Research Article

Use of Both Serum Cystatin C and Creatinine as Diagnostic Criteria for Cardiac Surgery-Associated Acute Kidney Injury and Its Correlation with Long-Term Major Adverse Events

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Keywords

Cardiac surgery · Acute kidney injury · Diagnosis · Prognosis · Risk stratification

Abstract

Background/Aims: Cardiac surgery-associated acute kidney injury (CSA-AKI) was traditionally defined as an increase in serum creatinine (sCr) after cardiac surgery. Recently, serum cystatin C (sCyC) has been proposed to be a better biomarker in the prediction of AKI. The clinical utility and performance of combining sCyC and sCr in patients with AKI, particularly for the prediction of long-term outcomes, remain unknown. **Methods:** We measured sCyC together with sCr in 628 patients undergoing cardiac surgery. sCyC and sCr were assessed at baseline and 24 and 48 h after surgery. CSA-AKI determined by sCr (CSA-AKI_{sCr}) was defined as an sCr increase greater than 0.3 mg/dL or 50% from baseline. Major adverse events (MAEs; including death of any cause and dialysis) at 3 years were assessed. **Results:** CSA-AKI_{sCr} developed in 178 patients (28.3%). Three-year follow-up was available for 621 patients; MAEs occurred in 42 patients (6.8%). An increase in sCyC concentration $\geq 30\%$ within 48 h after surgery was detected in 228 patients (36.3%). This was the best sCyC cutoff for CSA-AKI_{sCr} detection (negative predictive value = 88.8%, positive predictive value = 58.3%). To evaluate the use of both sCyC and sCr as CSA-AKI diagnostic criteria, we stratified patients into 3 groups: non-CSA-AKI, CSA-AKI detected by a single marker, and CSA-AKI detected by both markers. By multivariable logistic regression analysis, the independent predictors of MAEs at 3 years

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were group 2 (non-CSA-AKI group as the reference, CSA-AKI detected by a single marker: odds ratio [OR] = 3.48, 95% confidence interval [CI]: 1.27–9.58, $p = 0.016$), group 3 (CSA-AKI detected by both markers: OR = 5.12, 95% CI: 2.01–13.09; $p = 0.001$), and baseline glomerular filtration rate (OR = 2.24; 95% CI: 1.27–3.95; $p = 0.005$). **Conclusion:** Combining sCyC and sCr to diagnose CSA-AKI would be beneficial for risk stratification and prognosis in patients after cardiac surgery.

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Background

Acute kidney injury (AKI) is the most common major complication of cardiac surgery and is associated with high mortality and morbidity rates [1–3]. Serum creatinine (sCr) remains the clinical standard for AKI diagnosis, and increases of 0.3 mg/dL or higher are independently associated with a longer hospital stay and both in-hospital and long-term death [4–6]. However, its usefulness may not be ideal in the postoperative setting due to hemodilution [7] and blood loss [8]. Furthermore, decreases in creatinine generation from muscle [9] may occur in the perioperative setting. Thus, sCr is known as an insensitive and nonspecific parameter for renal function evaluation.

Responding to the need for early and sensitive identification of patients with AKI, several biomarkers have been proposed over the past few years [10–13]. Perhaps most well-studied is cystatin C, a 13-kDa cysteine protease inhibitor that is produced by all nucleated cells at a constant rate and is renally cleared. Therefore, serum cystatin C (sCyC) level is determined by the glomerular filtration rate [14]. Based on its physiological metabolism characteristics, the life cycle of sCyC is merely half of that of sCr (1.5–2 vs. 4 h). Namely, once renal function is fluctuating, sCyC changes much earlier than sCr [15, 16]. Recently, sCyC has been proposed as a superior marker to sCr for detection of early changes in GFR and as a marker of acute injury to the kidney [17, 18]. Besides, sCyC can be assayed easily, and routine laboratory measurement increasingly is becoming available to clinicians. However, use of sCyC level for cardiac surgery-associated AKI (CSA-AKI) diagnosis remains controversial, and limited data exist on whether changes in the composite of sCyC and sCr are superior to sCr in predicting future major adverse events (MAEs) following cardiac surgery [19].

In the present study, we performed a prospective study comparing changes in sCr and sCyC in patients at risk for CSA-AKI following cardiac surgery. The main purposes of this study were to (1) assess the optimal sCyC cutoff point to detect CSA-AKI; (2) determine whether the use of both sCyC and sCr would help to capture associations of in-hospital changes in renal function with prognosis after hospital discharge.

