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Long-Term Renal Outcomes in Children With Acute Kidney Injury Post Cardiac Surgery

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Introduction: The long-term renal outcomes of survivors of pediatric acute kidney injury (AKI) are varied within the current literature, and we aim to establish long-term renal outcomes for pediatric patients after cardiac surgery. We studied long-term renal outcomes and markers of kidney injury in pediatric patients after congenital cardiac surgery.

Methods: In a prospective case-control observational study (the Renal Outcomes in Children with acute Kidney injury post cardiac Surgery [ROCKS] trial) we reviewed all children who underwent cardiac surgery on cardiopulmonary bypass (December 2010–2017).

Results: During the study period, 2035 patients underwent cardiac surgery, of whom 9.8% developed AKI postoperatively. Forty-four patients who had postoperative AKI had a long-term follow-up, met our inclusion criteria, and were compared with 49 control subjects. We conducted a univariate analysis of reported parameters. At a median follow-up of 41 months, the cases had significantly higher urine levels of neutrophil gelatinase–associated lipocalin (NGAL), interleukin-18 (IL-18), and kidney injury molecule-1 (KIM-1). The biomarkers remained higher after adjusting for the urine creatinine, and the ratio of urine KIM-1/urine creatinine was significantly higher among cases. None of the patients had proteinuria or hypertension on follow-up. The presence of AKI, AKI stage, and younger age were not associated with the occurrence of low glomerular filtration rate (GFR) at follow-up.

Conclusions: Urinary biomarker abnormalities persist years after a congenital cardiac surgery in children, who may have a low GFR on follow-up. The presence of AKI, AKI stage, and younger age at surgery are not associated with the occurrence of low GFR at follow-up. Children with a higher surgical complexity score have lower GFR on follow-up.

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AKI is common in children after surgery for congenital heart disease. The incidence of AKI varies from 35% to 65%.[1–3] Postoperative AKI in children is known to have adverse outcomes, including increased ventilation days, length of stay in a pediatric intensive care unit, and mortality.[1–8] It is now well known that the risk of AKI increases as the age of the child undergoing surgery decreases, with the risk being as high as 50% to 60% in neonates, depending on the complexities of the surgery.[3,4,9,10]

Animal studies and adult cohorts have shown an association between AKI and the long-term risk of chronic kidney disease (CKD), even in post–cardiac surgery settings.[11–15] There is a paucity of literature on the long-term outcomes of AKI in children.[16–22]

There are reports of CKD in adults with congenital heart disease; however, there are relatively few reports in children.[23,24] AKI after cardiac surgery in children is an excellent model to demonstrate AKI because the

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exact timing of the insult to the kidney is known and there are no confounding factors, such as septicemia or diabetes and hypertension, as in adult patients. It is unclear whether physicians and the institute should allocate resources to actively look for underlying chronic kidney injury after cardiac surgery in early childhood. There is a need to have evidence of the association of AKI with CKD and hypertension later in life to further strengthen the follow-up guidelines in these children.

The aim of the present study (the Renal Outcomes in Children with AKI post cardiac Surgery [ROCKS] trial) was to evaluate the burden of adverse renal outcome in pediatric patients (<18 years of age) who had an AKI after a congenital cardiac surgery done in the years 2010 to 2017 in terms of proteinuria, urinary biomarker excretion, hypertension, and reduced estimated GFR (eGFR <90 ml/min/1.73 m^2). Secondary objectives of the study were to look for the determinants of low GFR at follow-up and whether a complex cardiac surgery performed in a child <2 or 3 months of age predisposes them to a lower GFR later in life.

METHODS

Design and Setting

This cross sectional study was performed on a prospectively followed cohort who underwent cardiopulmonary bypass in the Medanta – The Medicity, India from December 2010 to December 2017. This study was approved by the institutional review board of our institution. A written informed consent was obtained from all parents or legal guardians, along with assent where appropriate for pediatric participants.

Inclusion Criteria

We reviewed all infants and children (<18 years of age) with AKI who were admitted to the pediatric cardiac intensive care unit after congenital cardiac surgery on cardiopulmonary bypass (performed from December 2010 to December 2017).

Exclusion Criteria

Patients were excluded if they had pre-existing CKD (including kidney transplant and long-term dialysis), a history of hypertension, AKI from a primary kidney disease (such as acute glomerulonephritis or obstructive uropathy), and a previous history of AKI.

