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Kidney injury biomarkers 5 years after AKI due to pediatric cardiac surgery

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Abstract

Background—We previously showed that children undergoing cardiac surgery are at high risk for long-term chronic kidney disease (CKD) and hypertension, although postoperative acute kidney injury (AKI) is not a risk factor for worse long-term kidney outcomes. We evaluated if renal injury biomarkers 5 years after cardiac surgery are associated with postoperative AKI or long-term CKD and hypertension.

Methods—This prospective cohort study recruited children 1 month to 18 years old undergoing cardiopulmonary bypass. At 5 years post-cardiac surgery, we measured urine interleukin-18, kidney injury molecule-1 (KIM-1), monocyte chemoattractant protein-1 (MCP-1), YKL-40, and neutrophil gelatinase–associated lipocalin (NGAL). Biomarker levels were compared between patients with AKI *VS.* without. We also performed a cross-sectional analysis of the association between these biomarkers with CKD and hypertension.

Results—305 subjects survived hospitalization: 4 (1.3%) died after discharge; 110 (42%) participated in the 5-year follow-up. 49/110 (45%) had AKI. Patients with *VS.* without post-

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Compliance with ethical standards

Informed consent was obtained from parents or legal guardians, along with assent, when appropriate, from children. This study was approved by the institutional review board of each participating institution.

Disclosures

Dr. Devarajan reported being a coinventor on the neutrophil gelatinase–associated lipocalin patent. No other disclosures were reported.

operative AKI did not have significantly different biomarker concentrations at 5 years. None of the biomarker concentrations were associated with CKD or hypertension at 5-years, although CKD and hypertension were associated with a higher proportion of participants with 5-year abnormal NGAL.

Conclusions—Post-operative pediatric AKI is not associated with urinary kidney injury biomarkers 5 years after surgery. This may represent a lack of chronic renal injury after AKI, imprecise GFR estimation, that longer follow-up is needed to detect chronic renal damage, or that our studied biomarkers are inadequate for evaluating subclinical chronic renal injury.

Keywords

biomarker; acute kidney injury; long-term outcomes; CKD; cardiopulmonary bypass; children

Introduction

Pediatric acute kidney injury (AKI) is common after cardiac surgery and is associated with increased inpatient mortality, length of ventilation, and length of stay [1, 2]. However, much less is known about the long-term outcomes after AKI in children [3, 4]. We previously reported that hypertension and chronic kidney disease (CKD) were common five years after cardiac surgery, although postoperative AKI was not associated with an increased risk of long-term kidney outcomes [5]. Likewise, Cooper et al. found that seven years after cardiac surgery there was no association of AKI with CKD, but that patients with AKI had an elevation of urine kidney injury biomarkers at follow-up [6]. Most recently, a retrospective study evaluating administrative data from Denmark found that children with AKI after cardiac surgery are 3.8 times more likely to develop CKD [7]. Research findings in adult cohorts have clearly demonstrated the association between AKI and risk of long-term CKD, in multiple settings including cardiac surgery [8, 9].

One of the explanations for the conflicting findings on AKI outcomes in the pediatric literature may be the limitations of our current CKD biomarkers, serum creatinine and proteinuria. Proteinuria and serum creatinine may increase late in the course of CKD [10]. Up to 50% of renal mass may be lost without any change in serum creatinine levels, due to compensatory glomerular hypertrophy and hyperfiltration [11]. Therefore, serum creatinine may go unchanged for years in children with CKD [12]. Additionally, serum creatinine is a marker of glomerular filtration and is not specific for identifying tubular or interstitial damage. Proteinuria has up to a 40% intraday variability and is often absent in patients with CKD [10]. Thus, there is clearly a need for more sensitive and predictive biomarkers to study patients at risk for CKD.

