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Presurgical Serum Cystatin C and Risk of Acute Kidney Injury After Cardiac Surgery

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Abstract

Background—Acute kidney injury (AKI) following cardiac surgery is associated with poor outcomes, but is challenging to predict from information available prior to surgery.

Study Design—Prospective cohort study

Setting & Participants—The TRIBE-AKI Consortium enrolled 1,147 adults undergoing cardiac surgery at six hospitals from 2007–2009; participants were selected for high AKI risk.

Predictors—Pre-surgical cystatin C, creatinine, and creatinine-based estimated glomerular filtration rate (eGFR) were categorized into quintiles and grouped as ‘Best’ (quintiles 1–2), ‘Intermediate’ (quintiles 3–4), and ‘Worst’ (quintile 5) kidney function.

Outcomes—The primary outcome was AKI Network (Acute Kidney Injury Network) Stage 1 or higher; ≥ 0.3 mg/dL or 50% rise in creatinine.

Measurements—Analyses were adjusted for characteristics used clinically for pre-surgical risk stratification.

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Results—The average age and kidney function were: 71 ± 10 years (mean $\pm$ standard deviation), serum creatinine 1.1 ± 0.3 mg/dL, eGFR-Cr, 74 ± 9 mL/min/ 1.73m^2 , and cystatin C, 0.9 ± 0.3 mg/L. A total of 407 (36%) participants developed AKI during hospitalization. Adjusted odds ratios for intermediate and worst kidney function by cystatin C were 1.9 (95% CI, 1.4–2.7) and 4.8 (95% CI, 2.9–7.7) compared with 1.2 (95% CI, 0.9–1.7) and 1.8 (95% CI, 1.2–2.6) for creatinine and 1.0 (95% CI, 0.7–1.4) and 1.7 (95% CI, 1.1–2.3) for eGFR-Cr categories, respectively. After adjustment for clinical predictors, the C statistic to predict AKI was 0.70 without kidney markers, 0.69 with creatinine, and 0.72 with cystatin C. Cystatin C also substantially improved AKI risk classification compared to creatinine, based on a net reclassification index of 0.21 ($p < 0.001$).

Limitations—The ability of these kidney biomarkers to predict risk for dialysis-requiring AKI or death could not be reliably assessed in our study due to a small number of patients with either outcome.

Conclusions—Pre-surgical cystatin C is better than creatinine or creatinine-based eGFR at forecasting the risk of AKI after cardiac surgery.

Keywords

acute renal failure; creatinine; prognosis

Cardiac surgery is performed worldwide in approximately 2 million patients each year. Acute kidney injury (AKI) is among the adverse complications that occur in the post-surgical period. Defined by serum creatinine elevations of 0.3 mg/dL (26 $\mu\text{mol/L}$) or higher, AKI associates independently with a longer hospital stay, and an approximate 2-fold higher risk of inhospital¹ and long-term mortality.^{2,3} Due to the importance of AKI as a complication of cardiac surgery that influences patient morbidity and prognosis,⁴ it is critical that patients and providers have a realistic pre-surgical understanding of AKI risk. An accurate assessment of pre-surgical AKI risk may allow clinicians to alter peri-surgical approaches to minimize AKI⁵ or to consider preventative therapies that prove effective in clinical trials.⁶

One of the most important determinants for both mortality and AKI outcomes is the patient's renal reserve prior to surgery, as determined by the pre-surgical assessment of kidney function.^{7–11} Pre-surgical risk assessment for mortality after cardiac surgery is conducted uniformly in the U.S. under the guidance and organization of the Society of Thoracic Surgeons (STS), and a risk assessment tool for dialysis-requiring AKI has been developed.⁹ Pre-surgical chronic kidney disease (CKD), measured using serum creatinine or a formula to estimate glomerular filtration rate (eGFR), associates with a higher risk of AKI following cardiac surgery. In this study, we evaluated the ability of cystatin C to improve pre-surgical risk assessment for AKI relative to creatinine and creatinine-based eGFR.