Study Data Collection

Cases (those who had AKI after cardiopulmonary bypass) were compared with control subjects (those who did not have AKI after cardiopulmonary bypass during the same time period). All patients were seen in follow-up in the cardiology clinic, and their families were contacted to participate in the study. The study flow is shown in Figure 1. The children were reviewed for eligibility and invited to participate.

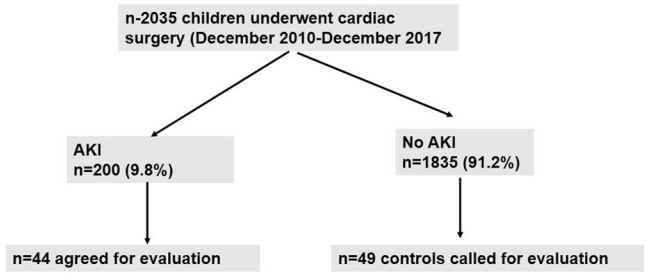

Figure 1. Flow chart of the study protocol. AKI = acute kidney injury.

Initial Cardiac Surgery Admission Details

The following data were recorded from the basic patient demographic data and the initial cardiac surgery admission: diagnosis, native congenital heart disease for which surgery was performed, cyanotic or acyanotic disease, aortic cross clamp time, total cardiopulmonary bypass time, and number of intensive care admission days. Complexity of cardiac surgery was categorized using the Risk Adjustment for Congenital Heart Surgery (RACHS-1), the consensus-based scoring system commonly used to classify the complexity of cardiac surgeries, with higher scores indicating more complex surgeries.[25] We also recorded The Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery (STAT) score, a more objective score for evaluation of our cohort.[10,25] A detailed clinical history, including history of medications taken, duration of hospital stay, and need for dialysis was recorded. A detailed laboratory history including the underlying cardiac disease, duration of cardiopulmonary bypass, course of postoperative stay, and daily serum creatinine monitoring was also recorded. The following records were taken from the intensive care unit admission: sepsis, need for inotropes, daily serum creatinine values, hourly urine output, need for peritoneal dialysis, and the use of nephrotoxic medications.

Study Visit Clinical Data

A complete history of the child's postsurgery hospitalization, medications, and other significant history were taken during the visit. Blood (minimum 2.5 ml) and urine (minimum 5 ml) samples were collected.

Study Visit Clinical Examination

The study clinical examination staff was blind to the past AKI status. Three measures of height on a stadiometer and weight on a precision weighing scale were recorded. Three automated blood pressure measurements were performed using a manual method, in a quiet setting (to reduce anxiety and performed before the blood sampling), seated, using size-appropriate

cuffs on the right arm (unless contraindicated). The average of the 2 lowest blood pressure measurements was used to calculate the age, gender, and height-specific blood pressure percentile. Blood pressure percentiles were calculated per the 2017 American Academy of Pediatrics Guidelines.[26]

Study Visit Laboratory Data

After obtaining consent, the children were seen in the clinic by a pediatric nephrologist and blood and urine samples were collected. Biochemical evaluation consisted of eGFR (measured by the Schwartz formula), serum blood urea nitrogen, serum creatinine, urine albumin/creatinine ratio, serum cystatin C levels, and serum beta-trace protein. Urinary biomarkers consisted of NGAL, liver-type fatty acid binding protein (L-FABP), KIM-1, and IL-18. Common biochemical parameters were measured in laboratory in compliance with ISO 15189;2012 guidelines. Serum creatinine was measured using the enzymatic method. Urine samples were centrifuged at 3000 rpm for 10 minutes and analysis for NGAL was done using chemiluminescent microparticle immunoassay kit (The ARCHITECT urine NGAL assay; Abbott, Abbott Park, Illinois, USA). Using the same aliquot, urine L-FABP, KIM-1, and IL-18 levels were measured using enzyme-linked immunosorbent assay. Serum cystatin C and beta-trace protein was measured on a Siemens BN Prospec nephelometer (Siemens AG, Munich, Germany). The individuals performing laboratory measurements were blinded to the clinical data. We measured biomarkers in duplicate and used the average of the 2 values.