A number of novel urinary biomarkers have been studied as candidate proteins of chronic kidney injury, primarily in adults [6, 13, 14]. These urinary biomarkers may rise earlier than serum creatinine and therefore may be used for the early prediction of incident CKD or CKD progression. Additionally, novel biomarkers may capture the variability in CKD progression left unexplained by serum creatinine and proteinuria. Since CKD is a multifactorial disease process we measured a biomarker panel in children five years after cardiac surgery that assessed tubular injury (interleukin-18 (IL-18), kidney injury

molecule-1 (KIM-1), neutrophil gelatinase–associated lipocalin (NGAL)), inflammation/repair (monocyte chemoattractant protein-1 (MCP-1)), and fibrosis/repair (YKL-40). There is pre-clinical or human research to suggest that all five candidate biomarkers may detect late kidney injury and CKD [15–21]. We measured two biomarkers, MCP-1 and YKL-40, for the first time in this cohort at five years because they are candidate biomarkers of renal repair after injury [21–23]. The primary goal of the present study is to determine if AKI after cardiac surgery is associated with long-term evidence of subclinical kidney injury, detected using novel biomarkers. We hypothesized that children with at least stage I AKI would have higher five-year urinary biomarker levels when compared to children without AKI. We also evaluated the extent to which biomarkers (indexed and not indexed to urine creatinine or when expressed as abnormal using gender and age-specific threshold values), and the change in biomarker concentrations from preoperative to five-year follow-up are associated with 5-year CKD or hypertension.

Materials and Methods

Study Cohort

This is a prospective cohort study of children with congenital heart disease who were enrolled between July 2007 and December 2009. Children one month to 18 years old undergoing cardiac surgery with cardiopulmonary bypass at Cincinnati Children's Hospital, Montreal Children's Hospital, and Yale New-Haven Children's Hospital, were enrolled in the Translational Research Investigating Biomarker End Points in AKI (TRIBE-AKI) study [24–26]. Children were excluded if they had a history of renal transplantation or dialysis. Details around preoperative patient recruitment are published in previous reports [27, 28]. The children who consented to future contact during the index hospitalization were invited to participate in the current study. Informed consent was obtained from parents or legal guardians, along with assent, when appropriate, from children. This study was approved by the institutional review board of each participating institution.

Study visits

Five-year in-person visits were performed by a research nurse at the hospital clinic or at subject's home as previously described [5]. Height, weight, and blood pressure were measured and blood and urine were collected at the time of the visits. Percentiles and z-scores of height, weight, and BMI were calculated using CDC growth charts [29]. Blood pressure percentiles were calculated as per The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents [29]. During the visit other details on the medical history, interim hospital admissions, medication history, and laboratory testing since cardiac surgery, were also collected. Discharge summaries from hospital admissions and other medical records were obtained for each hospitalization from the respective medical institutions. Full details of the serum creatinine, urine creatinine, and albuminuria measurements, including sample collection and processing have been previously described [5].

Data from the index cardiac surgery admission

The following detailed index cardiac surgery admission information was available in all participants from our prior in-hospital study: preoperative characteristics, operative details, and postoperative complications using the definitions of the Society of Thoracic Surgeons [30]. We utilized the risk adjustment for congenital heart surgery-1 (RACHS-1) consensus-based scoring system to categorize the complexity of surgery [30]. AKI was defined as the development of at least stage one AKI, defined by at least a ≥ 50% increase or a ≥0.3 mg/dL increase from baseline serum creatinine during hospitalization after cardiac surgery [31]. We also analyzed the outcome of stage two AKI, defined as a doubling in serum creatinine from baseline or receiving acute dialysis during the hospital stay. Details of the in-hospital study have been previously described [24–26, 32].

