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Early postoperative serum cystatin C predicts severe acute kidney injury following pediatric cardiac surgery

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In this multicenter, prospective study of 288 children (half under 2 years of age) undergoing cardiac surgery, we evaluated whether the measurement of pre- and postoperative serum cystatin C (CysC) improves the prediction of acute kidney injury (AKI) over that obtained by serum creatinine (SCr). Higher preoperative SCr-based estimated glomerular filtration rates predicted higher risk of the postoperative primary outcomes of stage 1 and 2 AKI (adjusted odds ratios (ORs) 1.5 and 1.9, respectively). Preoperative CysC was not associated with AKI. The highest quintile of postoperative (within 6 h) CysC predicted stage 1 and 2 AKI (adjusted ORs of 6 and 17.2, respectively). The highest tertile of percent change in CysC independently predicted AKI, whereas the highest tertile of SCr predicted stage 1 but not stage 2 AKI. Postoperative CysC levels independently predicted longer duration of ventilation and intensive care unit length of stay, whereas the postoperative SCr change only predicted longer intensive care unit stay. Thus, postoperative serum CysC is useful to risk-stratify patients for AKI treatment trials. More research, however, is needed to understand the relation between preoperative renal function and the risk of AKI.

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The development of acute kidney injury (AKI) is a risk factor for negative hospital outcomes in adults and children who undergo cardiac surgery.[1–3] Intense contemporary research has been directed toward validating novel biomarkers to predict AKI earlier than is feasible with acute changes in serum creatinine (SCr).[4–7] This is with the ultimate goal being to initiate potential AKI treatments in clinical trials and in clinical practice eventually.[8] Currently, early AKI diagnosis may direct clinicians to apply timely conservative treatments such as avoidance of nephrotoxins and optimization of fluid status.

Early AKI diagnosis is an especially challenging task in children. In a previous single-centre retrospective study, we found that a substantial proportion of children display signs of AKI defined by acute SCr rise within hours after cardiac surgery and that most AKI occurs within the first 2–3 postoperative days.[3] Therefore, preoperative and early postoperative clinical data and biological markers will offer the highest chance of capturing patients who will develop AKI or who are in the early stages of AKI. Some studies suggest that the presence of chronic kidney disease (CKD) is a risk factor for developing AKI in different settings,[1,9,10] although this remains inconclusive in adults[11,12] and has not been well studied in children.

Serum cystatin C (CysC) is a more accurate marker of glomerular filtration rate (GFR) than SCr in children with CKD.[13,14] The benefit of using serum CysC for early AKI diagnosis in critically ill patients has been controversial.[15] Because CysC is a marker of filtration, it is unclear whether it should be expressed as a percentage change from baseline levels, when measured postoperatively for AKI prediction (like SCr is), or whether raw concentration values should be used. In terms of preoperative AKI risk prediction in children, SCr concentrations are highly affected by multiple non-renal factors, including gender, age, growth, and muscle mass.[14] Therefore CysC may offer a novel method for AKI risk stratification before cardiac surgery.

In this multicenter, prospective study of children undergoing cardiac surgery, we sought to compare the abilities of (1) preoperative SCr and CysC, and of (2) first postoperative serum CysC and SCr to predict cardiac surgery-associated AKI as well as secondary outcomes including length of stay and duration of mechanical ventilation. Because of lack of previous literature on CysC, we also evaluated different methods of expressing postoperative CysC for evaluating the ability of CysC to predict AKI.

Table 1 | Characteristics and outcomes of the study cohort ($n = 288$)

