A small post-operative rise in serum creatinine predicts acute kidney injury in children undergoing cardiac surgery

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To predict development of acute kidney injury and its outcome we retrospectively studied children having cardiac surgery. Acute kidney injury (AKI) was defined using the serum creatinine criteria of the pediatric Risk Injury Failure Loss End-Stage (pRIFLE) kidney disease definition. We tested whether a small rise (less than 50%) in creatinine on post-operative days 1 or 2 could predict a greater than 50% increase in serum creatinine within 48 h in 390 children. AKI occurred in 36% of patients, mostly in the first 4 post-operative days. Using logistic regression, significant independent risk factors for AKI were bypass time, longer vasopressor use, and a tendency for younger age. Using Cox regression, AKI was independently associated with longer intensive care unit stay and duration of ventilation. Patients whose serum creatinine did not increase on post-operative days 1 or 2 were unlikely to develop AKI (negative predictive values of 87 and 98%, respectively). Percentage serum creatinine rise on post-operative day 1 predicted AKI within 48 h (area under the curve = 0.65). Our study shows that AKI after pediatric heart surgery is common and is a risk factor for poorer outcome. Small post-operative increases in serum creatinine may assist in the early prediction of AKI.

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Acute kidney injury (AKI) is a risk factor for mortality, longer length of stay and hospital costs in critically ill children and adults[1–4]. Cardiac surgery incurs risk for AKI through hypotension, inflammation and nephrotoxic medication use.[5] Previous pediatric heart surgery research has focused mostly on the incidence and risk factors of severe AKI or on dialysis requirement.[6–9] Disease patterns and severity spectrum of AKI after pediatric cardiac surgery are still unclear. Recent studies of adult cardiac surgery show the importance of mild post-operative serum creatinine (SCr) rise as a predictor of outcome.[10] With the recent derivation of an AKI definition, it is possible to provide a detailed epidemiological description of AKI in children undergoing cardiac surgery.[1,11,12] This population is of particular interest, as much of current early AKI biomarker research is emerging from this group of patients. AKI is currently defined as an acute (48 h) rise in SCr to $\geqslant$50% above baseline.[12] This definition was derived by expert consensus and was validated in children for AKI description in other pediatric populations.[4] It is not known whether a smaller SCr rise may also be clinically significant.

Our goals were (1) to describe the incidence and risk factors of AKI after pediatric cardiac surgery; (2) to determine whether AKI, defined by the standardized definition or by a 25% post-operative SCr rise, is independently associated with a longer length of stay and a longer length of mechanical ventilation; and (3) to calculate the predictive value of early small SCr rise in the prediction of 50% SCr within 48 h.

RESULTS

Study population

Twelve patients with no SCr data were excluded. Their mean age, intensive care length of stay, cardiopulmonary bypass time, gender, and surgical severity score distribution were not statistically different from those of the remaining sample (not shown). The remaining sample had 390 patients, mean ± s.d. (median (IQR)) age = 2.8 ± 4.7 (0.5 (3.8)) years (36.7% less than 3 months old), weight = 12.7 ± 15.3 kg (6.6 (10.6)),

baseline estimated glomerular filtration rate = 75.3 ± 30.8 (73.7 (49.4)) ml/min/1.73m^2. Of them, 222 (56.9%) were male patients, 337 (86.4%) underwent cardiopulmonary bypass (111.4 ± 86.1, 104 (77) min, all patients) and 261 (66.9%) underwent aortic cross-clamping (45.3 ± 41.4, 45.5 (73) min, all patients). The Aristotle score was 7.6 ± 2.3 (8 (3)) and 218 (55.9%) had a RACHS-1 surgical severity score ⩾3. Descriptive data are shown in Table 1.

Acute kidney injury incidence and characterization

The completeness of SCr data was as follows: 99% had daily SCr for ⩾25% of intensive care unit days, 91% had daily SCr for ⩾ half the days and 41.5% had daily SCr for ⩾90% of intensive care unit days. Of the 390 patients, 373 (95.6%) had baseline SCr available; 140 (35.9%) developed AKI by pediatric Risk, Injury, Failure, Loss, End-Stage Kidney Disease (SCr criteria, pRIFLE$_{SCr}$) criteria; 80 (20.5%)

Table 1 | Characteristics of all patients and of patients with versus without acute kidney injury (AKI)