Biomarker Measurements

We measured urinary NGAL, IL-18, and KIM-1 pre-operatively, on the first post-operative day, and at the five-year study visit. YKL-40 and MCP-1 were only measured at the five-year visit due to limited urine volumes. Perioperative NGAL and IL-18 were measured using the ARCHITECT® assay (Abbott Diagnostics, Abbott Park, IL) while KIM-1 was measured using a Sekisui Diagnostic assay (Sekisui Diagnostics LLC, Stamford, CT). Urine NGAL, IL-18, KIM-1, YKL-40, and MCP-1 at five years after surgery were measured using a Mesoscale Discovery (MSD) multiplex assay with intra-assay coefficients of variation of 2.1%, 7.1%, 7.6%, 1.7%, and 1.4%, respectively [25, 26]. MSD uses patterned arrays and an electrochemiluminescence detection method which is quantified using the MSD Quickplex SQ 120 instrument. To evaluate differences between the perioperative and five-year assays, 75 perioperative samples were re-measured on the MSD platform. The correlation between platforms was excellent (0.90 for IL-18 and 0.89 for KIM-1), but KIM-1 measurements from MSD were systematically lower than from Sekisui. Therefore, we did not include preoperative KIM-1 measurements in this study. Five-year biomarkers were primarily expressed as concentrations. For IL-18 and NGAL we also evaluated absolute change in biomarkers (delta) from preoperative to five-year follow-up concentrations. Biomarker age- and gender-specific abnormal thresholds (cutoffs) were available for urine KIM-1, IL-18, and NGAL. Based on prior published biomarker reference ranges in children, we determined whether five-year biomarker levels of IL-18, NGAL, and KIM-1 were greater than published age- and gender-specific cutoffs [33]. The 95th percentile biomarker cutoffs by age and gender were used as abnormal biomarker thresholds for NGAL [3–5 years old (yo) (Male(M) 26.1 ng/ml, Female(F) 52.2 ng/ml), 5–10 yo (M 10.9 ng/ml, F 139.5 ng/ml), 10–15 yo (M 25.5 ng/ml, 72.3 ng/ml), 15–18 yo (M 50.0 ng/ml, 138.6 ng/ml)], IL-18 [3–5 yo (M 78.3 pg/ml, F 100.5 pg/ml), 5–10 yo (M 41.7 pg/ml, F 79.0 pg/ml), 10–15 yo (M 58.5 pg/ml, 111.1 pg/ml), 15–18 yo (M 71.2 pg/ml, 273.1 pg/ml)], and KIM-1 [3–5 yo (M 983.7 pg/ml, F 1291.7 pg/ml), 5–10 yo (M 1276.6 pg/ml, F 1212.9 pg/ml), 10–15 yo (M 1156.6 pg/ml, 1103.5 pg/ml), 15–18 yo (M 1877.3 pg/ml, 1934.5 pg/ml)] [33].

Five-year outcome definitions: hypertension and CKD

For participants up to 18 years old, hypertension was defined as systolic or diastolic blood pressure ≥95th percentile for age, gender, and height [29]. For participants >18 years old,

hypertension was defined as systolic or diastolic blood pressure >140 mmHg or >90 mmHg, respectively [34]. Additionally, subjects were classified as having hypertension if they reported a history of hypertension. We calculated estimated glomerular filtration rate (eGFR) using the serum creatinine-based eGFR equation and the cystatin C-based eGFR equation of the Chronic Kidney Disease in Children study (CKiD) [35]. Albuminuria was defined as urine albumin to creatinine ratio >30 mg/g. CKD was defined as a serum creatinine-based eGFR <90 ml/min/1.73m^2 or albuminuria [36].

Statistical analysis

Baseline characteristics of participants who completed and did not complete follow-up visits were compared. For each outcome, only those participants with non-missing values were included in the analysis. Continuous variables were compared with two-sample t-test or Wilcoxon rank sum test, and dichotomous variables with the chi-squared test or Fisher's exact test. Five-year urine biomarker concentrations were compared between patients with and without post-operative AKI and multiple linear regression was performed to evaluate this association, adjusting for age, race, gender, RACHS-1, cardiopulmonary bypass time, and study site. Patients with *VS.* without CKD and patients with *VS.* without hypertension were compared for five-year biomarker concentrations, preoperative to five-year biomarker concentration change and presence/absence of elevated biomarkers at five years. SAS version 9.4 was used for analyses.

Results

Study population

Of the 311 children enrolled in the TRIBE-AKI cohort, 305 survived the index hospitalization (Figure 1). 105 children declined future contact and therefore 200 children were eligible for consent. 131 children participated in the five-year follow-up study of which urine samples were available in 110 at a median of 5.4 years of follow-up. Patient baseline and perioperative characteristics by AKI status are shown in Table 1. Children with postoperative AKI had a higher pre-operative eGFR, longer cardiopulmonary bypass time, and a higher RACHS-1 category when compared to children without postoperative AKI. Out of 110 children, 49 (44%) children developed AKI after their index cardiac surgery.