Methods

Design and Setting

The TRIBE-AKI (Translational Research Investigating Biomarker Endpoints in Acute Kidney Injury) Study is an investigator-initiated study that was funded by the NHLBI. The primary objective of this study is to investigate novel biomarkers for the early detection of AKI; a second aim of the study is to identify novel pre-surgical biomarkers for AKI, with cystatin C having been proposed as the leading candidate. We conducted a prospective cohort study of adults undergoing cardiac surgery (coronary artery bypass grafting [CABG], surgery for valve disease and both) at six academic medical centers in North America between July 2007 and December 2009. The median time between the pre-surgical visit and the cardiac surgery was 4.6 (25th–75 percentile, 1.6–11.5) days; 1,087 (95%) of pre-surgical

visits occurred within 30 days, and only 2 patients had visits more than 90 days prior to surgery (367 and 371 days before surgery). All patients were at high risk for AKI, defined by the presence of one or more of the following criteria: pre-existing reduced kidney function (baseline serum creatinine >2 mg/dL [177 μ mol/L]), ejection fraction $<35\%$ or grade 3 or 4 left ventricular dysfunction, age >70 years, diabetes mellitus, concomitant CABG and valve surgery, or repeat revascularization surgery. Adult patients were excluded if they had evidence of AKI prior to surgery, prior kidney transplant, pre-surgical serum creatinine level >4.5 mg/dL (400 μ mol/L) or end-stage renal disease. All participants provided written informed consent and the study was approved by each institution's research ethics board. This clinical study has been registered at Clinicaltrials.gov as NCT00774137.

Predictors

The primary predictor was pre-surgical kidney function as assessed by cystatin C, creatinine, and creatinine-based estimated glomerular filtration rate (eGFR). The most commonly used cystatin C eGFR equation does not include demographic coefficients;¹² therefore, we did not separately evaluate cystatin C eGFR, as our analysis that ranked participants' cystatin C levels would be unchanged by transformation to the GFR estimate. At the pre-surgical visit, a blood sample was collected, centrifuged and processed, aliquoted in 0.5 mL vials and stored at -80°C . Using one of the vials and without any additional freeze-thaw, cystatin C measurements were conducted in a large batch using a BN II® nephelometer (Siemens AG, www.siemens.com). Pre-surgical creatinine was measured as part of routine clinical care in each hospital's clinical lab, which all use modified-Jaffe's creatinine assay. In addition, all sites used IDMS-calibrated serum creatinine levels. The eGFR was calculated using the CKD-EPI equation.¹³ Albumin-creatinine ratio (ACR) was calculated using urine albumin measurements taken from participant urine stored at -80°C .

Secondary pre-surgical predictors were used for multivariable adjustment, and were obtained from the patient and the clinical record, using standardized definitions of the STS data collection tool. We chose all variables that had been included in the prior STS registry risk-assessment tool for predicting AKI after cardiac surgery, as well as others related to kidney function estimation. These included demographics (age, sex, race), co-morbidities (hypertension, diabetes mellitus, heart failure, prior myocardial infarction), surgery characteristics (elective or urgent; bypass, valvular surgery, or both; prior cardiac operation; on/off pump CABG), and ACR. Patients requiring emergent surgery were excluded from this study.

Outcomes

The outcome of AKI was determined by the daily creatinine measurements during the first five hospital days; 93% of participants had at least four of the five daily creatinine values. Our primary outcome was AKI, defined by AKIN stage 1 or higher: an absolute creatinine increase ≥ 0.3 mg/dL or a $\geq 50\%$ relative increase.¹⁴ We evaluated a secondary outcome of persistent AKI, defined as having AKI for a duration of 48 hours or longer.

We further evaluated severe AKI (AKIN Stage 2 or higher), defined by either a doubling of creatinine or the requirement of acute hemodialysis.

Statistical Analysis

Using pre-surgical cystatin C, creatinine, and eGFR, we a priori categorized our cohort into quintiles. To improve the precision for some analyses, we then categorized the quintiles into three groups defined by "Best" (quintiles 1–2), "Intermediate" (quintiles 3–4), and "Worst" (quintile 5) pre-surgical kidney function; the "Worst" quintile represented the 20% of participants with the highest cystatin C, highest creatinine, and lowest eGFR, respectively.