		Mean ± s.d., median (IQR)	
Characteristic	All (*N* = 390)	With AKI (*N* = 140)	No AKI (*N* = 250)
Continuous			
Age (years)	2.8 ± 4.7, 0.5 (3.8)	1.7 ± 4.1, 0.3 (1.1)	3.4 ± 4.9, 0.7 (4.9)**
Weight (kg)	12.7 ± 15.3, 6.6 (10.6)	9.3 ± 12.7, 5.4 (5.3)	14.7 ± 16.3, 7.8 (12.8)**
Baseline eGFR (ml/min/1.73 m^2)	75.3 ± 30.8, 73.7 (49.4)	75.6 ± 32.2, 72.5 (49.5)	75.1 ± 30.1, 75.0 (50.4)
Aristotle score	7.6 ± 2.3, 8 (3)	8.2 ± 2.1, 8 (3)	7.3 ± 2.3, 7.5 (3.0)**
CPB time (min)	111.4 ± 86.1, 104 (77)	146.1 ± 107.3, 128 (66)	91.4 ± 63.2, 90 (74)**
X-clamp (min)	45.3 ± 41.4, 45.5 (73)	60.8 ± 40.9, 61 (49)	36.4 ± 39.1, 30 (63)**
Intra-op blood (cc/kg)	35.0 ± 34.8, 27.7 (60.5)	46.2 ± 33.3, 46.3 (45.3)	28.6 ± 34.1, 16.1 (48.6)**
POD1 lowest BP	74.1 ± 17.5, 74.5 (25)	66.5 ± 16.3, 65 (20)	78.3 ± 16.7, 78.5 (25)**
Days ventilated	4.4 ± 6.3, 2 (4)	6.1 ± 6.0, 4 (6)	3.4 ± 6.3, 2 (3)**
Days on pressors	4.2 ± 4.6, 3 (3)	6.2 ± 5.6, 4 (5)	3.0 ± 3.5, 2 (3)**
Days on Abx	4.0 ± 5.7, 2 (2)	5.2 ± 6.3, 2 (5)	3.4 ± 5.3, 2 (2)**
Days in hospital before PICU	3.3 ± 11.3, 0 (2)	3.6 ± 11.0, 0 (2.5)	3.1 ± 11.5, 0 (2)
PICU LOS	7.9 ± 8.8, 5 (6)	10.3 ± 9.0, 7 (8)	6.6 ± 8.4, 4 (4)**
Hospital LOS	20.3 ± 30.4, 12 (14)	22.0 ± 17.2, 15 (18)	19.3 ± 35.7, 10 (13)**
		N (%)	
Categorical			
Male	222 (56.9)	85 (60.7)	137 (54.8)
RACHS-1			
1	10 (2.6)	0	10 (4.0)
2	208 (53.3)	72 (51.4)	136 (54.4)
3	122 (31.3)	43 (30.7)	79 (31.6)
4	30 (7.7)	16 (11.4)	14 (5.6)*
5	0	0	0
6	12 (3.1)	5 (3.6)	7 (2.8)
Other	8 (2.1)	4 (2.9)	4 (1.6)
Diagnosis			
ASD/VSD	87 (22.3)	33 (23.6)	54 (21.6)
TOF/DORV	60 (15.4)	34 (24.3)	26 (10.4)
TGA[b]	23 (5.9)	9 (6.4)	14 (5.6)
HLHS[b]/	34 (8.7)	18 (12.9)	16 (6.4)
Hypolastic arch			
RV–PA conduit	16 (4.1)	3 (2.1)	13 (5.2)
Aortic coarc	18 (4.6)	2 (1.4)	16 (6.4)
Vascular ring	5 (1.3)	1 (0.7)	4 (1.6)
Fontan procedure	25 (6.4)	10 (7.1)	15 (6.0)
Others	122 (31.3)	30 (21.4)	92 (36.8)**
CPB (yes)	337 (86.4)	135 (96.4)	202 (80.8)*
X-clamp (yes)	261 (66.9)	116 (82.9)	145 (58.0)**
Antibiotic use	348 (89.2)	121 (86.4)	227 (90.8)
ECMO	5 (1.3)	3 (2.1)	2 (0.8)
Dialysis	7 (1.8)	6 (4.3)	1 (0.4)*
PD only	*n* = 4	*n* = 3	*n* = 1
CRRT only	*n* = 1	*n* = 1	
Combination of modalities	*n* = 2	*n* = 2	
Mortality	4 (1.0)	4 (2.9)	0*

ABx, antibiotics; aortic coarc, aortic coarctation; ASD/VSD, atrial septal defect/ventricular septal defect; CPB, cardiopulmonary bypass; CRRT, continuous renal replacement therapy; eGFR, estimated glomerular filtration rate; HLHS, hypoplastic left heart syndrome; LOS, length of stay; PD, peritoneal dialysis; PICU, pediatric intensive care unit; POD1 lowest BP, lowest blood pressure on post-operative day 1; RACHS-1, risk adjustment in congenital heart surgery surgical severity score; TGA, transposition of the great arteries; TOF/DORV, tetralogy of fallot/ double-outlet right ventricle; RV–PA, right ventricle to pulmonary arterty; X-clamp, cross-clamp.
*P < 0.05, **P < 0.005, comparing AKI versus non-AKI groups.

