Observational Study

Medicine

OPEN

Role of serum cystatin C in the prediction of acute kidney injury following pediatric cardiac surgeries

A single center experience

Marwa Zakaria, MD[a,*], Tamer Hassan, MD[a], Ali Refaat, MD[b], Manar Fathy, MD[a], Mustafa I.A. Hashem, MD[a], Naglaa Khalifa, MD[c], Ahmed A. Ali, MD[a], Ahmed Elhewala, MD[a], Ahmed Ramadan, MD[a], Alaa Nafea, MD[a]

Abstract

Intense contemporary research is directed towards validating novel biomarkers to predict acute kidney injury (AKI) in children undergoing cardiothoracic surgeries. We aimed to evaluate the role of cystatin C in early prediction of AKI following cardiac surgery in children with congenital heart disease. Prospective observational cohort study was conducted on 40 children with congenital heart disease undergoing cardiac surgery. 40 healthy children with matched age and sex were enrolled as a control group. Children were subjected to physical examination, routine blood tests, echocardiography, and measurement of plasma cystatin C level on different occasions. The median age of the patients was 3.65 years, a range from 1 to 5 years with no significant difference regarding the age and sex of cases and control groups. The mean serum cystatin C level in patients was 0.75 ± 0.15, 1.35 ± 0.34 and 1.21 ± 0.38 mg/dL (preoperative, at 6 h and at 24 h postoperative, respectively) with statistically significant difference $P < .05$. 30% of the patients developed postoperative AKI with significantly higher serum cystatin C at 6 hours postoperative >1.33 mg/dL compared to preoperative level p $P < .05$. Serum cystatin C level was positively correlated with cardiac bypass time, ischemic time and length of hospital stay at 6 hours postoperative. Serum cystatin C is a sensitive marker for early detection of AKI following cardiac surgery in children with congenital heart disease and it was positively correlated with cardiac bypass time, ischemic time and length of hospital stay.

Abbreviations: AKI = acute kidney injury, AUC = area under the curve, CPB = cardiopulmonary bypass, GFR = glomerular filtration rate, ICU = intensive care unit, NPV = negative predictive value, PPV = positive predictive value, SCr = serum creatinine, VSD = ventricular septal defect.

Keywords: acute kidney injury, congenital heart disease, cystatin C

1. Introduction

AKI in children with congenital heart disease is being one of the most common and serious complications in patients undergoing cardiac surgery.[1] Patients with AKI are usually asymptomatic. Unfortunately, manifestations become obvious only when a major proportion of kidneys have lost their functions.[2] In addition, the gold standard criteria for the early diagnosis of AKI are still lacking.[3]

Current clinical practice relies on the assessment of serum creatinine (SCr) and urine output as indicators of AKI; however, these indicators are late and insensitive as well as they poorly correlate with the onset and progression of AKI.[3,4] In addition, SCr is highly affected by multiple non-renal factors, including age, gender, growth, and muscle mass.[5] Consequently, it is critical to find a novel biomarker assisting in the early diagnosis and progression of AKI to the irreversible stage. Research on new biomarkers for early AKI diagnosis has aimed to achieve more timely AKI treatment for use in clinical practice.[6,7]

Cystatin C is a 13 Kilo-Dalton proteinase inhibitor, belonging to the cystatin superfamily of cysteine protease inhibitors. Cystatin C is a key player in the intracellular catabolism of proteins and peptides. Serum cystatin C has emerged as an easily measurable biomarker of the renal functions that is less influenced by the non-glomerular filtration rate (GFR) determinants, such as muscle mass, and it is eliminated solely by glomerular filtration.[8] Moreover, cystatin C has been shown to be a stronger predictor for cardiovascular events, mortality, and other adverse outcomes in community-based studies.[9] Although prior

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] *Pediatrics Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt,* [b] *Cardiothoracic Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt,* [c] *Clinical Pathology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt.*

**Correspondence: Marwa Zakaria, Pediatric Department, Faculty of Medicine, Zagazig University, Zagazig 44519, Egypt (e-mail: marwazakaria12@yahoo.com).*

How to cite this article: Zakaria M, Hassan T, Refaat A, Fathy M, Hashem MIA, Khalifa N, Ali AA, Elhewala A, Ramadan A, Nafea A. Role of serum cystatin C in the prediction of acute kidney injury following pediatric cardiac surgeries: A single center experience. Medicine 2022;101:49(e31938).