Methods

Design and Participants

Between July 2011 and March 2013, patients over 18 years of age who were scheduled to undergo cardiac surgery (including coronary artery bypass grafting [CABG], valve surgery, combined CABG and valve procedures, and other cardiac surgeries such as congenital heart disease repair, aorta aneurysm, others) at Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China were prospectively recruited. Exclusion criteria include patients under 18 years of age, patients with pre-existing end-stage kidney disease, patients receiving any form of dialysis therapy before surgery, and patients who had died during hospitalization.

Table 1. New definition of CSA-AKI using both sCr and sCyC

Group	Definition	Risk stratification
Group 1	Non-CSA-AKI: sCr increase <0.3 mg/dL and 50% from baseline; and sCyC increase <30% from baseline	No risk
Group 2	CSA-AKI detected by a single marker: fulfilling only 1 of the criteria below: (1) sCr increase >0.3 mg/dL or 50% from baseline; (2) sCyC increase ≥30% from baseline	Potential risk
Group 3	CSA-AKI detected by both markers: sCr increase >0.3 mg/dL or 50% from baseline; and sCyC increase ≥30% from baseline	High risk

CSA-AKI, cardiac surgery-associated acute kidney injury; sCr, serum creatinine; sCyC, serum cystatin C.

Data Collection, Biomarker Measurement, and Follow-Up

Prespecified demographic and clinical data were recorded for each participant. Blood samples for biomarker measurement were collected at baseline and postsurgery day 1 and day 2 (at the time of routine morning blood collection). Blood samples were collected, centrifuged at 2,000 *g* for 5 min, and the supernatants aliquoted and stored at –80 °C. sCyC was measured by immunonephelometry (Dade Behring, Marburg, Germany) using a fully automatic chemistry analyzer (Hitachi 7180). sCr was measured by a modified Jaffe method with protein precipitation using an alkaline picrate reaction. sCr and sCyC were measured in the central biochemistry laboratory of Renji Hospital. All the participants were scheduled to follow-up until 3 years postsurgery by outpatient clinic visit or telephone interview. Reported events were carefully evaluated and recorded.

Definitions and Risk Factors

CSA-AKI as determined by sCr (CSA-AKI_{sCr}) was defined as an increase greater than 0.3 mg/dL or 50% in sCr from baseline within 48 h after surgery [20], which differs from the Kidney Disease: Improving Global Outcomes (KDIGO) definition by not incorporating oliguria as evidence of CSA-AKI. CSA-AKI as determined by sCyC was identified as CSA-AKI_{sCyC}. Preoperative variables and surgery types known to be or which could potentially be associated with AKI or other adverse outcomes were collected. These included age, gender, hypertension (SBP ≥140 mm Hg and/or DBP ≥90 mm Hg), diabetes mellitus (using oral hypoglycemic agents or insulin), peripheral artery disease (determined by clinical diagnosis or imaging results), cerebrovascular disease (previous cerebral vascular accident such as ischemic or hemorrhagic), NY Heart Association (NYHA) functional class III or IV, chronic obstructive pulmonary disease (COPD), recent myocardial infarction (MI; i.e., <30 days before surgery), and hyperuricemia (a serum uric acid >6.6 in women and >7.0 mg/dL in men), left ventricular ejection fraction (LVEF) (assessed preoperatively by echocardiography), and proteinuria (urine dipstick test result of 1+ or greater). The eGFR was calculated with the MDRD4 equation. The Cleveland Clinic Score was calculated according to the algorithm reported by Thakar et al. [21]. MAEs were defined as death from any cause and further deterioration of renal function requiring chronic dialysis.

Statistical Analyses

Continuous variables were expressed as mean ± SD and analyzed by unpaired Student's *t* test. Non-parametric variables were expressed as median and 25–75% percentiles and analyzed by Mann-Whitney's test. Categorical variables were expressed as absolute (*n*) and

Table 2. Clinical and biochemical characteristics of patients undergoing cardiac surgery ($n = 628$)