Postoperative AKI and five-year biomarkers

Figure 2 displays AKI *VS.* non-AKI biomarker concentrations from preoperative, postoperative and five-year time points for KIM-1, NGAL, and IL-18. As shown, KIM-1 changed very little throughout all time points, whereas NGAL and IL-18 rose acutely postoperatively but then decreased at the five-year follow-up. At the five-year visit, median urine IL-18, KIM-1, MCP-1, YKL-40, and NGAL were not significantly different in patients with *VS.* without stage 1 or worse AKI (Table 2). Similarly, stage 2 or worse AKI was not associated with five-year biomarker levels (data not shown). In multivariable analyses (adjusted for age, race, gender, RACHS-1, cardiopulmonary bypass time, and study site), there was still no association between postoperative AKI and five-year biomarker levels (Supplementary Table 1).

Five-year biomarkers and kidney outcomes

At the five-year follow-up visit, the median (IQR) urine albumin to creatinine ratio and serum creatinine-based eGFR in children was 5.1 (2.8–12.6) mg/g and 113 (103–126) mL/min/1.73m^2, respectively (Table 2). Hypertension and CKD was present in 20 (18%) and 18 (17%) children, respectively. Five-year median urine IL-18, KIM-1, MCP-1, YKL-40, and NGAL were not significantly higher in children with *VS.* without hypertension or CKD at five-years (Table 3 for hypertension, Table 4 for CKD). Median five-year urine KIM-1 was lower in patients with CKD (0.33 [IQR: 0.19–0.55) than in patients without CKD (0.63 [IQR: 0.3–1.0) (p=0.04). Similarly, there was no significant difference in absolute change in urine biomarker concentrations (KIM-1, NGAL, IL-18) from preoperative to five-years in patients with *VS.* without hypertension (Table 3) or CKD (Table 4). Both hypertension (*VS.* no hypertension) and CKD (*VS.* no CKD) were associated with a higher proportion of patients with five-year NGAL concentrations above normal for age (Tables, 3 and 4, respectively); they were not associated with abnormal five-year KIM-1 or IL-18 concentrations (Tables 3 and 4). There was no change in our five-year biomarker results in patients with or without CKD when we used a cystatin C-based equation to estimate GFR (data not shown). Additionally, the lack of association with AKI, CKD, and hypertension remained unaffected when we adjusted five-year biomarker concentrations for urinary creatinine (Supplementary Tables 2, 3, and 4).

Discussion

This is the largest prospective study to examine the association between postoperative AKI and long-term kidney injury biomarkers in children who underwent cardiopulmonary bypass. We found that postoperative AKI was not associated with later elevations of urine biomarkers of kidney injury and that children with five-year CKD and hypertension did not generally have higher kidney biomarkers at follow-up.

A previous study by Cooper et al. found that children with AKI after cardiac surgery had significantly higher IL-18, KIM-1, and L-FABP at approximately 7 years post-operatively, when compared to children without AKI [6]. These findings suggested that despite a lack of association of AKI with later CKD, there may have been ongoing subclinical kidney injury in the long-term, only detectable by more sensitive urine kidney injury biomarkers. Several differences between our study and the Cooper study may explain our differing findings. The Cooper study had a smaller sample size (n=51) from a single center, but was enriched with patients who developed severe AKI (postoperative doubling of serum creatinine). However, when we evaluated stage two AKI or worse, we did not find an association between more severe AKI and 5-year biomarker concentrations. The follow-up in the Cooper study was longer, with a median of 7 years; it is thus conceivable that patients in their cohort had more time to develop differential biomarker concentrations between AKI groups over time. Finally, patient characteristics between the two studies also differed, with the Cooper study including neonates at the time of surgery, longer cardiopulmonary bypass time, and higher RACHS-1 scores which may have placed them at overall increased risk for long-term subclinical renal damage [37]. However, when we performed a multivariable regression analysis and controlled for potential confounders, there was still no association with AKI

and five-year biomarkers. Importantly, biomarker concentrations were quite different between the two cohorts and were measured with different assays, which lends to difficulties in comparing the two studies. Our study does not confirm the findings of the Cooper study that AKI leads to long-term subclinical renal injury, as evidenced by elevated kidney injury biomarkers, but also highlights the importance of validation of biomarker studies in larger cohorts from multiple centers.