Main Exposure

The primary exposure was AKI during a pediatric cardiothoracic ICU stay. Patients fulfilled AKI per the Kidney Disease: Improving Global Outcomes serum creatinine and urine output guidelines criteria. If the patient fulfilled both or one of the criteria, the highest AKI stage was selected for severity classification. The baseline serum creatinine was taken as the creatinine taken $\geq$3 months before admission (if available) or preoperative lowest creatinine or lowest creatinine after the resolution of AKI. If the patient was taking diuretics postsurgery, serum creatinine was used to grade AKI.

Outcomes

The primary outcome was the proportion of children with abnormal proteinuria, urinary biomarker excretion, hypertension, and a reduced eGFR (eGFR $<$90 ml/min/1.73 m^2).

For participants $\leq$13 years of age, hypertension was defined as systolic or diastolic blood pressure at or above the 95th percentile for age, gender, and height. For participants $>$13 years of age, hypertension was defined as per the recent American Academy of Pediatrics guidelines as systolic or diastolic blood pressure $>$130 mm Hg or $>$80 mm Hg, respectively. We calculated the eGFR using the bedside Schwartz serum creatinine–based eGFR equation.[27–29] Albuminuria was defined as urine albumin to creatinine ratio $>$30 mg/g. The modified Schwartz equation was used to estimate GFR based on cystatin C.[30] CKD was defined as a serum creatinine–based eGFR $<$90 ml/min/1.73 m^2 or albuminuria. The urinary biomarkers NGAL, IL-18, L-FABP, and KIM-1 were measured and compared with those of control subjects (children who did not get AKI during their postoperative course).

Statistical Analysis

The data were entered in the Microsoft Excel and SPSS software (version 20; IBM, Chicago, Illinois, USA) was used for statistical analyses. All variables were tested for normality using the Kolmogorov-Smirnov test. Categorical variables are summarized as frequencies and percentages, while continuous variables as medians and interquartile ranges (IQRs; 25th to 75th percentiles). Cases were compared with control subjects who had cardiac surgery during the same time period. To determine whether a complex surgery done at a younger age puts a child at risk for CKD, children were also evaluated in groups (age at the time of surgery $<$2 months vs $>$2 months). Univariate analysis (using the χ^2 or Fisher exact tests for categorical variables and the Mann-Whitney U test for continuous variables) was carried out to compare the cases with the control subjects and to assess the association between different variables and GFR values at follow-up. All tests were 2-sided, and $P < .05$ was considered statistically significant.

RESULTS

During the study period (2010–2017), 2035 patients $<$18 years of age underwent congenital cardiac surgery on cardiopulmonary bypass, of whom 9.8% (200/2035) developed AKI postoperatively. Forty-four patients who had postoperative AKI and met our inclusion criteria and therefore they were compared with 49 control subjects (Figure 1). AKI was seen within postoperative day 3 in 21 patients (47.7%) and postoperative day 5 in 40 patients (91%).

Baseline Characteristics of the Patients at the Time of Surgery

The study included 93 subjects (44 cases with AKI and 49 control subjects without AKI). A total of 64.5% (60/93) subjects were $<$1 year of age (cases 72.7% [32/44]; control subjects 57.1% [28/49]). Among cases, 7

Table 1. Comparison of categorical and continuous variables between cases and control subjects at baseline

Categorical variables, n (%)	Cases (n = 44)	Control subjects (n = 49)	*P* value
Male	37 (78.7)	39 (84.8)	.450
Cyanotic present	27 (57.4)	24 (52.2)	.609
Sepsis present	4 (9)	1 (2)	.056
Ionotropes used	44 (93.6)	43 (93.5)	1.000
AKI stage			
0	0 (0)	49 (100)	N/A
1	7 (15.9)	0 (0)	
2	16 (36.4)	0 (0)	
3	21 (47.7)	0 (0)	
RACHS-1 score			
2	15 (34.1)	31 (63.3)	.011
3	26 (59.1)	17 (34.7)	
4	3 (6.8)	1 (2)	
STAT score			
1	1 (2.3)	1 (2)	.070
2	16 (36.4)	30 (61.2)	
3	11 (25)	9 (18.4)	
4	16 (36.4)	9 (18.4)	
Surgery <2 months			
RACHS-1 (3 score)	14 (93.3)	2 (100)	1.000
RACHS-1 (4 score)	1 (6.7)	0 (0)	
Continuous variables, median (IQR)			
Age surgery, months	3.5 (0.59–14.25)	9 (5–37)	.003
Weight, kg	16 (13.2–21.9)	14.5 (11.7–18.6)	.197
Height, cm	104 (90.25–122.5)	100 (87.5–116)	.391
ACC time, minutes	50 (35–75)	45 (35–55)	.270
CPB time, minutes	65 (45–100)	60 (45–75)	.380
ICU days	5.5 (3–9)	3 (2–5)	.004
Baseline creatinine (mg/dl) before surgery	0.4 (0.3–0.5)	0.3 (0.2–0.3)	<.001
Max creatinine (mg/dl) during ICU stay	0.75 (0.6–0.98)	0.4 (0.4–0.5)	<.001