Received: 24 June 2022 / Received in final form: 30 October 2022 / Accepted: 31 October 2022

http://dx.doi.org/10.1097/MD.0000000000031938

studies concerned with the diagnostic accuracy of cystatin C in AKI were conflicting, cystatin C could be considered as a reliable biomarker in the detection of the minor changes in GFR early after cardiothoracic surgery, for example, cardiopulmonary bypass (CPB).[2] Dharnidharka et al[10] and Ross et al[11] reported that cystatin C is superior to serum Cr as a marker of GFR since the serum level of cystatin C was found to rise within the first 24 hours of admission in patients with AKI. This work was designed to determine the accuracy of early serum cystatin C measurements for the prediction of AKI following cardiac surgery in children with congenital heart diseases as a primary outcome and to study the relationship between serum cystatin C level and clinical outcomes (cardiac bypass time, ischemic time, and the length of hospital stay) as a secondary outcome.

2. Materials and methods

This prospective observational cohort study enrolled 40 children who underwent corrective cardiac surgery for the congenital cardiac anomaly or malformation between January 2020 and February 2021. Diagnosis of the congenital heart diseases based on echocardiographic findings.

The study protocol was approved by the Research Ethics Committee of the Faculty of Medicine, Zagazig University. Informed written consent and/or assent were obtained from the parents or guardians of each child. Forty patients (21 boys and 19 girls) were recruited, their ages ranged from 1 year to 5 years. Children with preexisting renal insufficiency (based on age-adjusted normal ranges for SCr), advanced chronic kidney disease (CKD), diabetes mellitus, peripheral vascular diseases, use of nephrotoxic agents up to 1 week before or during the study period, age >18 years old, need for urgent surgery, or repeated revascularization surgery, and high risk of AKI were excluded. In addition, 40 apparently healthy children were matched to cases by age and sex.

2.1. Definitions

Patients with high risk of AKI, defined as the presence of 1 or more of the following criteria: preexisting decreased kidney function (baseline SCr >2 mg/dL [>177 mol/L]), ejection fraction <35% or grade 3 or 4 left ventricular dysfunction, age >70 years, diabetes mellitus, concomitant coronary artery bypass grafting and valve surgery.[12] Stages of AKI:[13]

- Stage 1 AKI defined by Acute Kidney Injury Network (AKIN) as at least a ≥50% rise or a ≥0.3 mg/dL rise from baseline SCr during hospitalization after cardiac surgery.
- Stage 2 AKI was defined as a doubling in SCr from baseline.
- Stage 3 AKI was defined as a tripling in SCr from baseline or receiving acute dialysis during the hospital stay.
- AKI progression was defined as a worsening of AKI stage: from stage 1 to stage 2 or 3 or from stage 2 to 3.

All the study participants were subjected to complete physical examination including anthropometric measurements, full routine blood tests (complete blood count, liver, and kidney function tests) as well as pre and postoperative echocardiography. Plasma cystatin C and SCr levels were estimated preoperative, at 6 hours and at 24 hours postoperative.

2.2. Laboratory analysis

2.2..1. Estimation of plasma cystatin C. Plasma cystatin C was measured by a fully automated PETIA. The reagents were obtained from DAKO (Dako A/S, Glostrup, Denmark) and the determination was performed on the Hitachi Modular P analysis system. The total analytical imprecision was 2.1% for a control sample at a concentration of 1.0 mg/L and 1.7% for a control sample at 4.0 mg/L. Reference range: 0.55 to1.15 mg/L for age 1 to 50 years and 0.63 to 1.44 mg/L for age >50 years. Reagent catalogue number: 06600239190—DAKO. The Tina-quant a Cystatin C is a latex particle-enhanced immunoturbidimetric assay. Roche cobas 6000, MODULAR ANALYTICS SWA and COBAS INTEGRA instruments were included in the study. Method comparison studies were carried out against 2 turbidimetric methods (Dako Cystatin C, Gentian Cystatin C), and 1 nephelometric method (Siemens N-Latex Cystatin C).

Routine laboratory investigations were performed according to our local standards.

2.3. Statistical analysis

Continuous variables were expressed as mean ± SD if normally distributed or median (range) if not normally distributed. Categorical variables were expressed as absolute frequencies (number) and relative frequencies (percentage). Normality was checked by Kolmogorov-Smirnov test. The differences were considered significant at $P < .05$. All statistical comparisons were two-tailed. Statistical analyses were performed by Statistical Package of Social Science version 24 (SPSS) software (IBM, New York, USA). We performed ROC curve analysis for each category and we chose the cut off values at which we got best sensitivity and best specificity.