The incidences of AKI were calculated by quintile of each of the three kidney function measures. We compared the strength and independence of the association between each kidney function measure and AKI across Best, Intermediate, and Worst groups. We used multivariate logistic regression analyses to determine the associations of kidney function categories with AKI, with the Best kidney function group as the referent. The models were adjusted for demographics, co-morbidities, and procedural variables as listed above. Cystatin C models were also adjusted for serum creatinine.

To evaluate the added effect of each kidney function test on risk discrimination, we constructed receiver operator characteristic (ROC) curves and calculated the c-statistic. The c-statistic was determined for the multivariate model without any measure of kidney function, and then repeated separately with creatinine, eGFR and creatinine plus cystatin C; this process was repeated for the severe AKI outcome.

As a second step to evaluate the impact of cystatin C on AKI risk prediction, we determined the Net Reclassification Index (NRI) and the Integrated Discrimination Improvement (IDI) indices.^{15–16} The NRI evaluates the appropriateness of reclassification between models before and after cystatin C is added, tabulating the frequency of appropriate versus inappropriate reclassification; a significant P value indicates that significantly more are being reclassified appropriately than inappropriately.¹⁷ In contrast, the IDI determines how much an individual's predicted risk changes with the use of different models.¹⁷

For NRI analyses, we initially categorized all participants as being at low (<25%), medium (25–50%), or high (>50%) AKI risk, based on a prediction model that incorporated all clinical variables and creatinine. The AKI risk was then re-calculated with cystatin C added to creatinine, and participants were re-classified into low, medium, and high risk groups. We then determined the NRI, and we described AKI risk for individuals who were moved to lower and higher risk groups by cystatin C.

Results

Baseline Characteristics

Among the 1,220 adults enrolled into this study, 73 participants did not have serum cystatin C results, leaving 1,147 subjects with all three measurements of kidney function. Age was 71 ± 10 years (mean $\pm$ standard deviation); 68% (n=780) were men and 93% (n=1,072) were white. Among the surgical procedures, 48% (n=551) were bypass only, 29% (n=332) were valve only, and 30% (n=263) were both; 80% of surgeries were elective and 13% were re-operations. Pre-surgical kidney function levels were: cystatin C 0.93 ± 0.32 mg/L, creatinine 1.1 ± 0.33 mg/dL, and eGFR 74 ± 9 mL/min/1.73m². We compared baseline characteristics across quintiles of cystatin C. The most striking differences across quintiles were that persons in the highest cystatin C quintiles were older, more likely to have hypertension and heart failure, and more likely to undergo a combined bypass and valve surgery (Table 1). As expected, creatinine levels were higher and eGFR levels lower in the higher cystatin C quintiles.

Association of Kidney Function Measurements with AKI

During follow-up, 407 participants (36%) had AKI and 51 (4.4%) had severe AKI. Among all participants, 14% had persistent AKI, and 4% had persistent severe AKI. Based on all three measures of kidney function, Worst pre-surgical kidney function portended a higher risk of AKI. For AKI, the risk gradient across quintiles of kidney function was steepest when determined by cystatin C, ranging nearly three-fold (21% to 58%) from quintiles 1 to 5 (Figure 1). Quintiles of serum creatinine had a less steep risk gradient with AKI risk, from 27% to 50%, and eGFR quintiles had the weakest association (30% to 49%) (Figure 1).

Associations of kidney function with severe AKI were less linear across quintiles, but the Worst quintile of kidney function had by far the highest risk: – 11% for cystatin C and 9% for either creatinine or eGFR (Figure 2).

Risk Prediction for AKI by Kidney Function Markers

After adjustment for covariates, cystatin C clearly had the strongest independent association with AKI; compared with the Best kidney function category by cystatin C, approximately two-fold and five-fold adjusted odds were observed for the Intermediate and Worst cystatin C categories, respectively (Table 2). Adjusted odds for persistent AKI were slightly stronger than for the broader AKI outcomes (Table 2). In contrast, for creatinine, the Intermediate kidney function group had no significant, independent association with AKI and the Worst kidney function group had approximately two-fold adjusted odds of AKI. These associations were much stronger for persistent AKI, increasing to approximately two-fold and six-fold in the Intermediate and Worst groups, respectively (Table 2). Results for eGFR were slightly weaker than creatinine: 1.0 (95% CI, 0.7–1.4) for the Intermediate kidney function group, and 1.7 (95% CI, 1.1–2.3) for the Worst kidney function group.