ACC, aortic cross-clamp; AKI, acute kidney injury; CPB, cardiopulmonary bypass; ICU, intensive care unit; IQR, interquartile range; N/A, not applicable; RACHS-1, Risk Adjustment in Congenital Heart Surgery; STAT, Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery.

(15.9%) subjects had stage 1 AKI, 16 (36.4%) had stage 2 AKI, and 21 (47.7%) had stage 3 AKI. A higher proportion of cases had a RACHS-1 score of ≥3 (29 [65.9%] vs 18 [36.7%], $P = .0110$ and a STAT score ≥3 (27 [61.4%] vs 18 [36.8%], $P = .07$) compared with control subjects (Table 1). At baseline, the cases compared with the control subjects were younger at the time of surgery (median [IQR], 3.5 [0.6–14.3] vs 9.0 [5.0–37.0] months, $P = .003$), had a longer ICU stay (5.5 [3.0–9.0] vs 3 [2.0–5.0] days, $P = .004$], had a higher creatinine level before surgery (0.4 [0.3–0.5] vs 0.3 [0.2–0.3] mg/dl, $P < .001$), and had a higher maximum creatinine level during their ICU stay (0.8 [0.6–1.0] vs 0.4 [0.4–0.5] mg/dl, $P < .001$; Table 1). None of the patients had systolic or diastolic blood pressure above the 90th percentile in cases or control subjects.

Characteristics of Patients at the Last Follow-Up

The follow-up period was observed to be significantly higher among cases compared with control subjects (median [IQR] 41 [30–64] vs 32 [26–41] months, $P = .002$). At follow-up, the mean (SD) of eGFR as per cystatin C was lower in cases 93.6 (22.4) ml/min/1.73 m^2 versus the control subjects (96.3 [12.9] ml/min/1.73 m^2), which was not statistically significant. Similarly, the eGFR as per the Schwartz bedside formula was also numerically lower in cases but was not statistically significant (Table 2).

At follow-up, the cases compared with control subjects had a significantly higher urine NGAL value (6.30 [3.60–12.90] vs. 3.95 [0.90–8.35] ng/dl, $P = .037$), IL-18 value (29.00 [24.83–34.86] vs. 19.02 [14.23–25.77] pg/dl, $P < .001$), KIM-1 value (0.27 [0.21–0.41] vs. 0.20 [0.12–0.29] ng/dl, $P = .002$), and statistically insignificant L-FABP (7.99 [5.08–16.05] vs. 7.62 [5.22–10.84] ng/dl, $P = .87$). The values of these biomarkers remained higher even after adjusting for the creatinine value and the ratio of urine KIM-1/urine creatinine was observed to be significantly higher among cases compared with control subjects (0.01 [0.00–0.01] vs. 0.00 [0.00–0.01], $P = .023$). None of the patients had systolic or diastolic blood pressure above the 90th percentile on follow-up in cases or control subjects. However, the GFR value was lower among cases compared with control subjects (108.41 [96.20–124.28] vs. 119.77 [101.01–133.88] ml/min/1.73 m^2, $P = .085$), although the difference was not statistically significant (Table 2).