2.4. Statement of ethics

This study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1964, as revised in 2000. The study protocol Number (0296298) was approved by the Research Ethics Committee of the Faculty of Medicine, Zagazig University. Informed written consent and/or assent were obtained from the parents or guardians of each child.

3. Results

This study enrolled 80 subjects, 40 patients were diagnosed with congenital heart disease based on their initial clinical presentation and echocardiographic findings (30% had atrial septal defect [ASD], 25% had Fallot tetralogy, 15% had ventricular septal defect (VSD), 15% had ventricular septal defect (VSD) plus PM and 15% had sub aortic membrane). About 53% of patients group were boys. The median age of the studied patients was 3.65 years old, with a range from 1 to 5 years old. The mean weight of the patients was 14.04 ± 2.12 kg. No significant differences in the age and sex of both patients and controls were recorded. Preoperative SCr level was significantly higher in cases than controls ($P = .01$) while other preoperative characteristics were similar between cases and controls ($P > .05$) (Table 1).

The mean preoperative serum cystatin C level in cases was 0.75 ± 0.15 mg/L while at 6 hours postoperative the percent of change in cystatin level was 53.13% from preoperative level and at 24 hours postoperative was 23.13% from preoperative level ($P < .001$). The mean preoperative SCr level in our cases was 0.80 ± 0.15 mg/dL with a range from (0.22–0.9). The percent of change in SCr was 3.12% and 23.13% at 6 hours and at 24 hours postoperative, respectively ($P < .001$) (Table 2) (Fig. 1). The median of CPB time was 29 minutes with a range from (13–65 min). Also, the median ischemic time was 10.5 minutes, with a range from (7–55 min). About 1/3 of the patients developed AKI, 1/2 of them were stage 1 AKI and the other 1/2 were stage 2 AKI. The median duration for hospital stay was 2 days with a range from 1 to 8 days (Table 3).

In-hospital mortality was 20% and other clinical outcomes were demonstrated in Table 3. A statistically significant association between serum cystatin C level and development of postoperative AKI existed. All patients who developed AKI stage 1 and 2 had significantly higher serum cystatin C level at 6 hours

Table 1

Demographic and preoperative characteristics among the studied groups.

Item	Cases (N = 40)		Controls (N = 40)		Test	*P* value
Age (yr) Median (range)	3.65 (1.0–5)		3.25 (2–6)		χ^2 = –0.136	0.892
Sex					Z = 0.802	0.37
Male	21	52.5	23	57.5		
Female	19	47.5	17	42.5		
Renal function tests						
S. creatinine (mg/dL)						
Mean (range)	0.80 ± 0.12 (0.22–0.90)		0.70 ± 0.21 (0.24–0.80)		t = –2.615	0.01
S. cystatin C (mg/dL)						
Mean (range)	0.75 ± 0.15 (0.51–1.22)		0.78 ± 0.13 (0.66–1.28)		t = 0.956	0.3421
S. urea (mg/dL)						
Mean ± SD	19.8 ± 1.47		19.3 ± 1.42		t = –1.547	0.1259
Albumin (g/dL)						
Mean ± SD	4.31 ± 0.44		4.5 ± 0.45		t = 1.909	0.0599
Hemoglobin (g/dL)						
Mean ± SD	12.33 ± 1.25		12.55 ± 1.40		t = 0.741	0.4607
INR						
Mean ± SD	1.01 ± 0.11		1.00 ± 0.1		t = –0.425	0.6717
K level (mEq/L)						
Mean ± SD	3.36 ± 0.94		3.44 ± 0.83		t = 0.403	0.6877

χ^2 = Chi-square test, *Z* = Mann-Whitney test.

Table 2

Percentage of change in serum creatinine and serum cystatin C level among the patients.

Renal function test	Preoperative	6 h postoperative	24 h postoperative	Median % change pre- post 1	Median % change pre-post 2
S. Creatinine (mg/L)					
Mean ± SD	0.80 ± 0.15	0.85 ± 0.16	1.14 ± 0.28	3.12%	23.13%
‡*P*-value 1	<0.001*				
#*P*-value 2	Ref	0.001*	0.003*		
	-------	Ref	0.16		
Cystatin C (mg/L)					
Mean ± SD	0.75 ± 0.15	1.35 ± 0.34	1.14 ± 0.28	53.13%	23.13%
‡*P*-value 1	<0.001*				
#*P*-value 2	Ref	<0.001*	<0.001*		
	------	Ref	<0.001*		

‡ P1: *P*-value for repeated measure ANOVA test.