For severe AKI, only the Worst kidney function quintile was independently associated with the outcome; this category by cystatin C had an approximately four-fold adjusted odds of AKI or persistent AKI, whereas the Worst creatinine group had a two-fold adjusted odds for AKI and persistent AKI. There was no significant independent association for eGFR categories and severe AKI.

In models with each kidney function variable as a linear predictor per standard deviation, the adjusted associations with AKI were 1.7 (95% CI, 1.4–1.9) for cystatin C, 1.2 (95% CI, 1.0–1.5) for creatinine, and 0.8 (95% CI, 0.7–0.9) for eGFR. For severe AKI, these odds ratios, respectively, were 1.4 (1.1, 1.8), 1.3 (0.9, 1.7), and 0.8 (0.6, 1.1).

The ROC curve for the outcome of AKI had a c-statistic of 0.70 using the STS pre-surgical risk variables without any measure of kidney function (Figure 3). Addition of cystatin C plus creatinine provided a moderate and significant incremental increase (0.72, $p < 0.01$ for difference), compared with smaller and non-significant changes with the addition of creatinine alone (0.69) or eGFR (0.70). These were substantially higher for persistent AKI, and the cystatin C model remained significantly stronger than creatinine alone: creatinine was 0.76 versus 0.80 ($p < 0.01$ for difference). For the severe AKI outcome, the c-statistic was 0.73 for pre-surgical risk variables alone, and with the addition of either creatinine or eGFR, increased to 0.77; cystatin C only marginally and non-significantly increased the c-statistic to 0.78 ($p = 0.6$ for difference). Results for persistent severe AKI were similar: 0.80 for creatinine and 0.81 with the addition of cystatin C.

In addition to the c-statistic, we used the NRI and IDI to determine whether cystatin C materially affected AKI risk prediction. The NRI was highly significant and of substantial magnitude: 0.17 (95% CI, 0.10–0.23; $p < 0.001$); the IDI was also highly significant (0.04; 95% CI, 0.03–0.05; $p < 0.001$). We also compared estimated and observed AKI risks that were based on models including either creatinine or cystatin C (Table 3). Among the 763 persons initially categorized as Intermediate risk by eGFR, over one-third were reclassified into lower (25%, $n = 192$) or higher (14%, $n = 109$) risk categories. Among this Intermediate risk group defined by creatinine (overall AKI risk of 33%), AKI risks based on these cystatin C refined categories were 20%, 33%, and 60% for the low, intermediate, and high risk groups, respectively. Similarly, 23% of those initially categorized as low risk by creatinine and 22% of those initially labeled high risk by creatinine were reclassified by cystatin C. Risk prediction was improved by cystatin C for both those reclassified up from

the low risk group (30% vs. 22% AKI risk) and among those reclassified downward from the high risk group (31% vs. 68% AKI risk) (Table 3).

Discussion

Acute kidney injury is among the most morbid complications of cardiac surgery. Not only does AKI lead to a higher in-hospital mortality risk, but it also predisposes to long-term mortality risk, even among persons who appear to recover from the AKI episode.^{18–19} In this large, multi-center, prospective study, we compared the ability of pre-surgical measurement of serum cystatin C, an alternative marker of kidney filtration, with the clinical standard of serum creatinine to risk-stratify for post-surgical AKI. Although the post-surgical definition of clinical AKI is based on the magnitude of rise in the serum creatinine level, pre-surgical cystatin C levels had much stronger and more linear associations with AKI risk than pre-surgical serum creatinine. Furthermore, for the AKI outcome, cystatin C had a relevant improvement in risk discrimination, as demonstrated by a significant absolute increase in the c-statistic of 6%, and a substantial improvement in reclassifying individuals to low, intermediate, and high risk for AKI. Therefore, cystatin C may have a useful role for pre-surgical stratification among high-risk, adult cardiac surgery patients.