We evaluated the cross-sectional association between five-year urine biomarkers and the presence of functional kidney abnormalities or hypertension, with the rationale that if urine injury biomarkers were in fact indicative of chronic injury in this clinical context, they should be higher in patients with functional impairment. Overall, the utility of renal injury biomarkers in evaluating subclinical chronic kidney injury is still an active area of investigation; thus negative findings are as important as positive findings [16, 20, 38] [15] [39] [18, 40]. Biomarker concentrations were not significantly different in our cohort of children with (*VS*. without) CKD or hypertension. Although it is intriguing that children with hypertension and those with CKD had a higher prevalence of abnormally high urine NGAL, these results must be interpreted with caution, given the multiple testing performed in our study and the risk of spurious results. That said, several previous studies in patients with CKD associated with other diseases have also found that urine NGAL is associated with worse renal function [39, 41]. It is thus worth evaluating in future research the utility of abnormal NGAL levels to screen for and predict progression of renal disease after cardiac surgery. We found at the five-year visit, urine KIM-1 was lower in children with CKD as compared to those without CKD. Since KIM-1 is a tubular protein detected with kidney injury, this association is not supported by previous KIM-1 research and may be influenced by confounding factors [17, 42, 43].

Our overall lack of association of urine injury biomarkers with CKD or with hypertension may also be explained by other issues. It is possible that our studied biomarkers are not sensitive to detect renal damage in the non-acute setting in patients after cardiac surgery. Secondly, it is possible that our methods of evaluating renal disease (CKD and hypertension) are non-specific to chronic tubular injury-associated renal disease in the cardiac surgery population; other factors (e.g., hormonal, humoral, vascular, cardiac) which are not related to these kidney injury biomarkers may play a more important role in the renal disease pathophysiology. Thus, while our negative findings are relevant in directing future studies in the pediatric cardiac surgery long-term outcomes research, they should be evaluated separately in distinct populations (e.g., nephrotoxic AKI or non-cardiac surgery critical illness-associated AKI).

Our study has important limitations. We did not enroll infants less than one-month old and thereby we excluded many of the infants with the most complex cardiac disease. Due to the substantial limitations of serum creatinine as well as the pediatric AKI and CKD definitions available, there may have been misclassification of exposure status and outcomes. Importantly, we used the CKiD equation to estimate GFR even though it has not been validated in healthy children without CKD. Additionally, this pediatric cohort may have been sub-optimal to study CKD after AKI as many of our patients had non-progressive mild AKI, which may not lead to long-term kidney damage in children. Given this uncertainty,

future research should consider focusing on severe AKI as a risk factor for CKD. There were a large number of children who declined participation in this long-term follow-up study, although baseline characteristics were not different between those who did and did not participate [5]. When we determined the absolute change in urine biomarker concentrations we used different biomarker assays at the perioperative and five-year time points, although we measured inter-assay variability. Future prospective studies measuring the change of biomarkers in serial biospecimens should make an effort to use identical biomarker assays. There was also a wide age range at study enrollment and the temporal change of urinary biomarkers over five years may be influenced by substantial age-related changes in biomarker concentrations over time [33, 44].