P2: *P*-value of paired sample t test.

*Significant: *P*-value < 0.05.

postoperative ($P < .05$). Moreover, at 24 hours postoperative serum cystatin C level was significantly higher in patient who developed stage 2 AKI. ($P < .05$) (Table 4).

There was a highly significant increase in serum cystatin C level at 6 hours and 24 hours postoperative in patients who developed AKI compared to those who did not develop AKI ($P < .05$). On the contrary, there was no significant increase in SCr level at 6 hours and 24 hours postoperative in patients who developed AKI compared to those who did not develop AKI ($P > .05$) (Table 5). Ten patients out of 32 patients (31.3%) who were discharged had significantly higher serum cystatin C level at 6 hours postoperative and only 2 patients (6.3%) still had significantly high serum cystatin C level at 24 hours postoperative ($P < 0.001$) (Table 6). Serum cystatin C level at 6 and 24 hours postoperative was positively correlated with bypass time, ischemic time, and length of hospital stay ($P > .05$). However, SCr level was positively correlated with bypass time, ischemic time, and length of hospital stay only at 24 hours postoperative ($P < .05$).

3.1. Prognostic accuracy of serum cystatin c

As for prediction of the mortality, the cutoff level of cystatin C at 6 hours and 24 hours postoperative was ≥1.37 and ≥1.27 (g/L) respectively, with sensitivity of 100 %, specificity of 68.8%, positive predictive value (PPV) 44.4%, negative predictive value (NPV) 100% and accuracy 75%. In addition, the cutoff level of SCr at 6 hours and 24 hours postoperative for prediction of mortality was ≥0.87 and ≥1.165 (g/L) respectively, with sensitivity of 50% and 100% respectively 50% specificity, PPV 20%, NPV 80% and accuracy 50%. (Table 7). The previous data points to the superiority of the cystatin C in terms of being more specific and accurate in early detection of mortality.

4. Discussion

AKI is a common comorbidity after cardiac surgery in adults and children. This has driven current efforts to explore novel biomarkers for earlier and improved detection of AKI.[14] Cystatin C is a promising biomarker with physiologic characteristics that suggest it likely is a better estimate of glomerular filtration, at least in the ambulatory setting.[15] This study was designed to determine the accuracy of early serum cystatin C for the prediction of AKI following cardiac surgery in children with congenital heart disease. We found a significant difference between the mean preoperative serum cystatin C level and the mean postoperative cystatin C level with percent of change 53.13% at 6

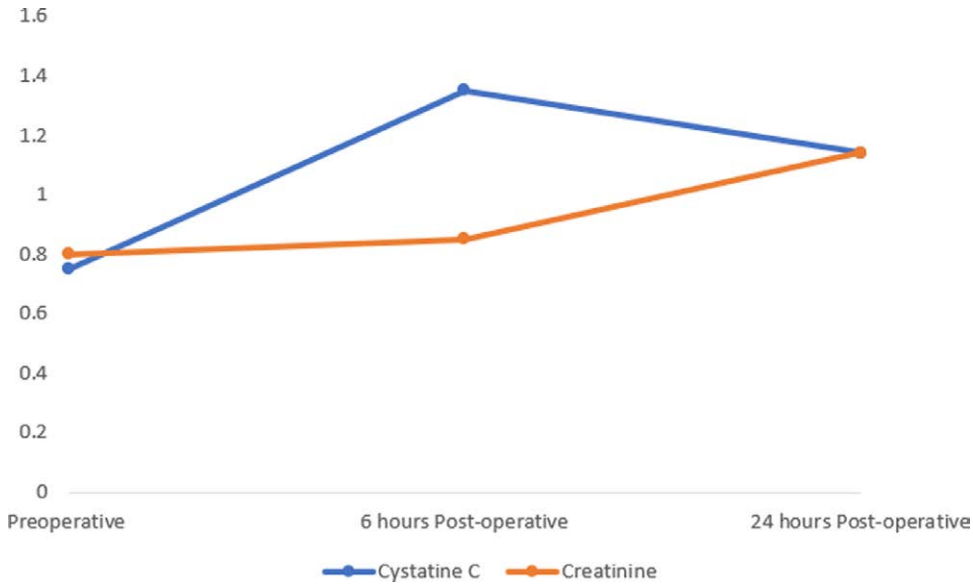

Figure 1. shows multiple line graph showing changes in serum cystatin C and serum creatinine among the patients.