Although cystatin C has been clinically available for several years and is FDA-approved as an alternative test of kidney function, it has not found widespread use or a specific clinical indication. Several studies in various settings have determined that cystatin C has much stronger associations with cardiovascular and other clinical outcomes in ambulatory patients,^{20–22} but prognostic value in the outpatient setting has not translated into routine clinical use. Since kidney function is an integral determinant of in-hospital outcomes, cystatin C could potentially have utility for risk stratification in the inpatient setting. One recent study of 150 patients from three academic medical centers found that cystatin C was better than creatinine for predicting post-surgical AKI using the same definition as in our study; however, perhaps related to their sample size, cystatin C only increased the c-statistic by 1%.²³ Another study found that cystatin C had much stronger associations than creatinine with clinical outcomes among patients hospitalized with acute coronary syndrome.²⁴

In our study, we observed an improvement in risk discrimination for the AKI outcome; a 6% increase in the c-statistic is a moderate difference for a single biomarker as is a NRI of 21%.¹⁷ However, the odds ratios and improvements in the c-statistic for severe AKI were smaller. It may be that the development of severe AKI is more dependent upon intra-surgical characteristics (e.g., long cardiopulmonary bypass time, intra-surgical hypotension) rather than pre-surgical variables, including pre-surgical kidney function. In addition, the smaller number of severe AKI outcomes may have limited the ability of kidney function markers to change the c-statistic, but the odds ratios for each kidney measure were also much weaker for severe AKI. In future studies, this cohort should combine with other large studies to generate a more powerful evaluation of whether cystatin C can improve risk discrimination for the less common outcomes of severe AKI and in-hospital death.

The value of these research findings must be appreciated in the context of the important role risk assessment has in cardiac surgery. Several sophisticated algorithms have been developed, including the STS tool used throughout the U.S., to generate a pre-surgical likelihood for the patient to survive cardiac surgery.^{10,25} These tools are used in part to allow individual patients to balance the risks and benefits of cardiac surgery, but they have even greater importance for monitoring the quality of care and outcomes of cardiac surgery by individual surgeons and hospitals. Due to the intense scrutiny on cardiac surgery outcomes, even mild improvements to help risk adjust for adverse outcomes could have great clinical importance. Since pre-existing chronic kidney disease is generally accepted as

one of the strongest risk factors for AKI and death,^{7,10,26–27} finer ascertainment of pre-surgical kidney function would help improve risk-assessment of patients undergoing cardiac surgery. One recent study has suggested that AKI risk should be an important factor for patients weighing the choice between cardiac surgery or percutaneous coronary intervention.²⁸ Therefore, if cystatin C can be validated further as a relevant marker for improving risk assessment for AKI or other adverse outcomes after cardiac surgery, then it could be of value to individual patients, clinicians, and hospitals.

The major strength of this study is that it is the largest, multi-center study to date to compare cystatin C and creatinine as measures of pre-surgical kidney function for determination of post-surgical AKI risk. The diverse settings of the six institutions ensured a broad inclusion of high-risk cardiac surgery patients. However, this study does have important limitations. Although our study had a very large number of AKI cases, we had few patients with either dialysis-requiring AKI (n=12) or who died (n=19). Therefore, the ability of these kidney biomarkers to predict risk for these outcomes could not be reliably assessed in our study. In the future, we will assess long-term survival and kidney function after cardiac surgery in this cohort, and we will compare the predictive value of pre-surgical creatinine and cystatin C measures. Another limitation is that 5% of pre-surgical visits occurred more than 30 days prior to surgery; however, only two patients had a pre-surgical visit more than three months prior to surgery. In these patients, it is possible that kidney function might have changed during the interval prior to surgery. The overall discrimination for AKI in this study was moderate, indicated by c-statistics of 0.71 and 0.74 for AKI and severe AKI, respectively. We believe that risk stratification was limited in our study, in part because we specifically recruited a cohort at increased risk for AKI. In addition, we did not have a validation set for our study, so confirmation will require future investigation in other settings. Furthermore, despite the multi-center design of our study, two-thirds of participants were men and over 90% were white. Finally, we relied on blood-based markers of kidney function that are easily measured in clinical care, rather than a criterion standard of measured GFR.