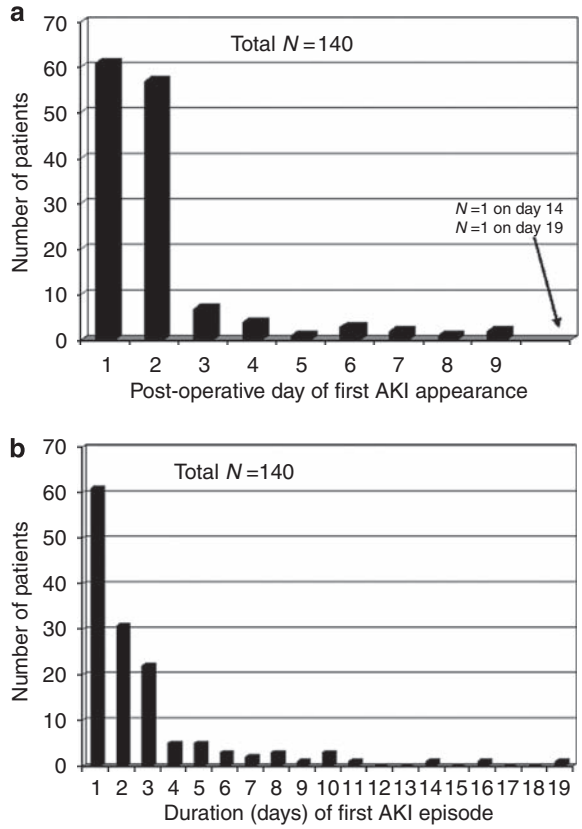

Figure 1 | Timing and duration of the first AKI episode. (**a**) Post-operative day of first evidence of acute kidney injury, defined as ⩾50% serum creatinine rise from baseline, on the *x* axis. The *y* axis depicts numbers of patients first attaining acute kidney injury on the given day. (**b**) Duration (days) of first acute kidney injury episode is displayed on the *x* axis. The *y* axis depicts the numbers of patients having a given duration of acute kidney injury.

developed $pRIFLE_{SCr}$ R; 41 (10.5%) developed $pRIFLE_{SCr}$ I; and 19 (4.9%) developed $pRIFLE_{SCr}$ F AKI. The AKI rate was similar from 2003 to 2006 inclusive, ranging from 32 to 39%. AKI rates ranged from 30% in winters to 40% in summers ($P > 0.05$, χ^2-test comparing the four seasons). There was little difference in the AKI rate whether AM or PM SCr was used; of 358 patients with AM and PM SCr, AKI occurred in 41% using AM SCr values and in 38% using PM SCr values ($P > 0.05$). Of the seven patients requiring dialysis, five had $pRIFLE_{SCr}$ I or F AKI, one had $pRIFLE_{SCr}$ R and one patient did not classify as having AKI. A ⩾25% SCr rise from baseline occurred in 232 of the 390 (59.5%) patients.

In 61 of 140 (43.6%) patients with AKI, AKI status was first attained on post-operative day (POD) 1 and in 57 of 140 (40.7%) on POD 2. Figures 1a and b display the distribution of post-operative days on which AKI first appeared and the duration (number of consecutive days) of the first AKI episode. As shown in Figure 1a, if AKI did not appear by POD 4, patients were very unlikely to develop AKI later. Mean ± s.d. (median (IQR)) number of days duration of the initial AKI episode was 2.8 ± 3.0 (2 (2)). As shown in Figure 1b, 43.6% of the first AKI episodes lasted for 1 day; 22.1% lasted for 2 days and 15.7% lasted longer. Of 101 patients whose initial AKI designation was $pRIFLE_{SCr}$ R, 19 (19%) progressed to a worse $pRIFLE_{SCr}$ stratum (12 patients to $pRIFLE_{SCr}$ I, 7 to $pRIFLE_{SCr}$ F). In the other 39 patients with AKI, the initial $pRIFLE_{SCr}$ stratum achieved was $pRIFLE_{SCr}$ I or F.

A repeat AKI episode was very uncommon. Four patients had AKI 'resolution' for 48 h or more, followed by a repeat episode. Each of these repeat episodes only lasted 1 day and did not attain higher than $pRIFLE_{SCr}$ R.