Table 3

Operative characteristic, AKI, and postoperative outcomes among the patients.

Item	Patients (N = 40)	
Cardiopulmonary bypass time (min)		
Median (range)	29 (13–65)	
Ischemic time (min)		
Median (range)	10.5(7–55)	
Stage of acute kidney injury	Patients (N = 40)	
	No.	%
NO	28	70.0
Stage 1	6	15.0
Stage 2	6	15.0
Dialysis		
No	28	70.0
Yes	12	30.0
Hospital length of stay (d)		
Median (Range) days	2(1–8)	
Outcome		
Discharged	32	80.0
Died	8	20.0

hours and 23.13% at 24 hours postoperative from the preoperative level. In support, Zappitelli et al reported in their study a significant difference between the percent of change in the serum postoperative cystatin C level from the preoperative level. In addition, 42% of the patients developed AKI stage 1 and 11% developed AKI stage 2 and 2% needed dialysis.[16] A study of Greenberg et al reported that only 3 (11%) of patients with AKI in progression need dialysis.[17]

The current work showed that the mean duration of hospital stay was 2.60 ± 1.5 days and 20% of the patients expired. Similarly, Zappitelli et al[18] reported in their study the mean duration for hospital stay was 5 days with a range from 6 to 7 days and there were fewer than 5 deaths. However, the mean duration for hospital stay was prolonged (8 ± 9.2 days).[18]

Krawczeski et al found in their study the mean bypass time was 138 ± 69 minutes in patients who developed AKI versus 105.4 ± 52.9 minutes in patients without AKI. The mean duration of hospital stays was 17.8 ± 31 in patients with AKI versus 9.6 ± 18.2 in patients without AKI. In addition to 4% of patients with AKI died compared to 1% in patients who did not develop AKI. And they concluded that the overall mortality was low in both groups (AKI and non-AKI).[19] Also, cystatin

Table 4

Level of cystatin C in relation to stage of AKI among the patients.

Cystatin C (mg/L)	No AKI (N = 28)		Stage 1 AKI (N = 6)		Stage 2 AKI (N = 6)		χ^2	*P*-value
	No	%	No	%	No	%		
Preoperative								
Low <0.63	2	7.1	0	0.0	4	66.7	11.812	0.001*
Normal 0.63–1.33	26	92.9	6	100.0	2	33.3		
6 h postoperative								
Normal 0.63–1.33	22	78.6	0	0.0	0	0.0	17.63	<0.001*
High >1.33	6	21.4	6	100.0	6	100.0		
24 h postoperative								
Normal 0.63–1.33	24	85.7	6	100.0	0	0.0	13.356	<0.001*
High >1.33	4	14.3	0	0.0	6	100.0		

χ^2: Chi-square for test.
AKI = acute kidney injury.
**P*-value < 0.05 is statistically significant.

Table 5

Serum cystatin C and creatinine levels in relation to AKI.

	No AKI (N = 28)	AKI (N = 12)	t test	*P*-value
	Mean ± SD	Mean ± SD		
Serum cystatin C (mg/L)				
Preoperative	0.8 ± 0.22	0.66 ± 0.20	1.89	0.07
6 h postoperative	1.19 ± 0.27	1.78 ± 0.33	5.92	<0.001
24 h postoperative	0.92 ± 0.33	1.18 ± 0.36	2.2	0.03
Serum creatinine (mg/L)				
Preoperative	0.78 ± 0.15	0.82 ± 0.16	0.75	0.4
6 h postoperative	0.83 ± 0.17	0.87 ± 0.16	0.7	0.5
24 h postoperative	1.08 ± 0.28	1.22 ± 0.25	1.5	0.1

AKI = acute kidney injury.

Table 6

Level of cystatin C in relation to patient outcome.

Cystatin C (mg/L)	Discharged (N = 32)		Died (N = 8)		χ^2	*P* value
	No	%	No	%		
Preoperative						
Low <0.63	2	6.3	4	50.0	Fisher	0.01*
Normal 0.63–1.33	30	93.8	4	50.0		
6 h postoperative						
Normal 0.63–1.33	22	68.8	0	0.0	Fisher	0.001**
High >1.33	10	31.3	8	100.0		
24 h postoperative						
Normal 0.63–1.33	30	93.8	0	0.0	Fisher	<0.001*
High >1.33	2	6.3	8	100.0		

χ^2 Chi-square test.

