)	47.2 (41.30)	51.6 (46.8)	54.0 (53.2)	0.4
RACHS-1 score[≠]						0.03
1	4 (7)	6 (9)	5 (8)	1 (2)	2 (3)	
2	34 (61)	28 (42)	32 (53)	24 (45)	27 (43)	
3	18 (33)	32 (48)	21 (35)	26 (49)	26 (41)	
4	0 (0)	1 (1)	2 (3)	1 (2)	7 (12)	
Not categorized				1	1	

Note: Values for categorical variables are given as number (percentage); values for continuous variables are given as median [interquartile range] or mean +/− standard deviation. Conversion factor for Serum Creatinine in mg/dL to μmol/L, x88.4.

[¶] Perfusion time is reported for the patients who had CPB and cross clamping

[†] eGFR was calculated by the Schwartz formula. Percentile-estimated GFR, normative values from children with normal kidney function was used for percentile derivation.

‡The RACHS-1 consensus-based score system categorizes the complexity of surgery.

eGFR = estimated glomerular filtration rate

CPB= cardiopulmonary bypass

RACHS, Risk Adjustment in Congenital Heart Surgery; CysC, cystatin C; Q, quintile

Table 3

Odds of Developing AKI at Early Postoperative Period, by CysC quintile in Adults

	Mild AKI			Severe AKI		
	No. patients	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)[†]**	**No. patients**	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI) [†]**
0–6 h Timepoint						
Urinary CysC Category[¶]						
Q1: <0.02 mg/L	69 (28.3)	1.00 (reference)	1.00 (reference)	7 (2.9)	1.00 (reference)	1.00 (reference)
Q2: 0.02–0.12 mg/L	79 (32.8)	1.24 (0.84–1.82)	1.16 (0.76, 1.75)	12 (5.0)	1.77 (0.69, 4.59)	1.62 (0.62, 4.26)
Q3: 0.13–0.20 mg/L	91 (37.6)	1.53 (1.04, 2.24)	1.46 (0.97, 2.19)	9 (3.7)	1.31 (0.48, 3.57)	1.17 (0.42, 3.25)
Q4: 0.21–0.28 mg/L	87 (37.7)	1.53 (1.04, 2.25)	1.42 (0.94, 2.15)	9 (3.9)	1.37 (0.50, 3.75)	1.23 (0.44, 3.42)
Q5: >0.28 mg/L	90 (36.7)	1.47 (1.07, 2.16)	1.39 (0.93, 2.09)	19 (7.8)	2.85 (1.17, 6.90)	2.38 (0.97, 5.89)
Unadjusted p for trend[*]	0.03	…	…	0.04	…	…
Adjusted p for trend [**]	0.3	…	…	0.1	…	…
6–12 h Timepoint						
Urinary CysC Category[***]						
Q1: <0.01 mg/L	54 (24.2)	1.00 (reference)	1.00 (reference)	11 (4.9)	1.00 (reference)	1.00 (reference)
Q2: 0.02–0.12 mg/L	75 (33.8)	1.60 (1.06, 2.41)	1.39 (0.89, 2.16)	8 (3.6)	0.72 (0.28, 1.83)	0.66 (0.254, 1.71)
Q3: 0.13–0.20 mg/L	88 (34.7)	1.66 (1.11, 2.48)	1.67 (1.09, 2.56)	8 (3.2)	0.63 (0.25, 1.59)	0.59 (0.23, 1.54)
Q4: 0.21–0.28 mg/L	85 (38.1)	1.93 (1.28, 2.90)	1.84 (1.19, 2.84)	10 (4.5)	0.91 (0.38, 2.18)	0.84 (0.34, 2.08)
Q5: >0.29 mg/L	82 (36.9)	1.83 (1.22, 2.76)	1.81 (1.17, 2.81)	14 (6.3)	1.30 (0.58, 2.92)	1.26 (0.54, 2.91)
Unadjusted p for trend[*]	0.003	…	…	0.5	…	…
Adjusted p for trend [**]	0.004	…	…	0.5	…	…

Note: N = 1203. Patients in each category given as number (percentage). Mild AKI defined as AKIN Stage 1 or higher. Severe AKI defined as 100% increase from preoperative baseline or receipt of dialysis during hospitalization.

[†] Adjusted for Age, sex, white race, estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration creatinine equation), diabetes, hypertension, congestive heart failure, non-elective surgery, cardiac catheterization 72 hours, type of surgery, myocardial infarction, and cardiopulmonary bypass time > 120 minutes.