We have previously shown that children undergoing cardiac surgery are at very high risk for long-term CKD and hypertension; however, we have not found an association of AKI with CKD or hypertension development, and the current study does not support the existence of a relationship between urine injury biomarkers and long-term post-cardiac surgery CKD or hypertension. Future research should determine which renal injury biomarkers detect the presence of renal disease or of hypertension in the unique and high-risk cardiac surgery population, while accounting for effects of age and other patient and disease characteristics on determining biomarker concentrations. Future research should also determine the extent to which our studied biomarkers are (or are not) predictive of post-AKI development of CKD or hypertension in other, non-cardiac surgery, populations, in order to guide future AKI outcome translational research. Such research may identify markers of early subclinical renal injury to allow intervention prior to development of renal functional decline or cardiovascular effects of hypertension.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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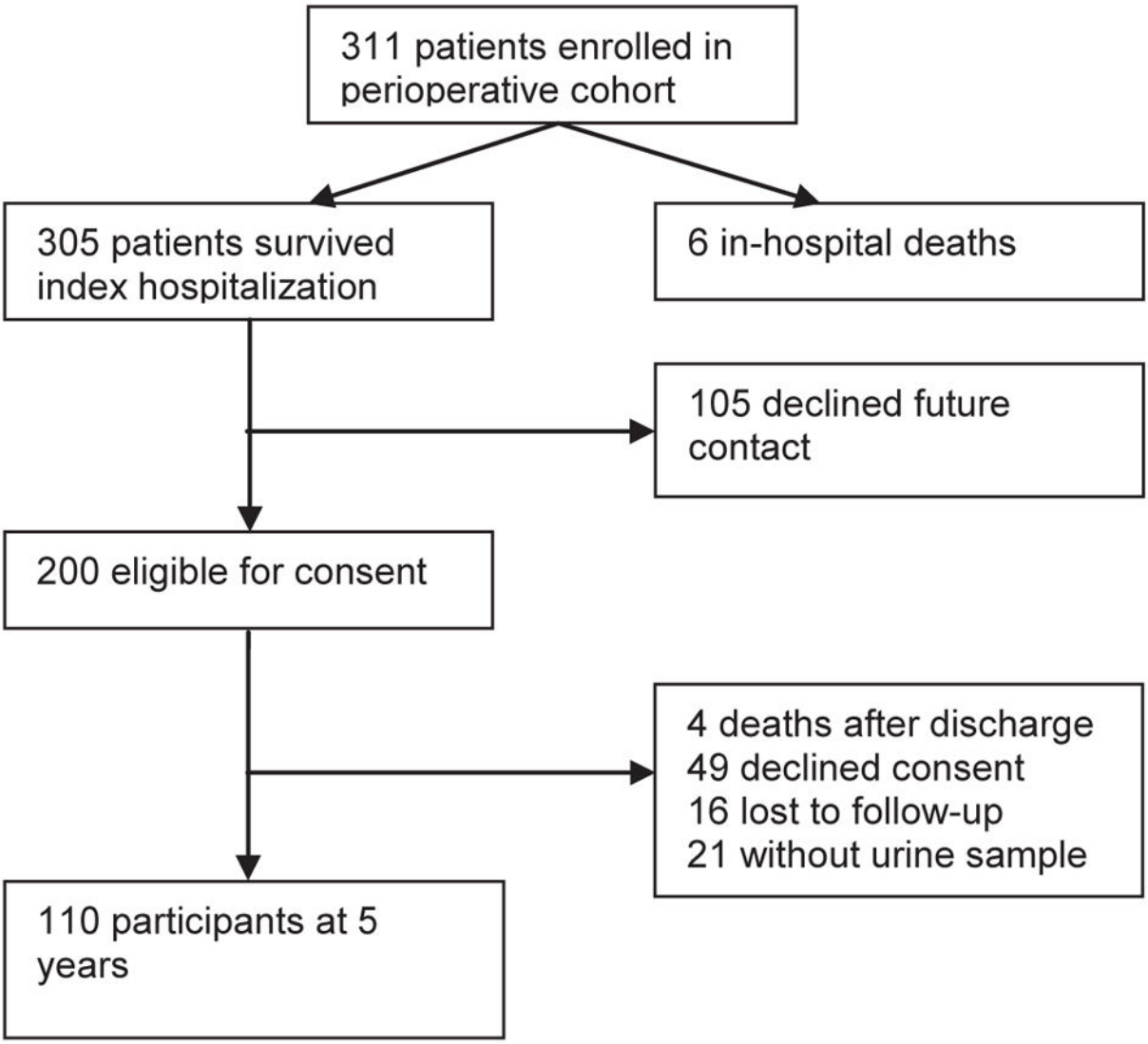