**P*-value < 0.05 is statistically significant.

Table 7

Cystatin C and creatinine cutoff level in relation to patient outcome with ROC curve.

Variable	AUC	95% CI.	Sensitivity	Specificity	PPV	NPV	*P*-value	Accuracy	Optimal cutoff level
6 h postoperative									
Cystatin C (mg/dL)	0.781	0.58–0.97	100%	68.8%	44.4%	100%	0.015*	75%	1.37
Creatinine (mg/dL)	0.422	0.12–0.72	50%	50%	20%	80%	0.499	50%	0.87
24 h postoperative									
Cystatin C (mg/dL)	1	1.0–1.0	100%	87.5%	66.7%	100%	<0.001*	90%	1.27
Creatinine (mg/dL)	0.789	0.65–0.93	100%	68.8%	44.4%	100%	0.012*	75%	1.165

AUC = area under the curve, PPV = positive predictive value, NPV = negative predictive value.

* *P*-value < 0.05 is statistically significant.

C was reported to be superior to creatinine level in predicting contrast-induced kidney injury.[20]

Our results showed a significant association between postoperative serum cystatin C level and development of AKI. All patients who developed AKI stage 1 and 2 had higher serum cystatin C level at 6 hours postoperative, and patients who developed stage 2 AKI still had higher serum cystatin C level at 24 hours postoperative. While this is not the situation regarding SCr level where was no significant increase in SCr level at 6 hours and 24 hours postoperative in patients who developed and who did not develop AKI ($P > .05$).

Herget-Rosenthal et al documented in their study in critically ill patients that Cystatin C level was shown to detect AKI 1 to 2 days earlier than creatinine level.[21] In corroboration, Wald et al reported a positive association between cystatin C levels and AKI development in their study.[15]

Also, Zappitelli et al reported in their study that the first postoperative cystatin C level was independently associated with development of stage 1 AKI (adjusted OR = 6.4, 95% confidence interval (CI) = 1.9–22.3) and stage 2 AKI (adjusted OR = 20.0, 95% CI = 4.1–97.5) and they concluded that postoperative cystatin C level was more effective at predicting AKI in pediatric cardiac surgery patients.[16]

In agreement with our results, Krawczeski and coworkers found in their study that serum cystatin C level began to increase in the AKI patients at 2 hours after onset of CPB and became significantly higher at 12 and 24 hours after CPB.[19]

On the contrary, Koyner et al reported no difference between the preoperative baseline plasma cystatin C values of those with and without AKI in addition to no significant difference between the maximum plasma cystatin C values of those with and without AKI in the early postoperative period (post-CPB, intensive care unit [ICU] arrival, and 6 h ICU time points: the "early composite" period), although there was a trend toward higher values in the AKI group.[22]

Contrast to our results, Spahillari et al reported that SCr detected more cases of AKI than cystatin C (35% vs. 23%) $P < .001$ and when using the ≥50% cutoff, the incidences of AKI were 14% and 8% by SCr and cystatin C, respectively, whereas the ≥100% cutoff resulted in an incidence of AKI of 4% and 2% by SCr and cystatin C.[23]

We found that all the deceased patients had high serum cystatin C level both at 6 and 24 hours postoperative, on the other hand 10 patients (31.3%) out of 32 patients who were discharged had high serum cystatin level only at 6 hours postoperative and 2 patients (6.3%) still had high serum cystatin C level when measured at 24 hours postoperative.

In our study serum cystatin C level was positively correlated with each of cardiac bypass time, ischemic time, and length of stay at 6 and 24 hours postoperative. On the other hand, SCr level was positively correlated with cardiac bypass time, ischemic time, and length of hospital stay only at 24 hours postoperative. Also, Krawczeski et al found that patients who developed AKI had longer CPB time, and longer hospital length of stay than patients who did not develop AKI. At 12- and 24-hour time-points, they found that serum cystatin C concentration at 12 hours significantly correlated with greater SCr change, longer hospital stay, and longer CPB time. The same relationships were observed at the 24-hour time-point.[19] Similarly, Greenberg et al reported in their large study that CPB time was significantly longer (142.3 min) in patients who develop AKI than patients who did not develop AKI (116 min). Also, patients with AKI had longer duration of hospital stay (19.2 d) and longer duration of stay in ICU (10.7 d) than patients without AKI (9.6 d and 4.4 d) respectively.[17]

Zappitelli et al, reported in their study longer CPB time and aortic cross clamp time in patients with AKI by both SCr and cystatin C. Also, patients with AKI by both SCr and cystatin C had the longest hospital stay.[18]

We were able to determine cutoff level of cystatin C at 6 hours and 24 hours postoperative was ≥1.37 and ≥1.27 (gm/L) respectively, with sensitivity of 100%, specificity of 68.8%, PPV 44.4%, NPV 100% and accuracy 75%.