Risk factors of AKI

Table 1 describes patients' characteristics, outcomes, and univariate analyses comparing patients with and without AKI. In summary, patients with AKI were younger (median ages 1.1 *vs* 4.9 years), had slightly higher mean Aristotle scores (8.2 *vs* 7.3), longer mean cardiopulmonary bypass and cross-clamping times (146.1 *vs* 91.4 and 60.8 *vs* 36.4 min, respectively), received more intraoperative blood (median = 46.3 *vs* 16.1 cc/kg), and had lower trough systolic blood pressure on POD 1 (66.5 *vs* 78.3 mm Hg) (all $P < 0.005$, shown in Table 1). They received mechanical ventilation and vasopressors for a longer duration (medians = 4 *vs* 2 days for both) and had longer intensive care and hospital stays (medians = 7 *vs* 4 and 15 *vs* 10 days, respectively) (all $P < 0.005$). All four deaths occurred in patients who had AKI.

A multiple logistic regression analysis was performed to evaluate for risk factors of development of AKI. We initially considered all potential risk factors listed in Table 1, particularly those with statistical and clinical significance in univariate analyses. A correlation matrix (displaying the correlation between all variables that might be entered into a regression model) of these potential risk factor variables revealed high collinearity for baseline estimated glomerular filtration rate (with age), weight (with age), lowest POD 1 systolic blood pressure (with age and days receiving vasopressors), intraoperative blood per kg (with age and weight) and days ventilated (with days receiving vasopressors). Moreover, all patients who underwent cross-clamp also received cardiopulmonary bypass. We therefore included the six remaining variables, namely, age, gender, cardiopulmonary bypass time, days on vasopressors, days on antibiotics and Aristotle scores and interaction terms between age and each of the other variables. In addition, we repeated the analyses substituting Aristotle score with the presence of RACHS-1 score ⩾*vs* <3. In our final model, longer cardiopulmonary bypass time (Odds Ratio or OR = 1.01, 95% CI = 1.003–1.01, $P = 0.001$) and higher number of days of receiving vasopressors (OR = 3.68, 95% CI = 2.15–6.30, $P < 0.001$) were independently associated with AKI development. Younger age trended toward an association with AKI (OR = 0.68, 95% CI = 0.45–1.002, $P = 0.057$). The analyses replacing the Aristotle score for the RACHS-1 score ⩾versus <3 were almost identical (not shown).

Table 2 | Association of AKI with PICU, length of hospital stay, and length of mechanical ventilation

	Unadjusted hazard ratio[a] (95% confidence interval)			Adjusted hazard ratio (95% confidence interval)		
AKI category	PICU LOS	Hospital LOS	Days of ventilation	PICU LOS	Hospital LOS	Days of ventilation
25% SCr rise or worse	0.6 (0.5–0.7)*	0.7 (0.6–0.9)*	0.6 (0.5–0.7)*	0.7 (0.5–0.9)*	0.8 (0.6–1.0)	0.7 (0.6–0.9)*
50% SCr rise or worse	0.6 (0.5–0.7)*	0.7 (0.6–0.8)*	0.6 (0.5–0.7)*	0.7 (0.5–0.9)*	0.9 (0.7–1.1)	0.7 (0.6–0.9)*

AKI: acute kidney injury; LOS, length of hospital stay; PICU, pediatric intensive care unit; SCr, serum creatinine.
[a]A hazard ratio below zero denotes less likelihood of achieving the event, which is hospital discharge or extubation. Therefore hazard ratio <1 equates to longer length of stay and longer duration of ventilation.
*$P<0.05$.

To determine whether, in patients who underwent cardiopulmonary bypass, cross-clamp time was associated with AKI, we repeated the analysis in patients who underwent cardiopulmonary bypass, including all other variables. Only longer vasopressor duration was strongly associated with AKI (OR = 3.31, 95% CI = 2.00–5.47, $P<0.001$), and longer cross-clamp time was marginally associated (OR = 1.01, 95% CI = 1.00–1.01, $P=0.046$).

AKI as a risk factor of longer length of stay and length of ventilation

Table 2 shows unadjusted and adjusted ORs of AKI as a risk factor for longer intensive care and hospital stays and ventilation duration. We defined AKI by the traditional $\geqslant$50% SCr rise and repeated analyses when defining AKI as a $\geqslant$25% SCr rise from baseline. In unadjusted analyses, AKI defined both ways was associated with increased risk for longer intensive care and hospital stays and for longer ventilation duration (all ORs ranging from 0.6 to 0.7, shown in Table 2). When adjusting for age, gender, cardiopulmonary bypass time, baseline estimated glomerular filtration rate, Aristotle (or RACHS-1) score and the presence of vasopressors, AKI was independently associated with a longer intensive care stay and mechanical ventilation duration (Table 2), whether defined by a 25 or 50% SCr rise. Longer cardiopulmonary bypass time and younger age were also independently associated with longer lengths of stay and days of ventilation in all analyses (not shown).