In conclusion, we found that pre-surgical cystatin C levels had a stronger and more linear association with AKI risk than serum creatinine or eGFR based on serum creatinine, the clinical standards. For the outcome of AKI, cystatin C impressively improved risk discrimination based upon changes in the c-statistic of the ROC curve and by reclassifying categories of AKI risk. If confirmed in other studies, cystatin C may have importance for pre-surgical risk stratification among potential high-risk surgical candidates.

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Figure 1.
Incidence of Acute Kidney Injury by Quintiles of Cystatin C, Creatinine, and Estimated Glomerular Filtration Rate (eGFR-Creatinine)

*Note: eGFR-Cr quintiles are in opposite order, from Quintile 5 to Quintile 1.

Abbreviations: Estimated glomerular filtration rate (eGFR-Cr)

Figure 2.

Incidence of Severe Acute Kidney Injury by Quintiles of Cystatin C, Creatinine, and Estimated Glomerular Filtration Rate (eGFR-Creatinine)

*Note: eGFR-Cr quintiles are in opposite order, from Quintile 5 to Quintile 1.

Abbreviations: Estimated glomerular filtration rate (eGFR-Cr)

Figure 3.
Incremental Changes to the Receiver Operator Characteristic (ROC) Curve for AKI by
Adding Cystatin C or Creatinine to the Multivariate Risk Analysis

Table 1

Baseline Characteristics by Cystatin C among 1,147 Patients Undergoing Cardiac Surgery

	Quintile 1 (0-0.70 mg/L)	Quintile 2 (0.70-0.81 mg/L)	Quintile 3 (0.81-0.92 mg/L)	Quintile 4 (0.92-1.13 mg/L)	Quintile 5 (1.13-2.9 mg/L)	P Value for Trend
No. of patients	229	230	228	226	234	
Age (y)	68+/-12	70+/-9	72+/-10	74+/-8	74+/-9	<0.001
+/-						
<65 years	75 (33)	57 (25)	44 (19)	36 (16)	35 (15)	<0.001
65-75 years	90 (39)	104 (45)	87 (38)	79 (35)	77 (33)	0.4
75-85 years	59 (26)	65 (28)	87 (37)	95 (42)	102 (44)	0.02
>85 years	5 (2)	4 (2)	13 (6)	15 (7)	20 (9)	0.2
Male	153 (67)	160 (70)	161 (71)	158 (70)	148 (63)	0.5
White Race	212 (93)	216 (94)	216 (95)	218 (96)	210 (90)	0.5
Diabetes	100 (44)	80 (45)	95 (42)	89 (39)	107 (46)	0.4
Hypertension	159 (69)	175 (76)	180 (79)	196 (87)	193 (82)	<0.001
Heart Failure	44 (19)	45 (20)	51 (22)	61 (27)	94 (40)	<0.001
Surgical Characteristics						
Prior Cardiac Surgery	26 (11)	29 (13)	27 (12)	35 (15)	32 (14)	0.3
Elective Surgery	177 (77)	194 (84)	186 (82)	186 (82)	169 (72)	0.1
Cardiac Catheterization in last 48hrs	15 (6)	13 (6)	10 (4)	9 (4)	13 (6)	0.5
Surgery						<0.001
CABG	127 (55)	133 (58)	112 (49)	92 (41)	87 (37)	
Valve	64 (28)	51 (22)	62 (27)	76 (34)	79 (34)	
CABG and Valve	38 (17)	46 (20)	53 (23)	58 (26)	68 (29)	
Kidney Function						
Presurgical SCr (mg/dL)	0.9+/-0.2	1.0+/-0.2	1.0+/-0.2	1.1+/-0.2	1.5+/-0.4	<0.001
Presurgical eGFR (mL/min/1.73m ²)	84+/-14	75+/-14	70+/-14	61+/-14	46+/-16	<0.001
Pre-surgical Serum Biomarker						
Cystatin C (mg/L)	0.63 (0.57, 0.67)	0.75 (0.73, 0.78)	0.86 (0.83, 0.88)	1.0 (0.95, 1.07)	1.33 (1.20, 1.53)	<0.001

Note: continuous variables shown as mean +/- SD or median (25th, 75th percentile); categorical variables as number (percentage). Conversion factors for units: SCr in mg/dL to mmol/L, x88.4; eGFR in mL/min/1.73 m² to mL/s/1.73 m², x0.01667.