Determinants of GFR at Follow-Up

The 93 subjects were categorized into 2 groups based on their GFR value at the follow-up (low, <90 ml/min/1.73 m^2

Table 2. Comparison of variables between cases and control subjects at follow-up

	Cases		Control subjects		
Variables	n	Median (IQR)	n	Median (IQR)	*P* value
Follow-up, months	44	41 (30–64.48)	49	32 (26–41)	.002
Age at follow-up, months	44	48.5 (36–84.25)	49	48 (33.5–71)	.551
Blood urea, mg/dl[a]	44	24 (20.25–29.75)	49	25 (21.5–30)	.592
Serum creatinine, mg/dl[a]	44	0.4 (0.33–0.5)	49	0.4 (0.3–0.4)	.078
Urine albumin, mg/dl[a]	44	6.3 (3.47–10.52)	48	6.68 (3.69–9.92)	.994
Urine creatinine, mg/dl[a]	44	55.1 (33.2–85.95)	48	56.7 (35.55–93.15)	.904
Serum cystatin, mg/dl[a]	44	0.74 (0.68–0.83)	49	0.71 (0.65–0.8)	.15
Urine NGAL, mg/dl[a]	43	6.3 (3.6–12.9)	48	3.95 (0.9–8.35)	.037
IL-18, pg/dl[a]	43	29 (24.83–34.86)	48	19.02 (14.23–25.77)	<.001
L-FABP, ng/dl[a]	43	7.99 (5.08–16.05)	48	7.62 (5.22–10.84)	.871
KIM-1, ng/dl [a]	41	0.27 (0.21–0.41)	48	0.20 (0.12–0.29)	.002
BTP, mg/l[a]	44	0.68 (0.57–0.71)	49	0.64 (0.56–0.75)	.979
Albumin creatinine ratio	44	0.11 (0.08–0.15)	48	0.1 (0.07–0.14)	.458
eGFR Schwartz, ml/min/1.73 m^2	44	108.41 (96.2–124.28)	49	119.77 (101.01–133.88)	.085
eGFR cystatin C, ml/min/1.73 m^2	44	90.8 (83.8–100.2)	49	98.3 (88.8–105.5)	.082
Urine IL-18/urine creatinine	43	0.46 (0.27–1.07)	48	0.35 (0.21–0.78)	.079
Urine L-FABP/urine creatinine	43	0.15 (0.0–0.46)	48	0.15 (0.09–0.32)	.697
Urine KIM-1/urine creatinine	41	0.005 (0.003–0.011)	48	0.003 (0.002–0.006)	.023
Urine NGAL/urine creatinine	43	0.12 (0.07–0.19)	48	0.08 (0.02–0.19)	.120

BTP, beta-trace protein; eGFR, estimated glomerular filtration rate; IL-18, interleukin-18; IQR, interquartile range; KIM-1, kidney injury molecule-1; L-FABP, liver-type fatty acid binding protein; NGAL, neutrophil gelatinase-associated lipocalin.
[a]Last follow-up visit.

and normal, ≥90 ml/min/1.73 m^2). Eighty-five subjects belonged to the normal GFR group (median [IQR] GFR value 115.64 [102.32–131.13] ml/min/1.73 m^2) and 8 to the low GFR group (80.33 [78.34–87.25] ml/min/1.73 m^2). Eight patients in the normal GFR group had very high excretion of urinary NGAL, IL-18, KIM-1, and L-FABP (defined as >90th percentile). The presence of AKI, AKI stage, younger age at surgery (<2 months of age) were not associated with the occurrence of low GFR at the follow-up. Even among subjects with AKI (cases), younger age at surgery was not associated with the occurrence of low GFR at the follow-up. Of all the included baseline values, only the STAT score differed significantly between the 2 groups, such that a higher proportion of subjects with low GFR had a STAT score of 4 compared with those with high GFR (4 [50.0%] vs. 21 [24.7%], $P = .046$). Regarding follow-up variables, the subjects with low GFR compared with high GFR had significantly higher blood urea (29.5 [26.8–33.0] vs. 24.0 [21.0–29.0] mg/dl, $P = .026$) and serum creatinine values (0.5 [0.4–0.6] vs. 0.4 [0.3–0.4] mg/dl, $P = .005$) but significantly lower IL-18 values (18.1 [9.8–19.1] vs. 25.3 [17.8–32.1] pg/dl, $P = 0$).