On the other hand, the cutoff level of SCr at 6 hours and 24 hours postoperative for prediction of mortality was ≥0.87 and ≥1.165 (gm/L) respectively, with sensitivity of 50% and 100% respectively 50% specificity, PPV 20%, NPV 80% and accuracy 50%.

Similarly, Krawczeski et al calculated ROC curves of cystatin C for each time-point after CPB (2, 12, and 24 h) and found that area under the curve (AUC) were 0.59 (95% CI: 0.50–0.69) for the 2-hour cystatin C, 0.81 (95% CI: 0.74 to 0.88) for the 12-hour cystatin C ($P < .0001$), and 0.84 (95% CI: 0.78 to 0.91) for the 24-hour cystatin C ($P < .0001$). These values indicate that the 12- and 24-hour cystatin C ≥1.16 mg/L is a valid threshold for the early detection of AKI. With additional accuracy and clinical prognostic information and concluded that, serum cystatin C is an early predictive biomarker for AKI and its clinical outcomes after pediatric CPB. Serum cystatin C offers a unique opportunity to dramatically impact the management of AKI by delivering diagnostic, severity, and prognostic information at an early time-point following a renal insult such as CPB.[19]

Also, Nakhjavan-Shahraki et al in 2017 reported in their large meta-analysis study that overall AUC of serum cystatin C in prediction of AKI was 0.83 (95% CI: 0.80–0.86). The AUC in cutoff points of 0.4 to 1.0 mg/L and 1.01 to 2.5 mg/L were 0.83 (95% CI: 0.80–0.86) and 0.85 (95% CI: 0.82–0.88), respectively and they concluded that the best sensitivity (value = 0.85; 95% CI: 0.78–0.90) and specificity (value = 0.61; 95% CI: 0.48–0.73), were observed for the serum concentration of cystatin C and in the cutoff points between 0.4 and 1.0 mg/L.[2]

5. Conclusions

From the previous data we concluded that serum cystatin C rises earlier than SCr in response to AKI. Serum cystatin C could be a potential substitute for SCr assessment for early detection of AKI following cardiac surgery in children with congenital heart disease. More research on wider scales is still required to support our findings.

Acknowledgments

All authors thank all participants in the study for their unstinted cooperation.

Author contributions

MZ, TH and AR designed the study research. MF, MH, AAA, AE, AR and AN recruited patients and collected their data. NK performed the laboratory part of this work. All authors participated in data analysis, performed the statistics, and wrote the paper. MZ submitted the final manuscript.

Conceptualization: Marwa Zakaria, Ahmed Elhewala, Alaa Nafea.
Data curation: Marwa Zakaria, Ali Refaat, Manar Fathy, Mustafa Hashem, Ahmed Ramadan.
Formal analysis: Marwa Zakaria, Manar Fathy, Ahmed Elhewala, Alaa Nafea.
Investigation: Ali Refaat.
Methodology: Marwa Zakaria, Manar Fathy, Ahmed A. Ali, Ahmed Elhewala, Alaa Nafea.
Project administration: Marwa Zakaria.
Supervision: Tamer Hassan, Ahmed Elhewala.
Validation: Manar Fathy, Ahmed A. Ali.
Visualization: Ahmed A. Ali, Alaa Nafea.
Writing – original draft: Marwa Zakaria, Tamer Hassan, Mustafa Hashem, Ahmed Ramadan.
Writing – review & editing: Marwa Zakaria, Tamer Hassan, Manar Fathy, Mustafa Hashem, Ahmed A. Ali, Ahmed Elhewala, Ahmed Ramadan, Alaa Nafea.