Prediction of AKI using early small SCr rise

On POD 1, 324 patients had SCr measurement and did not have AKI defined by the standard $\geqslant$50% SCr rise. Of those, 68 (21%) had a 25 to 50% SCr rise on POD 1 (that is, 'early' SCr rise). A 25–50% SCr rise-predicted progression to $\geqslant$50% SCr within 48 h with good specificity and a negative predictive value on POD 1 (83 and 85%, respectively) and POD 2 (78 and 97%, respectively). The presence of any SCr rise from baseline on POD 1 predicted a further progression to $\geqslant$50% within 48 h with good sensitivity and a negative predictive value on POD 1 (78 and 87%, respectively) and with excellent sensitivity and a negative predictive value on POD 2 (91 and 98%, respectively). The area under the curve of percentage rise in SCr to predict future rise to $\geqslant$50% above baseline in patients without AKI yet was similar on POD 1 and 2 (0.68 and 0.65, respectively, both ROC curves shown in Figure 2). Diagnostic characteristics and 95% CIs are displayed in Table 3.

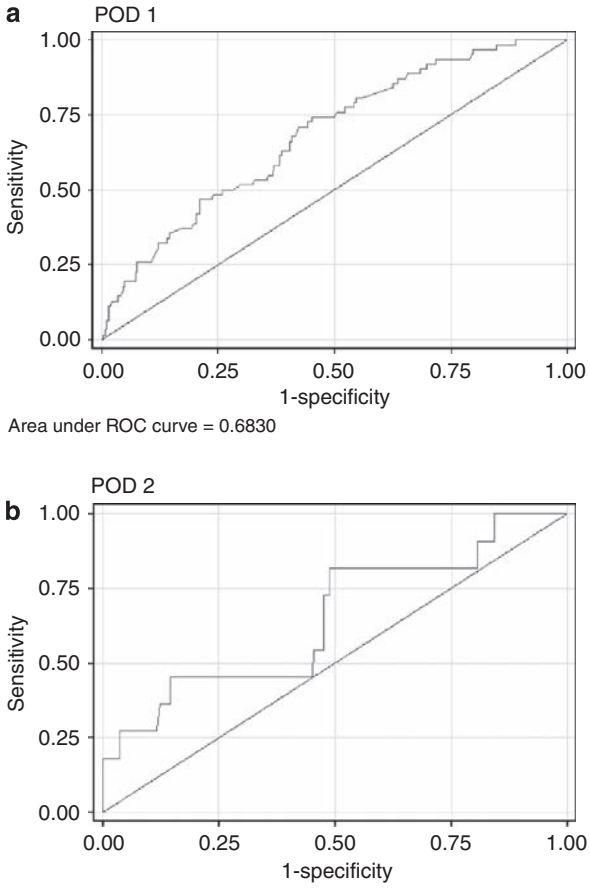

Figure 2 | Prediction of AKI using percentage serum creatinine rise from baseline as a predictor. Receiver operating characteristic (ROC) curve (sensitivity versus 1-specificity plot) showing percentage serum creatinine rise from baseline on post-operative day 1 (**a**) and post-operative day 2 (**b**) to predict a $\geqslant$50% SCr rise within 48 h. AKI, acute kidney injury; POD, post-operative day, SCr, serum creatinine.

DISCUSSION

This is the first study describing AKI incidence, severity, risk factors, and effect on outcome using the recently accepted pRIFLE definition in children undergoing cardiac surgery.

Thirty-six percent of patients developed AKI, mostly within 3 days after surgery. Table 4 shows recent studies describing AKI in similar populations, using different AKI definitions. The AKI rate in our cohort was similar to that described in an American pediatric cohort using a similar definition.[13–16] Several past studies used SCr doubling

Table 3 | Diagnostic characteristics of different criteria for small serum creatinine rises to predict AKI[a] within the following 48 h

	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	AUC, % (95% CI)
Post-operative day (POD) 1 (only patients with no AKI on POD 1)					
SCr[b] 25–50% above baseline (yes or no)	37.1 (25.2–50.3)	82.8 (77.7–87.2)	33.8 (22.8–46.3)	84.8 (79.8–88.9)	—
Any SCr rise above baseline (yes or no)	77.9 (73.4–82.4)	44.9 (39.5–50.4)	30.6 (25.6–35.6)	86.7 (83.0–90.4)	—
POD 1 SCr/baseline $\times$ 100 (%, continuous)[c]					0.68 (0.61–0.75)
POD 2 (only patients with no AKI on POD 1 or 2)					
SCr 25–50% above baseline (yes or no)	45.5 (16.8–76.6)	78.1 (72.4–83.1)	8.6 (2.9–19.0)	96.9 (93.4–98.9)	—
Any SCr rise above baseline (yes or no)	90.5 (86.8–94.2)	40.8 (34.6–47.0)	12.6 (8.4–16.7)	97.9 (96.0–99.7)	—
POD 2 SCr/baseline $\times$ 100 (%, continuous)[c]					0.65 (0.47–0.84)

AKI, acute kidney injury; AUC, area under the curve; NPV, negative predictive value; PPV, positive; predictive value; SCr, serum creatinine.
[a]AKI: defined by a $\geqslant$50% rise in SCr from baseline.
[b]SCr on the day of assessment was expressed as a percentage of baseline SCr (SCr/baseline $\times$ 100).
[c]This continuous variable was treated as a biomarker to predict further rise in SCr to 50% above baseline within 48 h.