DISCUSSION

Numerous research publications have shown that novel urinary biomarkers may be used as candidate proteins for assessing chronic kidney injury. Urinary biomarkers rise earlier than serum creatinine levels and can also help in predicting CKD earlier and prevent its progression.[18,21] We measured a biomarker panel in children who had undergone cardiac surgery that assessed tubular injury (IL-18, KIM-1, and NGAL) and glomerular injury (eGFR serum creatinine by Schwartz; eGFR cystatin C by Schwartz; beta-trace protein; and albuminuria).

Our study adds to the pediatric literature that urinary biomarkers remain elevated years after an episode of AKI after a congenital cardiac surgery performed during early childhood. Complex cardiac surgeries during childhood lead to low GFR on follow-up, regardless of age and events of AKI during the postoperative course.[16–22] Table 3 lists pediatric studies done on long-term renal outcomes after congenital cardiac surgery.

Ours was a cross sectional study done on a prospectively followed cohort by the pediatric cardiology department. A total of 44 follow-up patients with AKI and 49 age- and sex-matched control subjects were finally evaluated (Figure 1). Most of the children had stage 2 to 3 AKI (37/44 [84.1%]). Children who were evaluated were mostly infants, with the median age being 3.5 months (IQR 0.59–14.25 months) in cases and 9 months (IQR 5–37 months) in control subjects. Almost all children received inotropes postsurgery (93.6%) in cases and control subjects (93.5%). Most of the children who had AKI had a complex cardiac surgery (RACHS-score 3 or 4 in 65.9%).

At a median follow-up of 41 months (IQR 30–64 months) we found a statistically significant higher excretion of urine NGAL, urine IL-18, and urine KIM-1. When normalized for urine creatinine, the urine

Table 3. Comparison of studies done on long-term renal outcomes in pediatric cardiac surgery

Author, year	Study type	AKI definition	Children evaluated, n (with AKI)	Follow- up	Measures of renal outcome				Urinary biomarkers
					Proteinuria	Hypertension	Hyperfiltration	eGFR <90 ml/min/ 1.73 m^2	
Non-consensus AKI definition used									
Shaw *et al.*,[16] 1991	Cross-sectional study	Need for dialysis	11	1–5 years	18.2%	0%		18.2%	
Mel *et al.*,[17] 2014	Prospective cohort study	Need for dialysis	25	5.1 years	0%	0%	36%	4%	
Consensus-based AKI definition used									
Cooper *et al.*,[18] 2016	Cross sectional study	pRIFLE	51 (33 AKI)	7 years	3.9%	21.2%	0%	14.3%	Persistent urinary biomarker excretion: IL-18, KIM-1, and L-FABP
Greenberg *et al.*,[19] 2016	Prospective cohort study	AKIN	131 (57 AKI)	5.4 years	6%	11%	0%	0%	
Madsen *et al.*,[20] 2016	Prospective cohort study	KDIGO	382 (127 AKI)	4.9 years				12%	
Greenberg *et al.*,[21] 2018	Prospective cohort study	KDIGO	110 (49 AKI)	5 years					Normal excretion
Huynh *et al.*,[10] 2020	Prospective cohort study	KDIGO	58 (33 AKI)	6 years		0%		No relation of AKI with CKD	
Zappitelli *et al.*,[22] 2020	Prospective cohort study	KDIGO	124 (57 AKI)	3–48 months		49% at 1-year follow-up		No relation of AKI with CKD	
Current study	Prospective cohort study	KDIGO	93 (44 AKI)	41 months	0%	0%	0%	No relation of AKI with CKD	Persistent urinary biomarker excretion: urinary NGAL, IL-18, KIM-1, and KIM-1/creatinine ratio

AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IL-18, interleukin-18; KDIGO, Kidney Disease: Improving Global Outcomes; KIM-1, kidney injury molecule-1; L-FABP, liver-type fatty acid binding protein; pRIFLE, pediatric risk, injury, failure, loss, end-stage renal disease.

KIM-1/urine creatinine ratio was still statistically higher in children with AKI postoperatively ($P = .02$). The Follow-up Renal Assessment of Injury Long-term after AKI (FRAIL-AKI) study also demonstrated similar findings, with patients with AKI having higher excretion of urinary IL-18 and L-FABP at a mean follow-up of 7 years postsurgery. The patient population in the FRAIL-AKI study was similar to ours with infants being evaluated (mean age 0.5 years), with 45% children operated on 54.5% of children with a RACHS-1 score >3.[18] The TRIBE-AKI consortium examined 49 children with AKI at a follow-up of 5 years did not find statistically different biomarker concentrations. However, the patients enrolled by them were very old compared with our study and the FRAIL-AKI study (mean 3.73 years) and had a lower RACHS-1 cardiac surgery complexity (score 3/4 in 57%).[19] It appears that infants undergoing a complex cardiac surgery could have abnormal biomarker concentration months to years after the surgery, even after resolution of serum creatinine and proteinuria.