References

[1] Toda Y, Sugimoto K. AKI after pediatric cardiac surgery for congenital heart diseasesrecent developments in diagnostic criteria and early diagnosis by biomarkers. J Intensive Care. 2017;5:49.
[2] Nakhjavan-Shahraki B, Yousefifard M, Ataei N, et al. Accuracy of cystatin C in prediction of acute kidney injury in children; serum or urine levels: which one works better? A systematic review and meta-analysis. BMC Nephrol. 2017;18:120.
[3] Koyner JL, Garg AX, Coca SG, et al. Biomarkers predict progression of acute kidney injury after cardiac surgery. J Am Soc Nephrol. 2012;23:905–14.
[4] Bellomo R. Acute renal failure-definition, outcome measures, animal models. Fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative. 2004;8:R204–12.
[5] Schwartz GJ, Work DF. Measurement and estimation of GFR in children and adolescents. Clin J Am Soc Nephrol. 2009;4:1832–43.
[6] Koyner JL, Parikh CR. Clinical utility of biomarkers of AKI in cardiac surgery and critical illness. Clin J Am Soc Nephrol. 2013;8:1034–42.
[7] Vanmassenhove J, Vanholder R, Nagler E, et al. Urinary and serum biomarkers for the diagnosis of acute kidney injury: an in-depth review of the literature. Nephrol Dial Transplant. 2013;28:254–73.
[8] Herget-Rosenthal S, Trabold S, Pietruck F, et al. Cystatin C: efficacy as screening test for reduced glomerular filtration rate. Am J Nephrol. 2000;20:97–102.
[9] Shlipak MG, Wassel Fyr CL, Chertow GM, et al. Cystatin C and mortality risk in the elderly: the health, aging, and body composition study. J Am Soc Nephrol. 2006;17:254–61.
[10] Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. Am J Kidney Dis. 2002;40:221–6.
[11] Roos JF, Doust J, Tett SE, et al. Diagnostic accuracy of cystatin C compared to serum creatinine for the estimation of renal dysfunction in adults and children-a metaanalysis. Clin Biochem. 2007;40:383–91.
[12] Coca SG, Jammalamadaka D, Sint K, et al. Preoperative proteinuria predicts acute kidney injury in patients undergoing cardiac surgery. J Thorac Cardiovasc Surg. 2012;143:495–502.

[13] Mehta RL, Kellum JA, Shah SV. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11:R311–8.
[14] Bastin AJ, Ostermann M, Slack AJ, et al. Acute kidney injury after cardiac surgery according to risk/injury/failure/loss/end-stage, acute kidney injury network, and kidney disease: improving global outcomes classifications. J Crit Care. 2013;28:389–96.
[15] Wald R, Liangos O, Perianayagam MC, et al. Plasma cystatin C and acute kidney injury after cardiopulmonary bypass. Clin J Am Soc Nephrol. 2010;5:1373–9.
[16] Zappitelli M, Krawczeski CD, Devarajan P, et al. Early postoperative serum cystatin C predicts severe acute kidney injury following pediatric cardiac surgery. Kidney Int. 2011;80:655–62.
[17] Greenberg JH, Zappitelli M, Jia Y, et al. Biomarkers of AKI progression after pediatric cardiac surgery. J Am Soc Nephrol. 2018;29:1549–56.
[18] Zappitelli M, Greenberg JH, Coca SG, et al. Association of definition of acute kidney injury by cystatin C rise with biomarkers and clinical outcomes in children undergoing cardiac surgery. JAMA Pediatr. 2015;169:583–91.
[19] Krawczeski CD, Vandevoorde RG, Kathman T, et al. Serum cystatin C is an early predictive biomarker of acute kidney injury after pediatric cardiopulmonary bypass. Clin J Am Soc Nephrol. 2010;5:1552–7.
[20] Briguori C, Visconti G, Rivera NV, et al. Cystatin C and contrast-induced acute kidney injury. Circulation. 2010;121:2117–22.
[21] Herget-Rosenthal S, Marggraf G, Hüsing J, et al. Early detection of acute renal failure by serum cystatin C. Kidney Int. 2004;66:1115–22.
[22] Koyner JL, Bennett MR, Worcester EM, et al. Urinary cystatin C as an early biomarker of acute kidney injury following adult cardiothoracic surgery. Kidney Int. 2008;74:1059–69.
[23] Spahillari A, Parikh CR, Sint K, et al. TRIBE-AKI Consortium. Serum cystatin C-versus creatinine-based definitions of acute kidney injury following cardiac surgery: a prospective cohort study. Am J Kidney Dis. 2012;60:922–9.