Table 4 | Summary of selected studies since 2000 on acute kidney injury (AKI) in children undergoing cardiac surgery

First author	Population	AKI definition(s)	AKI rate
Skippen[18]	$N=101$; <16 years old; all CPB[a]	SCr doubling from baseline	11%
		Tripling of SCr	1%
		Need for dialysis	0
Kist-van Holthe[7]	$N=1075$; <17 years old; all CPB	SCr doubling if >8 weeks old or >75 μmol/l if <8weeks old	17%
		Need for dialysis	2.3%
Pedersen[8,9]	$N=1128$; <15.6 years old; all congenital heart surgeries; 41% RACHS-1 $\geqslant$3	Need for dialysis	11.5%
Chan[6]	$N=182$; <3 years old; open heart surgery excluded early (<72 h) deaths; 25% RACHS-1 $\geqslant$3	SCr >75 μmol/l or urine output <1 ml/kg/h for at least 4 h and need for dialysis	17%
Nguyen[16]	$N=106$; <18 years old; all CPB; study to investigate urine aprotinin to diagnose AKI; 48% RACHS-1 $\geqslant$3	$\geqslant$50% SCr rise from baseline within 3 post-operative days	30%[a]
Backer[17]	$N=2481$; <18 years old; all CPB; study comparing outcome with versus without aprotinin use; mean Aristotle score = 7.5	SCr doubling from baseline in first 3 post-operative days	5.5%
		Need for dialysis	<1%

CPB, cardiopulmonary bypass; RACHS-1, risk adjustment in congenital heart surgery surgical severity score; SCr, serum creatinine.
[a]These investigators report AKI (as defined in the table) rates ranging from 28 to 51% in other studies performed at their center in similar cohorts (13–15). Figure 1a). Day of first AKI episode.

(equivalent to $pRIFLE_{SCr}$ I) as the AKI definition, reporting AKI rates ranging from 6 to 17%,[7,17,18] similar to our finding of 10.5%. One study examined the rate of SCr tripling ($pRIFLE_{SCr}$ F) reported in 1% of their cohort, compared with 4.5% of ours. Using dialysis need as an AKI definition is subject to bias because of institutional practice, explaining the wide variation in dialysis after pediatric heart surgery, ranging from 0 to 17%.[6–8,17,18] Our center's practice is to initiate dialysis only with severe AKI or with severe diuretic-unresponsive fluid overload (1.8% of our patients). Unique to our study was our ability to examine several potential AKI risk factors because of our two prospectively collected institutional PICUes and Cardioaccess databases. We removed variables that had a high collinearity with other variables, which could lead to spurious results in interpreting significance. Longer cardiopulmonary bypass time (and in patients receiving cardiopulmonary bypass, longer aortic cross-clamp time), younger age and longer duration of vasopressor administration predicted AKI occurrence in multivariate models. Although no other study has evaluated risk factors of AKI in such an extensive manner, longer cardiopulmonary bypass time [6,8,9,16,18] and younger age [7–9] have consistently emerged as risk factors.

If the future of AKI research includes evaluating novel therapies, it is important to understand AKI disease patterns. We found that SCr first rises by 50% within the first 3–4 days after surgery, mirroring findings from a few other studies.[7,13,16] We explicitly showed that AKI episodes rarely last more than 5 days and that repeat AKI episodes are extremely uncommon. As our center does not routinely insert peritoneal dialysis catheters in children undergoing heart surgery, we provided a 'natural history' of post-operative AKI.

AKI, whether defined by a 25 or 50% SCr rise, was independently associated with longer length of stay and mechanical ventilation. The finding that even very mild acute perturbations in renal function have an effect on outcome has been found in studies of adults undergoing heart surgery and in noncardiac critically ill children.[1,3,10,19,20] In our study,

this effect was independent of several factors, including vasopressor use, antibiotic use, age, gender, and surgical severity score. The mechanism of the effect of such small SCr rises on outcome is unclear. It is not known to what extent kidney 'injury', defined pathologically by renal tubular cell death, actually occurs in patients with such a small, transient SCr rise. AKI biomarker studies help to answer this question. The mechanism of the negative effect of AKI on length of ventilation might be explained by fluid overload. It would be of interest in future studies to examine the interaction between presence of mild, moderate, and severe AKI, development of fluid retention, and their effect on respiratory compromise.