Variables	
<i>Clinical variables</i>	
Age, years	60.5±13.1 [18–81]
Male	403 (64.2)
Diabetes mellitus	115 (18.3)
Hypertension	201 (32.0)
Peripheral artery disease	11 (1.8)
Cerebrovascular disease	24 (3.8)
COPD	10 (1.6)
LVEF <45%	58 (9.2)
NYHA grade III–IV	113 (18.0)
Previous cardiac surgery	28 (4.5)
Recent MI	58 (9.2)
Anemia	222 (35.4)
Hyperuricemia	146 (23.2)
Proteinuria	36 (5.7)
Use of statins	248 (39.5)
Type of surgery	
CABG	246 (39.2)
Valve	289 (46.0)
CABG + valve	58 (9.2)
CHD	5 (0.8)
Aortic	19 (3.0)
Others	11 (1.8)
CPB	455 (72.5)
CPB time, min	101.0 [78.5–134.0]
<i>Biochemical variables</i>	
sCr, mg/dL	
Baseline	0.81 [0.66–0.98]
24–48 h postsurgery	1.01 [0.80–1.30]*
sCyC, mg/dL	
Baseline	1.02 [0.96–1.14]
24–48 h postsurgery	1.14 [0.94–1.47] [#]
Baseline eGFR, mL/min per 1.73 m ²	94.1 [75.6–117.8]
≥90	355 (56.5)
60–89	231 (36.8)
<60	42 (6.7)
Cleveland Clinic Score	
0–2	349 (55.6)
3–4	216 (34.4)
≥5	63 (10.0)

Continuous values are expressed as median and interquartile range [IQR] (sCr and CyC); categorical values are expressed as number (percentage). COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; MI, myocardial infarction; CPB, cardiopulmonary bypass; CABG, coronary artery bypass grafting; CHD, congenital heart disease; sCr, serum creatinine; sCyC, serum cystatin C; eGFR, estimated glomerular filtration rate; CSA-AKI, cardiac surgery-associated acute kidney injury. * $p < 0.05$, compared with sCr at baseline; [#] $p < 0.05$, compared with sCyC at baseline.

Table 3. Occurrence of MAEs at 3-year follow-up ($n = 621$)

Event	<i>n</i> (%)
All-cause death	41 (6.6)
Cardiac death	21 (3.4)
Pulmonary infection	12 (1.9)
Stroke	7 (1.1)
Tumor	1 (0.2)
Nephropathy requiring chronic dialysis	1 (0.2)
MAEs	42 (6.8)

MAEs, major adverse events.

relative (%) frequency and were analyzed by Chi-squared analysis, as appropriate. The diagnostic accuracy of the sCyC increment above baseline for predicting CSA-AKI as determined by sCr was evaluated by receiver operating characteristic (ROC) curve analysis. Subsequently, from the ROC analysis, a sCyC cutoff increment value was chosen on the basis of maximum sensitivity and specificity. Whether the change in sCyC was an independent predictor of MAEs was determined by multivariable logistic regression analysis using Firth's penalized-likelihood estimation as the number of 3-year MAEs was relative small [22]. Interaction effects between an sCyC increase greater than 30% and other covariates were assessed. Finally, a new definition of CSA-AKI (CSA-AKI_{New}) was proposed using both sCr and sCyC (Table 1). By this definition, participants were further stratified into 3 groups as follows: non-CSA-AKI, CSA-AKI detected only by a single marker, and CSA-AKI detected by both markers. Baseline characters, Cleveland Clinic Score, and MAEs incidence were compared across the 3 groups. CSA-AKI_{New} was included as a covariate in the multivariable logistic regression model using Firth's penalized-likelihood estimation to assess whether the new definition of CSA-AKI was an independent predictor of MAEs, along with age, diabetes mellitus, recent MI, NYHA grade, baseline eGFR, and Cleveland Clinic Score. If statistically significant, the interaction term was included into the regression model. $p < 0.05$ was considered significant throughout the analyses. All analyses were performed using SPSS 20.0 and R 3.3.2 software.

Results

Demographic Characteristics

A total of 628 participants were included in the study. Baseline characteristics of participants are listed in Table 2. Median sCr concentration in these participants significantly increased from baseline after surgery (Table 2). CSA-AKI_{sCr} occurred in 178 participants (28.3%). Three-year follow-up information was available for 621 participants (98.9%). MAEs occurred in 42 participants (6.8%, Table 3). In particular, death occurred in 41 patients (6.6%) and chronic dialysis in 1 patient (0.2%).