Abbreviations: coronary artery bypass grafting (CABG); estimated glomerular filtration rate (eGFR); SCr, serum creatinine

Table 2

Association of Pre-Surgical Kidney Function Categories and AKI Risk Following Cardiac Surgery

	Best (Quintile 1–2)	Intermediate (Quintile 3–4)	Worst (Quintile 5)
<u>CYSTATIN C</u>			
AKI			
Incidence (%)	23	37	59
Unadjusted OR	1.0 (ref)	1.8 (1.4, 2.3)	4.2 (3.1, 5.7)
Adjusted OR *	1.0 (ref)	1.9 (1.4, 2.7)	4.8 (2.9, 7.7)
Adjusted Persistent AKI **	1.0 (ref)	2.5 (1.5, 4.3)	7.1 (3.6, 13.7)
Severe AKI			
Incidence (%)	3.0	4.3	10.8
Unadjusted OR	1.0 (ref)	1.1 (0.7, 1.7)	2.6 (1.6, 4.3)
Adjusted OR *	1.0 (ref)	1.6 (0.7, 3.7)	3.6 (1.3, 10.1)
Adjusted Persistent AKI **	1.0 (ref)	1.5 (0.6, 3.9)	4.7 (1.5, 14.2)
<u>CREATININE</u>			
AKI			
Incidence (%)	30	37	52
Unadjusted OR	1.0 (ref)	1.4 (1.1, 1.9)	2.6 (1.9, 3.7)
Adjusted OR *	1.0 (ref)	1.2 (0.9, 1.7)	1.8 (1.2, 2.6)
Adjusted Persistent AKI **	1.0 (ref)	2.3 (1.3, 3.8)	5.8 (3.4, 10.1)
Severe AKI			
Incidence (%)	3.8	5.4	8.8
Unadjusted OR	1.0 (ref)	1.2 (0.7, 2.7)	2.1 (1.1, 3.8)
Adjusted OR *	1.0 (ref)	1.7 (0.8, 3.4)	2.0 (0.9, 4.5)
Persistent AKI **	1.0 (ref)	1.5 (0.7, 3.3)	2.2 (1.0, 5.3)

* Note: For adults, adjusting for age, gender, race, non-elective surgery, diabetes, hypertension, type of surgery, myocardial infarction, contrast use in 48 hours, albumin-creatinine ratio (ACR), site, LVEF, and on/off pump CABG. Cystatin C models are also adjusted for creatinine.

** Adjusted OR Including Creatinine. Persistent AKI defined as having a duration of >48 hours.

AKI defined as during entire hospitalization, AKI defined as $\geq 50\%$ or ≥ 0.3 , severe AKI defined as $\geq 100\%$ or dialysis.

95% confidence intervals are shown in parentheses.

Abbreviations: Acute kidney injury (AKI), estimated glomerular filtration rate (eGFR); ref, reference; OR, odds ratio

Table 3

Comparison of Risk Classification for AKI, Based on CysC and SCr

SCr-based Risk Classification	CysC-based Risk Classification*			All
	<25% risk	25–50% risk	>50% risk	
<25% risk	162 (22)	50 (30)	1 (0)	213
25–50% risk	192 (20)	462 (33)	109 (60)	763
>50% risk	0 (NA)	32 (31)	115 (68)	147
All	354	544	225	1123

Values shown are number (AKI risk percentage).

* Risk classification is based on the following predictors: age, gender, race, non-elective surgery, diabetes, hypertension, type of surgery, myocardial infarction, chronic heart failure, contrast use in 48 hours, and either measure of kidney function.

Each cell in the table depicts: a) the number of participants with the combination of predicted AKI risks by SCr (rows) and CysC (columns) and b) the observed AKI risk for those individuals in this study. In these analyses, 67 subjects were excluded because they were missing information (myocardial infarction, n=21; proteinuria, n=14; on/off pump CABG, n=29) and/or contrast use (n=3).

SCr, serum creatinine; CysC, cystatin C; AKI, acute kidney injury