Figure 1.
Study Population. TRIBE-AKI Long Term Follow-Up

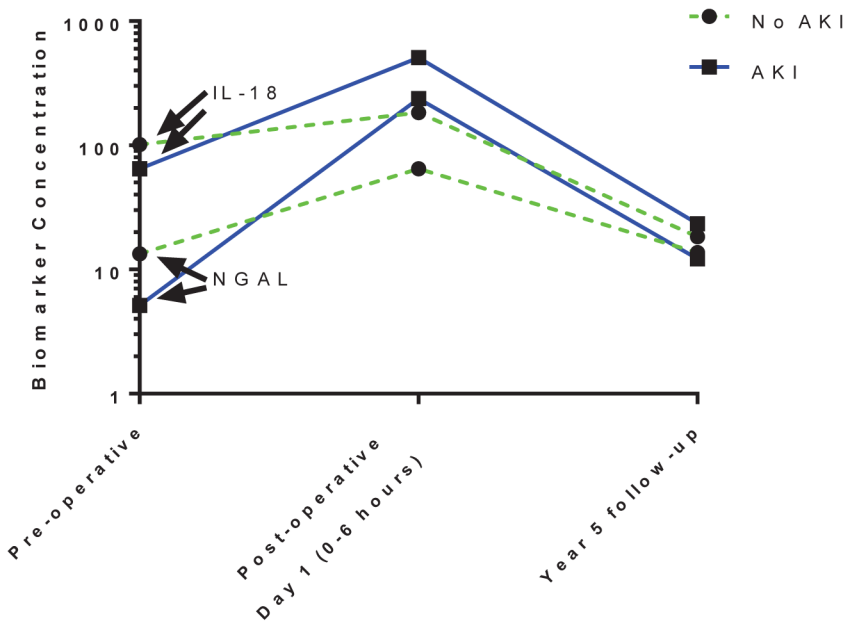

Figure 2.

Urine IL-18 and urine NGAL at pre-operative, post-operative, and year five follow-up. The biomarkers are presented in the following units: IL-18 (pg/mL), NGAL (ng/ml).

Table 1

Baseline and post-operative characteristics of study cohort by AKI status

Characteristic	Overall n=110	AKI (n=49)	No AKI (n=61)	P value
Pre-operative/baseline				
Age (years), (mean (SD)	3.73 (3.9)	3.54 (4.17)	3.89 (3.7)	0.33
Male gender	57 (52%)	28 (57%)	29 (48%)	0.32
Non-white	14 (13%)	7 (14%)	7 (11%)	0.66
Pre-operative estimated SCr-GFR (mean (SD))	97.59 (25.82)	103.33 (30.04)	92.9 (20.89)	0.05
CPB time (minutes)	104.88 (66.29)	124.59 (81.2)	89.05 (46.23)	0.03
RACHS-1 surgical category 1	7 (6%)	0	7 (11%)	0.01
RACHS-1 surgical category 2	48 (44%)	21 (43%)	27 (44%)	
RACHS-1 surgical category 3	50 (45%)	23 (47%)	27 (44%)	
RACHS-1 surgical category 4	5 (5%)	5 (10%)	0	
Elective vs. Urgent Surgery				
Elective	105 (95%)	46 (94%)	59 (97%)	0.48
Urgent	5 (5%)	3 (6%)	2 (3%)	
Type of Surgery				
Septal defect repair	36 (35%)	14 (30%)	22 (38%)	0.47
Inflow/outflow tract or valve procedure	23 (22%)	9 (20%)	14 (24%)	
Combined procedure	45 (43%)	23 (50%)	22 (38%)	
Index Hospitalization				
Peak post-op SCr rise from baseline, mg/dL (median (IQR))	0.2 (0.3, 0.7)	0.7 (0.5, 1)	0.2 (0, 0.3)	<0.001
Length of hospital stay (days)	8.03 (9.25)	10.76 (12.38)	5.84 (4.67)	<0.001
Length of ICU stay (days)	3.62 (5.53)	5.53 (7.77)	2.08 (1.37)	<0.001
Renal replacement	3 (2%)	3 (5%)	0	0.04

Abbreviations: **AKI**, Acute Kidney Injury, **IQR**, interquartile range, **SCr**, serum creatinine (in mg/dl. 1mg/dl = 88.4 μmole/L), **GFR**, glomerular filtration rate (ml/min/1.73m^2), **CPB**, cardiopulmonary bypass, **RACHS-1**, risk adjustment for congenital heart surgery, mg, milligram, **dL**, deciliter, **CRRT**, continuous renal replacement therapy.

Table 2

Five-year biomarkers by AKI status

	Overall n=110	AKI (n=49)	No AKI (n=61)	P value
Urine albumin/Cr (mg/g)	5.1 [2.8, 12.6]	5.8 [2.8, 10.3]	5.0 [2.8, 14.3]	0.79
Estimated GFR[a]	113 [103, 126]	118 [105, 132]	112 [98, 123]	0.09
Urine IL-18 (pg/mL)	14.7 [8.6, 23.4]	16.6 [9.5, 24.3]	13.9 [7.9, 21.8]	0.26
Urine KIM-1 (pg/mL)	250.6 [157.6, 568.5]	366.1 [157.6, 656.8]	336.3 [175.8, 525.4]	0.40
Urine MCP-1 (pg/mL)	109.9 [46.4, 169.4]	103.4 [45.3,169.4]	116.4 [47.4,167.3]	0.83
Urine YKL-40 (pg/mL)	338.6 [157.1, 615.1]	344.5 [184.2, 645.9]	330.1 [149.6, 614.8]	0.58
Urine NGAL (ng/ml)	4.4 [2.1, 10.2]	4.7 [2.2, 7.5]	4.29 [2.0, 14.3]	0.86