Serum Cystatin C and Predictive Value for Clinical Outcomes

Median sCyC concentration significantly changed from baseline after surgery (Table 2). The distributions in sCyC level changes after surgery are presented in Table 4. By ROC curve analysis, the change in sCyC from baseline significantly predicted the development of CSA-AKI_{sCr} (area under the curve [AUC] = 0.843, 95% CI = 0.809–0.877, $p < 0.001$) (Fig. 1). To optimize both sensitivity and specificity, an sCyC increase greater than 30% after surgery,

Table 4. Distribution of sCyC level changes after cardiac surgery and relationship with CSA-AKI_{sCr}

Changes in sCyC	Proportion, n (%)	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Youden index
≥20%	293 (46.7)	80	68	48.8	89.6	0.49
≥25%	256 (40.8)	77	75	53.5	89.0	0.52
≥30%	228 (36.3)	75	80	58.3	88.8	0.55
≥35%	199 (31.7)	69	84	62.3	87.4	0.53

sCyC, serum cystatin C; PPV, positive predictive value; NPV, negative predictive value.

Fig. 1. ROC curve and AUC showing the diagnostic performance of sCyC for CSA-AKI detection. AUC = 0.843 ($p < 0.001$).

which had an 75% sensitivity and 80% specificity, was chosen as the optimal cutoff value (Table 4). Using this definition, participants who developed CSA-AKI_{sCyC} had higher Cleveland Clinic Scores and experienced more MAEs compared with participants without CSA-AKI_{sCyC} (Fig. 2). Multivariable logistic regression analysis revealed that an sCyC increase greater than 30% was an independent predictor of 3-year MAEs (adjusted OR = 2.98, 95% CI: 1.41–6.30, $p = 0.004$).

Association of the New Definition of CSA-AKI with Long-Term MAEs

Based on the new definition of CSA-AKI listed in Table 1, participants were further stratified into 3 groups. The baseline characteristics revealed the risk of developing CSA-AKI increased across the 3 groups (Table 5). Participants in the non-CSA-AKI group had the lowest Cleveland Clinic Scores, and participants in the group with CSA-AKI detected by both markers had the highest Cleveland Clinic Scores (Fig. 3). A similar pattern was observed in the occurrence of MAEs. The occurrence of MAEs was lowest in the non-CSA-AKI group and the highest in participants with CSA-AKI detected by both markers (Fig. 3). By multivariable logistic regression analysis, a significant correlation was found between MAEs and the new definition

Table 5. Comparisons of clinical characteristics in patients stratified by composite of sCr and sCr (n = 628)

Variables	Non-CSA-AKI (n = 355)	CSA-AKI detected by a single marker (n = 140)	CSA-AKI detected by both markers (n = 133)	p value
<i>Clinical variables</i>				
Age, years	58.2±13.2	61.2±13.0	65.8±11.3	<0.001
Male	223 (62.8)	91 (65.0)	89 (66.9)	0.683
Diabetes mellitus	61 (17.2)	20 (14.3)	34 (25.6)	0.039
Hypertension	104 (29.3)	36 (25.7)	61 (45.9)	<0.001
Peripheral artery disease	2 (0.6)	4 (2.9)	5 (3.8)	0.030
Cerebrovascular disease	10 (2.8)	8 (5.7)	6 (4.5)	0.302
COPD	5 (1.4)	2 (1.4)	3 (2.3)	0.789
Hyperuricemia	67 (18.9)	35 (25.0)	44 (33.1)	0.004
Previous cardiac surgery	10 (2.8)	8 (5.7)	10 (7.5)	0.056
Recent MI	30 (8.5)	13 (9.3)	15 (11.3)	0.506
NYHA grade III–IV	45 (12.7)	26 (18.6)	42 (31.6)	<0.001
LVEF <45%	26 (7.3)	16 (11.4)	16 (12.0)	0.183
Preoperative use of statins	140 (39.4)	50 (35.7)	58 (43.6)	0.411
Anemia	106 (29.9)	52 (37.1)	64 (48.1)	0.001
Proteinuria	13 (3.7)	6 (4.3)	17 (12.8)	<0.001
Type of surgery				<0.001
CABG	148 (41.7)	51 (36.4)	47 (35.3)	
Valve	175 (49.3)	68 (48.6)	46 (34.6)	
CABG + valve	17 (4.8)	14 (10.0)	27 (20.3)	
CHD	3 (0.8)	1 (0.7)	1 (0.8)	
Aortic	7 (2.0)	3 (2.1)	9 (6.8)	
Others	5 (1.4)	3 (2.1)	3 (2.3)	
CPB	248 (69.9)	100 (71.4)	107 (80.5)	0.063
CPB time, min	95 [71–127]	100 [80–128]	128 [93–161]	<0.001
<i>Biochemical variables</i>				
Baseline eGFR, mL/min per 1.73 m ²				<0.001
≥90	234 (65.9)	70 (50.0)	51 (38.3)	
60–89	108 (30.4)	59 (42.1)	64 (48.1)	
<60	13 (3.7)	11 (7.9)	18 (13.5)	
Cleveland Clinic Score				<0.001
0–2	221 (62.3)	84 (60.0)	44 (33.1)	
3–4	117 (33.0)	37 (26.4)	62 (46.6)	
≥5	17 (4.8)	19 (13.6)	27 (20.3)	
sCr, mg/dL				
Baseline	0.78 [0.64–0.92]	0.85 [0.68–1.01]	0.88 [0.72–1.08]	<0.001
After 24 h	0.80 [0.67–1.00]	0.94 [0.79–1.16]	1.35 [1.06–1.63]	<0.001
After 48 h	0.75 [0.61–0.91]	0.92 [0.74–1.12]	1.42 [1.15–1.94]	<0.001
sCr, mg/dL				
Baseline	1.00 [0.96–1.04]	1.00 [0.82–1.04]	1.02 [1.01–1.06]	0.030
After 24 h	0.92 [0.76–1.07]	1.14 [0.97–1.34]	1.56 [1.22–1.93]	<0.001
After 48 h	0.97 [0.91–1.10]	1.31 [1.15–1.64]	1.73 [1.36–2.12]	<0.001