[*] Cochran-Armitage Trend Test

[**] Wald Chi-Square

¶ No. of patients per quintile: Q1, n=244; Q2, n=241; Q3, n=242; Q4, n=231; Q5, n=245

*** No. of patients per quintile: Q1, n=223; Q2, n=222; Q3, n=254; Q4, n=223; Q5, n=222.

AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; CysC, cystatin C; Q, quintile; OR, odds ratio; CI, confidence interval;

Table 4

Odds of Developing AKI in Early Postoperative Period, by CysC quintile in Children

	Mild AKI			Severe AKI		
	No. patients	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)†**	**No. patients**	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI) †**
0–6 h Timepoint						
Urinary CysC Category¶						
Q1: <0.07 mg/L	24 (42.9)	1.00 (reference)	1.00 (reference)	9 (16.1)	1.00 (reference)	1.00 (reference)
Q2: 0.07–0.12 mg/L	20 (29.9)	0.57 (0.27–1.19)	0.48 (0.21, 1.10)	9 (13.4)	0.81 (0.30, 2.21)	0.92 (0.30, 2.77)
Q3: 0.13–0.16 mg/L	18 (30.0)	0.57 (0.27, 1.23)	0.44 (0.19, 1.03)	5 (8.3)	0.48 (0.15, 1.52)	0.41 (0.12, 1.44)
Q4: 0.17–0.22 mg/L	24 (45.3)	1.10 (0.52, 2.35)	0.70 (0.30, 1.64)	9 (17.0)	1.07 (0.39, 2.94)	0.76 (0.25, 2.32)
Q5: >0.22 mg/L	38 (60.3)	2.03 (0.98, 4.21)	1.03 (0.45, 2.38)	17(27.0)	1.93 (0.78, 4.77)	1.09 (0.38, 3.08)
Unadjusted p for trend*	0.008	…	…	0.08	…	…
Adjusted p for trend **	0.2	…	…	0.9	…	…
6–12 h Timepoint						
Urinary CysC Category***						
Q1:: <0.09 mg/L	23 (41.1)	1.00 (reference)	1.00 (reference)	6 (10.7)	1.00 (reference)	1.00 (reference)
Q2: 0.10–0.14 mg/L	12 (23.5)	0.44 (0.19, 1.02)	0.31 (0.12, 0.78)	5 (9.8)	0.91 (0.30, 3.17)	0.67 (0.18, 2.60)
Q3: 0.15–0.19 mg/L	25 (44.6)	1.16 (0.55, 2.45)	0.72 (0.31, 1.71)	9 (16.1)	1.60 (0.53, 4.83)	0.86 (0.25, 2.92)
Q4: 0.20–0.24 mg/L	23 (36.5)	0.83 (0.39, 1.73)	0.45 (0.19, 1.03)	9 (14.3)	1.39 (0.46, 4.18)	0.68 (0.20, 2.28)
Q5: >0.25 mg/L	31 (56.4)	1.85 (0.87, 3.94)	0.98 (0.41, 2.34)	14 (25.5)	2.85 (1.00, 8.06)	1.14 (0.34, 3.82)
Unadjusted p for trend*	0.05	…	…	0.03	…	…
Adjusted p for trend **	0.9	…	…	0.8	…	…

Note: N = 299. Patients in each category given as number (percentage). Mild AKI defined as AKIN Stage 1 or higher. Severe AKI defined as 100% increase from preoperative baseline or receipt of dialysis during hospitalization.

† Adjusted for age (per year), sex, white race, CPB time > 120 minutes, non-elective surgery, Risk Adjustment in Congenital Heart Surgery–1 score ≥ 3 and preoperative estimated glomerular filtration rate (percentile)

* Cochran-Armitage Trend Test

** Wald Chi-Square

¶ Number of patients per quintile: Q1, n=56; Q2, n=67; Q3, n=60; Q4, n=53; Q5, n=63

*** No. of patients per quintile: 6–12 hour: Q1, n=56; Q2, n=51; Q3, n=56; Q4, n=63; Q5, n=55.

AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; CysC, cystatin C; Q, quintile; OR, odds ratio; CI, confidence interval;

Table 5

Areas Under the Curve for Urinary CysC and Clinical Model in Adults and Children

AKI	Time point	Adults (n=1203)				Children (n=299)			
		Biomarker	Clinical Model†	Biomarker + Clinical Model†	P*	Biomarker	Clinical Model§	Biomarker + Clinical Model§	P
Mild AKI **	0 – 6 h	0.67 (0.02)	0.67 (0.02)	0.67 (0.02)	0.2	0.76 (0.03)	0.75 (0.03)	0.76 (0.03)	0.4
	6–12 h	0.68 (0.02)	0.67 (0.02)	0.68 (0.02)	0.1	0.78 (0.03)	0.75 (0.03)	0.78 (0.03)	0.2
Severe AKI ***	0 – 6 h	0.72 (0.03)	0.69 (0.04)	0.72 (0.04)	0.09	0.80 (0.03)	0.78 (0.03)	0.80 (0.03)	0.3
	6–12 h	0.72 (0.03)	0.71 (0.04)	0.72 (0.04)	0.6	0.83 (0.03)	0.81 (0.03)	0.83 (0.03)	0.2

NOTE: Values in parentheses are ____.

† Clinical model is Age, sex, white race, estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration creatinine equation), diabetes, hypertension, congestive heart failure, non-elective surgery, cardiac catheterization 48 hours, type of surgery, myocardial infarction, and cardiopulmonary bypass time > 120 minutes.

§ Clinical model is age (per year), sex, white race, cardiopulmonary bypass time > 120 minutes, non-elective surgery, Risk Adjustment in Congenital Heart Surgery–1 score ≥ 3 and pre-operative estimated glomerular filtration rate (percentile).

* P value AUC of biomarker + clinical model compared to clinical model

** Mild AKI defined as AKIN Stage 1 or higher.

*** Severe AKI defined as 100% increase from preoperative baseline or receipt of dialysis during hospitalization.

AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; CysC, cystatin C