	Categorical variables: *n* (%) Continuous variables: mean ± s.d., median [interquartile range]
Male gender	159 (55%)
Age (years)	3.8 ± 4.5, 2.1 [5.0]
⩽2 Years old	144 (50%)
Height/length (cm)	90 ± 33, 81 [46.5]
Percentile	32 ± 32, 20 [58]
Standard deviation score	−0.9 ± 2.2, −0.8 [2.2]
Weight (kg)	16.4 ± 17.3, 10.5 [12.6]
Percentile	29 ± 33, 12 [54]
Standard deviation score	−1.1 ± 2.0, −1.2 [2.4]
Study site	
Cincinnati, Ohio	197 (68%)
Montreal, Quebec	57 (20%)
New Haven, Connecticut	34 (12%)
Operative characteristics	
RACHS-1 score ⩾3[a]	129 (45%)
Cardiopulmonary bypass time[b]	
<60 min	54 (19%)
61–90 min	80 (28%)
91–120 min	60 (21%)
121–180 min	65 (23%)
>180 min	29 (10%)
Renal function	
Preoperative CysC (mg/dl)	0.8 ± 0.2, 0.73 [0.29]
Preoperative estimated GFR (ml/min per 1.73 m^2)[c]	90.5 ± 25.4, 87.8 [31.6]
Preoperative estimated GFR percentile[c]	52.7 ± 34, 56 [66]
First postoperative markers	
Hours after surgery of 1st postoperative blood sampling	0.6 ± 1.3, 0.5 [0.33]
Cys C (mg/l)	0.77 ± 0.32, 0.69 [0.38]
% SCr change from baseline	15 ± 20, 16 [33]
% CysC change from baseline	−1 ± 27, −7 [29]
AKI and other outcomes	
Stage 1 AKI[d]	121 (42%)
Stage 2 AKI[d]	47 (11%)
Dialysis	5 (2%)
Length of intensive care unit stay (days)	4.0 ± 6.1, 2.0 [3.0]
Length of hospital stay (days)	8.0 ± 9.2, 5.0 [4.0]
Duration of mechanical ventilation (days)	1.4 ± 1.5, 1.0 [2.0]
Mortality	4 (1.4%)

Abbreviations: AKI, acute kidney injury; CysC, cystatin C; GFR, glomerular filtration rate; SCr, serum creatinine.
[a]Risk Adjustment in Congenital Heart Surgery (RACHS)-1 score.
[b]Four subjects who did not receive cardiopulmonary bypass were not included in these descriptive analyses.
[c]Estimated GFR (glomerular filtration) was calculated by the Schwartz formula.[18] For percentile estimated GFR, normative values from children with normal renal function was used for percentile derivation.[22]
[d]Stage 1 AKI: ⩾50% or 26.5 μmol/l SCr rise from baseline or need for dialysis; stage 2 AKI: ⩾doubling of SCr from baseline or need for dialysis.

RESULTS

Study population

Among 311 children in this study, 288 were available for analysis, after excluding subjects with missing biomarker data. Table 1 displays the baseline and outcome characteristics of the study cohort. Half the cohort was less than 2 years old and most subjects had normal preoperative estimated GFR (eGFR), with 27 subjects (9%) having preoperative eGFR below the 10th percentile of normative age-adjusted values (Figure 1). In all, 42% of the ($n = 288$) cohort developed stage 1 AKI or worse (⩾50% or 26.5 μmol/l SCr rise above baseline or need for dialysis) and 11% developed stage 2 AKI or worse (doubling of SCr or need for dialysis). All children who had a 26.5 μmol/l rise in SCr also had a ⩾50% SCr rise and all patients who had a ⩾50% SCr rise also had a 26.5 μmol/l rise in SCr from baseline. Four of the five subjects requiring dialysis had a ⩾50% SCr rise from baseline at the time of dialysis initiation.

Predicting AKI from preoperative renal function with serum creatinine and serum cystatin C

Table 2 displays the characteristics of different preoperative renal function measures for predicting postoperative stage 1

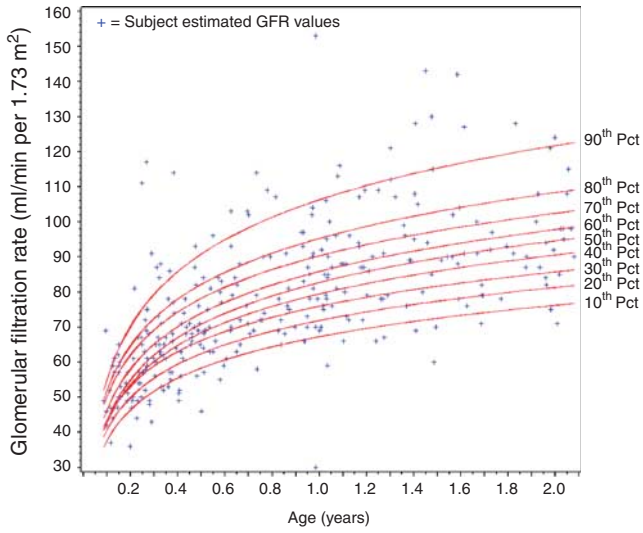

Figure 1 | Plotted glomerular filtration rate (GFR) percentile values for subjects less than 2 years old. Displays the percentile curves for GFR derived from normal children from infancy to young adulthood. Individual preoperative estimated GFR (eGFR) of subjects from this study are plotted on the curves (+). To the right of the graph, the value for each percentile (Pct) curve is shown.