Given the findings in adults of very small SCr rise-predicting mortality[10] and given the current era of identifying early AKI biomarkers, we hypothesized that very small SCr rises might predict a further AKI-defining 50% SCr rise. In other words, we used small SCr rise as an 'early biomarker' of AKI, similar to the way other new urine protein biomarkers have been studied.[15,21,22] Patients with no SCr rise from baseline on POD 1 were very unlikely to develop any AKI in the future (negative predictive value = 87%); on POD 2, patients who still did not have any SCr rise from baseline were extremely unlikely to develop AKI (negative predictive value = 98%). Percentage SCr rise from baseline on POD 1 or POD 2 resulted in an area under the curve of ~0.65 for predicting future AKI occurrence. Although this area under the curve is not very promising alone, one can imagine that in combination with new AKI biomarkers, paying close attention to very early rises in SCr might substantially contribute to our armamentarium in early AKI prediction.

The limitations of this study have mostly to do with the retrospective design, wherein problems with data accuracy must be considered. However, our research findings on AKI risk factors are in keeping with previous research, and fortunately, the level of missing data was extremely low. Our sample size did not allow us to examine all possible interaction terms when evaluating AKI risk factors or the effect of AKI on outcome, which could lead to spurious findings. This was a single-center study, impeding on generalizability. However, our population was very similar, in terms of surgical severity scores and in terms of AKI rates described using various definitions, to populations described in other studies (Table 4). Although we controlled for various surrogate illness severity measures, we cannot be completely sure that this vital factor was adequately controlled for when evaluating the effect of AKI on outcomes. We could not evaluate urine output as a marker of AKI or in defining AKI, as these data were not available from our databases. Previous research suggests that considering changes in urine output in addition to SCr to define AKI adds little to the final AKI designation and to the association between AKI and outcomes.[1,23] Nevertheless, future research should evaluate the utility of early urine output changes in defining AKI in this population. We also did not evaluate urine indices of AKI (such as fractional excretion of sodium), as data were not available. However, these indices are rarely used in the child post-operative cardiac population as almost all patients receive loop diuretics post-operatively, precluding the use of such markers.

This study supports the need for ongoing research to identify early AKI biomarkers and to study AKI treatments in the vulnerable population of children undergoing heart surgery. The detailed description of disease patterns will be useful for the design of future biomarker studies and clinical trials. The use of early small SCr rise as a biomarker and of selected clinical factors should be incorporated while studying early AKI prediction.

MATERIALS AND METHODS

Design, setting, and participant selection

This was a retrospective study at the Montreal Children's Hospital, Canada. Children undergoing open chest surgery between 28 December 2002 and 28 September 2007 were eligible. Patients with no SCr measured during their intensive care stay were excluded. Patients were identified from an institutional quality assurance database (Pediatric Intensive Care Evaluations (PICUEs) 3.2.3). Institutional ethics approval was received and the need for informed consent was waived.

Data sources and collection

Data were acquired from our institution's (1) 'PICUEs', (2) Cardioaccess and (3) clinical laboratory databases.

PICUes database. The PICUEs 3 software is a proprietary database used to record clinical, diagnostic, and outcome data prospectively on all pediatric intensive care unit patients since September 2002. The following variables were extracted: birth date, gender, hospital, and intensive care unit admission and discharge dates, intensive care unit admission weight and height, survival outcome and date of death, lowest systolic blood pressure (mm Hg) on POD 1, duration (days) of mechanical ventilation, vasopressor and antibiotic administration and number of days of receiving extracorporeal support including renal replacement therapy (hemodialysis, continuous renal replacement therapy, peritoneal dialysis). POD 1 refers to the day of surgical procedure.

Cardioaccess database. The Cardioaccess database is a proprietary software that links to the Society of Thoracic Surgeons Congenital database and includes prospectively collected preoperative, operative, and post-operative variables. The following variables were extracted: primary diagnosis, operative procedure, cardiopulmonary bypass time, aortic cross-clamp time, and cc/kg blood (packed red blood cells) administered during surgery.

On the basis of diagnosis and procedure, two surgical severity scores were calculated: the Aristotle score[24] and the Risk Adjustment in Congenital Heart Surgery (RACHS-1) score.[25] The Basic Aristotle score is the sum of three weighted variables based on surgical procedure (anticipated morbidity, anticipated mortality, and surgical difficulty) and is associated with increased mortality.[24,26] Each variable has a numeric value from one to five, with a score range from 3 to 15.[24] RACHS-1 was developed by an expert panel, [25] which developed six categories designed to differentiate surgical risk on the basis of procedure. Increase in the RACHS-1 category is associated with an increase in mortality.[25,27] There is no RACHS-1 classification for heart transplantation or pacemaker insertion, hence these diagnoses were classified as 'other'. We also classified

patients as having a RACHS-1 score $<$ or $\geqslant 3$; patients requiring pacemaker insertion were classified with a RACHS-1 score <3 and those undergoing heart transplantation were classified with a score $\geqslant 3$.