Values are expressed as median [interquartile range]. GFR, glomerular filtration rate; Cr, creatinine; IL-18, interleukin-18; KIM-1, kidney injury molecule-1; MCP-1, monocyte chemoattractant protein-1: NGAL, neutrophil gelatinase–associated lipocalin; AKI, acute kidney injury,

[a]Estimated GFR is displayed as ml/min/1.73m^2 and calculated with the serum creatinine-based Chronic Kidney Disease in Children Study

Table 3

Urinary Biomarkers and Hypertension at the Five-Year Follow-up Visit

	Hypertension (N=20)	No Hypertension (N=89)	P value
IL-18 Year 5 (pg/mL)	17.1 (10.9, 40.7)	14.4 (8, 21.8)	0.24
IL-18 Elevated at Year 5	1 (5%)	3 (3%)	0.73
IL18 (Change from pre-op) (pg/mL)	2.7 (-25.5, 16.1)	-0.8 (-22.0, 9.1)	0.32
KIM-1 Year 5 (ng/mL)	0.48 (0.4, 0.8)	0.6 (0.3, 1.0)	0.78
KIM-1 Elevated at Year 5	1 (5%)	15 (17%)	0.18
NGAL Year 5 (ng/mL)	7.07 (2.1, 32.2)	4.3 (2.2, 8.4)	0.25
NGAL Elevated at Year 5	2 (10%)	1 (1%)	0.03
NGAL (Change from pre-op) (ng/mL)	2.7 (-2.5, 39.4)	0.8 (-3.3, 4.2)	0.14
MCP1 MSD Year 5 (pg/mL)	94.3 (38.8, 164.8)	112.3 (47.1, 169.4)	0.67
YKL-40 MSD Year 5 (pg/mL)	423.5 (187.5, 693.0)	317.7 (157.1, 614.8)	0.53

Values are expressed as median [interquartile range] or Number (%). IL-18, interleukin-18; KIM-1, kidney injury molecule-1; MCP-1, monocyte chemoattractant protein-1: NGAL, neutrophil gelatinase–associated lipocalin. Change from pre-op signifies the difference between the five-year biomarker level and the preoperative biomarker level

Table 4

Urinary Biomarkers and CKD at Five-Year Follow-up Visit

	CKD (N=18)	No CKD (N=89)	P value
IL-18 Year 5 (pg/mL)	14.4 (7.3, 19.8)	15.1 (8.7, 23.9)	0.35
IL-18 Elevated at Year 5	0 (0%)	4 (4%)	0.36
IL18 (Change from pre-op) (pg/mL)	-4.6 (-8.8, 2.4)	-0.6 (-22.1, 12.9)	0.50
KIM-1 Year 5 (ng/mL)	0.3 (0.2, 0.6)	0.6 (0.3, 1.0)	0.04
KIM-1 Elevated at Year 5	2 (11%)	14 (16%)	0.62
NGAL Year 5 (ng/mL)	3.5 (1.6, 12.8)	4.7 (2.3, 9.3)	0.67
NGAL Elevated at Year 5	2 (11%)	1 (1%)	0.02
NGAL (Change from pre-op) (ng/mL)	-0.08 (-3.4, 2.1)	1.5 (-2.5, 5.0)	0.43
MCP1 MSD Year 5 (pg/mL)	85.9 (29.8, 176.2)	103.4 (47.4, 163.2)	0.56
YKL-40 MSD Year 5 (pg/mL)	223.5 (157.1, 442.0)	379.9 (151.4, 639.4)	0.31

Values are expressed as median [interquartile range] or Number (%). IL-18, interleukin-18; KIM-1, kidney injury molecule-1; MCP-1, monocyte chemoattractant protein-1: NGAL, neutrophil gelatinase–associated lipocalin; CKD, chronic kidney disease. Change from pre-op signifies the difference between the five-year biomarker level and the preoperative biomarker level