Continuous values are expressed as median and interquartile range [IQR] (sCr and sCr); categorical values are expressed as number (percentage). COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; MI, myocardial infarction; CPB, cardiopulmonary bypass; CABG, coronary artery bypass grafting; CHD, congenital heart disease; sCr, serum creatinine; sCr, serum cystatin C; eGFR, estimated glomerular filtration rate; CSA-AKI, cardiac surgery-associated acute kidney injury.

Fig. 2. Portion of patients with Cleveland Clinic Score ≥5 (a) and incidence of MAEs (b) in the CSA-AKI_{sCyC} group and the non-CSA-AKI_{sCyC} group. *** $p < 0.01$.

Fig. 3. Portion of patients with Cleveland Clinic Score ≥5 (a) and incidence of MAEs (b) in patients stratified by the composite of sCyC and sCr. *** $p < 0.001$.

of CSA-AKI. Taking the non-CSA-AKI group as the reference, CSA-AKI detected by a single marker (adjusted OR = 3.48, 95% CI: 1.27–9.59, $p = 0.016$) and CSA-AKI detected by both markers (adjusted OR = 5.12, 95% CI: 2.01–13.09; $p = 0.001$) were independent predictors of MAEs at 3 years (Table 6).

Discussion

AKI is a major complication following cardiac surgery and associated with prolonged hospital stay, new-onset chronic kidney disease and increased mortality rate [2, 3]. Therefore, new diagnostic criteria of CSA-AKI that could predict adverse clinical outcomes and be commonly adopted are desperately needed. The main results of the present study are that sCyC seems to be a reliable marker (1) to detect CSA-AKI and (2) combining with sCr to predict the occurrence of 3-year MAE at follow-up in patients undergoing cardiac surgery.

In the past decade there has been increasing interest in incorporating urine and serum biomarkers of AKI into clinical practice. It is anticipated that these biomarkers will enable earlier diagnosis of AKI and facilitate prognostication [10–13, 17, 18]. Among these novel

Table 6. Predictors of MAEs at 3-year follow-up by multivariable logistic regression analysis using Firth's penalized-likelihood estimation

Covariate	OR	95% CI	p value
CSA-AKI detected by a single marker	3.48	1.27–9.58	0.016
CSA-AKI detected by both markers	5.12	2.01–13.09	0.001
Age ≥75 years	2.05	0.89–4.73	0.091
Diabetes mellitus	1.02	0.39–2.71	0.962
Recent MI	1.20	0.43–3.37	0.733
NYHA grade III–IV	0.90	0.27–3.04	0.865
Baseline eGFR (≥90; 60–89; <60)	2.24	1.27–3.95	0.009
Cleveland Clinic Score	1.36	0.87–2.13	0.174