Hospital laboratory database. We recorded the highest AM (midnight to noon) and PM (noon to 23:59) serum creatinine (SCr) for each intensive care admission day, beginning on POD 1. The higher of these two values was used for daily AKI classification. Baseline renal function was estimated using preoperative SCr values (within a week before surgery). If no recent SCr was available, we utilized the lowest SCr in the previous month (instead of the previous 3 months,[1,11] as a large proportion of our participants were very young, and also to account for growth-associated SCr rise). If no baseline estimate was available, it was estimated using minimum norms for age and gender.[4]

Description of outcomes

We defined AKI using pRIFLE criteria, which include SCr and urine output criteria. We did not have urine output available and therefore only used SCr criteria ($pRIFLE_{SCr}$).[4] We have shown that AKI defined by these criteria ($pRIFLE_{SCr}$) leads to an identical AKI distribution as when the more recent adult AKI definition (the Acute Kidney Injury Network staging) is used.[4] $pRIFLE_{Scr}$ defines AKI as 'Risk (R)' (mild): SCr rise between 1.5 and <2 times baseline; 'Injury' (I) (moderate): SCr rise between 2 and <3 times baseline; 'Failure' (F) (severe): SCr rise $\geqslant 3$ times baseline. The maximal SCr throughout intensive care unit admission was divided by the baseline SCr to derive the highest $pRIFLE_{SCr}$ attainment. Each intensive care unit day's $pRIFLE_{SCr}$ status was recorded to calculate the duration (days) of AKI episodes, to determine when AKI first occurred and to evaluate progression from $pRIFLE_{SCr}$ R (mild) AKI to more severe forms. We evaluated for 'repeat AKI episodes'. Patients with a 'new' SCr rise after an initial AKI resolution (no $pRIFLE_{SCr}$ AKI) for 48 h were classified as having a repeat AKI episode. Because of recent data displaying the potential importance of smaller SCr rises,[10] we performed subset analyses defining AKI as a $\geqslant 25\%$ SCr rise from baseline ($pRIFLE_{SCr}25$). Other outcomes for which the presence of AKI was the main predictor were intensive care and hospital lengths of stay and duration (days) of mechanical ventilation.

Statistical analysis and data management

Continuous variables were examined for distribution and expressed as mean $\pm$ s.d., median (interquartile range or IQR) as appropriate. Categorical variables were expressed as percentage (%). Univariate associations between risk factors and AKI were evaluated using Student's *t*-tests or χ^2-tests. Continuous variables following non-normal distributions were ln-transformed for use in parametric tests.

We evaluated multiple potential AKI risk factors (age, gender, baseline estimated glomerular filtration rate by the Schwartz formula,[28] cardiopulmonary bypass time, cross-clamp time, blood cc/kg given during surgery, Aristotle or RACHS-1 scores, days receiving mechanical ventilation, vasopressor or antibiotics and lowest POD 1 blood pressure) using univariate analyses. We used multiple logistic regression to evaluate independent AKI risk factors. We suspected collinearity between variables, hence before entering variables into the regression model, we evaluated the correlation matrix of all variables and eliminated variables with a high ($r>0.8$) correlation and chose *a priori* which variables to enter into the final model. Our sample size allowed us to evaluate interaction terms between age and other remaining variables. We repeated the logistic regression analysis using the Aristotle score and then using RACHS-1 staging ($<$ *vs* $\geqslant 3$).

We evaluated the effect of AKI on outcomes. We used Cox regression (death censored), controlling for potential confounders determined *a priori,* to evaluate the effect of AKI on intensive care and hospital lengths of stay and ventilation duration. Results were no different when linear regression was used (not shown). We evaluated the effect of a 25% SCr rise ($pRIFLE_{SCr}25$) on longer intensive care/hospital lengths of stay and duration of ventilation.

In patients who did not have a $\geqslant 50\%$ SCr rise on POD 1, we evaluated the diagnostic characteristics of 25 to $<50\%$ SCr rise on POD 1, as well as any SCr rise on POD 1 to predict a $\geqslant 50\%$ rise within 48 h. We evaluated the receiver operating characteristic curve and calculated the area under the curve, treating percentage rise of POD 1 SCr from baseline as a continuous variable. We performed the same analyses for POD 2, including only patients who did not have a $\geqslant 50\%$ SCr on POD 1 or POD 2. STATA 10 (College Station, TX, USA) was used for all analyses.

DISCLOSURE

All the authors declared no competing interests.

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