At the time of last follow-up, the GFR (Schwartz by serum creatinine or serum cystatin C) was lower in children who had AKI postoperatively, but the difference was not significant. It is important to note that children in our study were mostly young infants with a median age of 3.5 months (IQR 0.59–14.25 months). When evaluated, we could not find any association indicating that an age <2 months or 3 months leads to a lower GFR in the long run. There was no association of younger age at the time of surgery, even in the AKI subgroup. The only significant risk factor for a lower GFR in our group of patients was a high STAT score of 4. None of the patients required antihypertensive drugs on follow-up. Similar results were demonstrated by Huynh *et al.*[10] in a neonatal population—cardiac surgery–associated AKI was not associated with CKD (GFR <90 ml/min/1.73 m^2) or hypertension. They found, however, a CKD and hypertension prevalence as 17% and 30%, respectively, in the whole group on follow-up of 6 years.[10] Similar results were found in the TRIBE-AKI study[19] and Zappitelli *et al.*,[22] respectively, with no correlation of postoperative AKI and CKD on follow-up.[20,21] The TRIBE-AKI study found that 22 children (17%) had hypertension (10 times higher than the general pediatric population prevalence), 9 (8%), 13 (13%), and 1 (1%) had microalbuminuria, an eGFR <90 ml/min/1.73 m^2, and an eGFR <60 ml/min/1.73 m^2, respectively.[19] TRIBE-AKI also showed that CKD and hypertension were associated with a higher proportion of participants with 5-year abnormal NGAL, which was not found in our study. Zappitelli *et al.*[22] showed that AKI was associated with hypertension development at 12 months after discharge, but not at subsequent visits. Children <2 years of age at surgery had a significantly higher prevalence of

hypertension during follow-up than older children.[22] However, we did not any abnormalities in blood pressure in our subset of patients at follow-up.

The strengths of our study are recruitment of children (with infants being 72% of cases and 57% of control subjects) undergoing a complex cardiac surgery and doing a comprehensive renal evaluation from estimated GFR, proteinuria, hypertension, and urinary biomarker abnormalities. However, the limitation of the study is that biomarkers were evaluated at a cross-sectional visit, and not done at routine clinical visits at regular intervals to look at the trend. GFR was estimated by the Schwartz formula and not a nuclear scan, as would be desired to have an accurate measure.

When we analyzed the patients as per high biomarker excretion (defined as >90th percentile), there were 9 total such patients. Of these, 5 patients actually had no AKI after cardiac surgery, and still had very high biomarker excretion with a normal GFR. This may mean they had a subclinical AKI which was either not detected may be due to an impact of fluid overload in these patients.

Our findings reinforce the fact that children—especially infants who undergo a complex cardiac surgery—have an ongoing subclinical kidney injury that may persist despite the correction of serum creatinine and proteinuria. This may be detectable only by kidney injury biomarker assay. Persistent elevation of urinary KIM-1, IL-18, NGAL, and especially urinary KIM-1 corrected by urinary creatinine does suggest an ongoing kidney injury. There are preliminary studies reporting the potential use of KIM-1 as a CKD biomarker.[31–33] Even animal models of AKI to CKD transition have shown the upregulation of NGAL and KIM-1 proteins in the kidney, further suggesting their role as a biomarker for CKD.[34] As demonstrated in multiple studies, that though overall children who undergo a cardiac surgery have a low GFR, it is usually not demonstrated in the AKI subgroup. This may be caused by the kidney's compensation to a reduced functional reserve after AKI given that the usual measures of renal function assessment are not able to detect the dysfunction. The occurrence of subclinical renal dysfunction may have a deleterious effect on kidney function, even though the baseline GFR seems to return to normal.[35] This may have an important effect on long-term outcomes in such patients.

DISCLOSURES

All the authors declared no competing interests.

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