CSA-AKI, cardiac surgery-associated acute kidney injury; MI, myocardial infarction; NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate.

biomarkers, sCyC is considered the most promising functional marker for glomerular filtration [10, 17, 18]. Wan et al. [23] reported that the predictive value (the area under the ROC curve, AUC) of sCyC was 0.974, with high sensitivity and specificity, which were similar in Liu's [24], Yim's [25], and other studies. Our previous study corroborated this finding, demonstrating a significant rise in sCyC early after admission to the ICU following cardiac surgery in AKI patients [26]. However, with accumulating evidence, conflicting results have raised. Gaygısız et al. [27] and Martensson et al. [28] found that the predictive value (AUC) of sCyC was 0.67, with low sensitivity and specificity. In the present study, we found that a 30% increase in sCyC was highly accurate in diagnosing CSA-AKI, with AUC 0.843 (75% sensitivity and 80% specificity). Then, we confirmed that patients with a 30% increase in sCyC had higher Cleveland Clinic Score, which was a valid risk prediction model for severe CSA-AKI that requires dialysis. Moreover, a 30% increase in sCyC was found to be an independent predictor of 3-year MAEs. Taken together, these data suggest that a 30% increase in sCyC could be served as not only a reliable marker for ruling out CSA-AKI, but also an independent predictor of 3-year MAE.

To optimize risk stratification, we combined sCyC and sCr to create new diagnostic criteria for CSA-AKI. Among the entire cohort, 140 of CSA-AKI cases were detected by a single marker (sCyC only [$n = 95$] vs. sCr only [$n = 45$]). Subgroup analysis revealed that patients in this subcohort had higher risk profiles and substantially worse long-term MAEs compared with patients without CSA-AKI. 45 patients experienced an acute rise in sCr without sCyC rise. The potential explanations are unknown and the case volume prevented us from performing further analysis. Future study is needed to address the issue whether the difference exists between the patients with an acute rise in sCyC only and patients with an acute rise in sCr only. Another 133 CSA-AKI cases were detected by both sCyC- and sCr-based criteria. A significant increase in risk of long-term MAEs was observed in this group of patients. Multivariable logistic regression analysis showed that the predictability of MAEs increased stepwise across the 3 groups. Consistent with the results of previous studies, our data indicated that sCyC is a more sensitive marker than sCr in identifying CSA-AKI cases. The reason might be that sCyC is thought to be less influenced by non-glomerular filtration rate determinants, is extracellular, and has a smaller volume of distribution compared with creatinine [14–16]; it may be a better measure of AKI than creatinine in the perioperative period [24, 26]. Patients with both sCyC- and sCr-based CSA-AKI had the poorest long-term outcomes, implying that inclusion of both sCyC and sCr in defining CSA-AKI would increase the association between CSA-AKI and clinical outcomes. Equations to estimate GFR based on both sCyC and sCr have been developed [29]; combining sCyC and sCr to define CSA-AKI might be applied to clinical

practice in the future. In our center, testing of sCyC is readily accessible to most practitioners, which therefore is part of routine clinical practice. Preoperative renal dysfunction was identified as an important risk factor for the development of AKI [21]. Our data suggests that it may be more important than other risk factors for long-term MAEs, which go beyond circular reasoning.

Several limitations of the present study should be acknowledged. First, our data is derived from a single center study. The result of our data should be confirmed by a further larger multicenter study. Second, as we used unselected material we are unable to make any statement about the value of the new definition of CSA-AKI in specific subpopulations and circumstances. Third, other urine markers of CSA-AKI such as neutrophil gelatinase-associated lipocalin and kidney injury molecule 1 were not routinely measured. Data regarding the association between the new definition of CSA-AKI and renal injury markers were unavailable in the present study. Finally, only one new onset of end-stage renal disease requiring chronic dialysis was observed in the present cohort. The correlation between new AKI definition and adverse renal outcomes should be further assessed.

In conclusion, measurement of sCyC might be adopted not only as a diagnostic test for AKI but, more importantly, as a prognostic tool for future MAE among patients undergoing cardiac surgery. Moreover, abnormal values of both markers can potentially identify the highest-risk subset of CSA-AKI patients, in whom careful monitoring for adverse events is required.

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Statement of Ethics

The study protocol was approved by the Institutional Research Ethics Board. Informed consent was obtained from all participants.

Disclosure Statement

None of the other authors have any conflict of interest to declare.

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