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Association of Peak Changes in Plasma Cystatin C and Creatinine with Mortality post Cardiac Surgery

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Abstract

Background—Acute kidney injury is a risk factor for mortality in cardiac surgery patients. Plasma cystatin C and creatinine have different temporal profiles in the post-operative setting, but the associations of simultaneous changes in both filtration markers as compared to change in only one marker with prognosis following hospital discharge are not well described.

Methods—This is a longitudinal study of 1199 high-risk adult cardiac surgery patients in the TRIBE-AKI (Translational Research Investigating Biomarker Endpoints for Acute Kidney Injury) Consortium who survived hospitalization. We examined in-hospital peak changes of cystatin C and creatinine in the 3 days following cardiac surgery. We evaluated associations of these filtration markers with mortality, adjusting for demographics, operative characteristics, medical

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comorbidities, pre-operative estimated glomerular filtration rate, pre-operative urinary albumin to creatinine ratio, and site.

Results—During the first 3 days of hospitalization, nearly twice as many patients had a ≥ 25% rise in creatinine (30%) compared to a ≥ 25% peak rise in cystatin C (15%). Those with elevations in either cystatin C or creatinine had higher mortality risk (adjusted hazard ratio cystatin C 1.83 (95% CI 1.4–2.37) and creatinine 1.90 (95% CI 1.32–2.72)) compared with persons who experienced a post-operative decrease in either filtration marker, respectively. Patients who had simultaneous elevations of ≥ 25% in both cystatin C and creatinine were at similar adjusted risk for 3 year mortality (HR 1.79, 95% CI 1.03–3.1) as those with ≥ 25% increase in cystatin C alone (HR 2.2, 95% CI 1.09–4.47).

Conclusions—Elevations in creatinine post-operatively are more common than elevations in cystatin C. However, elevations in cystatin C appeared to be associated with higher risk of mortality after hospital discharge.

Keywords

acute kidney injury; cardiac disease; risk prediction

Acute kidney injury (AKI) is an independent predictor of mortality in cardiac surgery patients.[1–3] Serum creatinine remains the clinical standard for AKI diagnosis, and increases of ≥ 0.3 mg/dl are independently associated with longer hospital stay and both in-hospital and long-term mortality.[2] However, diagnosis of AKI using serum creatinine may not be ideal in the post-operative setting due to hemodilution[4] and blood loss.[5] Furthermore, decreases in creatinine generation from muscle[6] may occur in the perioperative setting. Blood cystatin C (cysC) level has been shown to be a stronger predictor than serum creatinine for cardiovascular events, mortality, and other adverse outcomes in community-based studies.[7–9] In previous studies in individuals undergoing cardiac surgery, cysC has been shown to be a sensitive measure of overall renal function.[10] Because cysC is thought to be less influenced by non-glomerular filtration rate determinants[11] is extracellular,[12] and has a smaller volume of distribution compared to creatinine,[13] it may be a better measure of AKI than creatinine in the perioperative period.[14]

In the prospective observational TRIBE-AKI (Translational Research Investigating Biomarker Endpoints for Acute Kidney Injury) cohort of adults undergoing cardiac surgery, we previously demonstrated that pre-operative blood cysC level was a stronger predictor of AKI than pre-operative creatinine level or glomerular filtration rate estimated from creatinine level,[15] but that changes in cysC were less sensitive in the identification of AKI.[14] However, confirming creatinine-based AKI diagnoses by changes in cysC levels identifies a subset of AKI patients with a substantially higher risk of in-hospital adverse outcomes.[14] While creatinine, cysC, and urine biomarkers of kidney injury have made the diagnosis of AKI more sensitive, identifying those at highest risk of poor outcomes remains difficult. To improve risk stratification of individuals undergoing cardiac surgery, we investigated patterns of filtration marker changes measured over two time periods (0–6 hours post-operatively and up to 3 days after surgery) and their associations with all-cause

mortality risk after hospital discharge up to 3 years. We sought to determine whether use of both filtration markers, cysC and creatinine, would help to capture associations of in-hospital changes in kidney function with prognosis following hospital discharge.

Subjects and Methods

Study Population

The TRIBE-AKI cohort has been described previously.[15, 16] Participants were recruited prior to their cardiac surgery (coronary artery bypass grafting, surgery for valve disease, or both) at 6 academic medical centers in North America between July 2007 and December 2009. We included 1199 participants who survived the hospitalization and had both pre-operative and at least 1 post-operative value for cysC and creatinine.

Specimen Collection

Study coordinators collected blood pre-operatively and daily for 3 days on everybody and up to 5 post-operative days in patients who were in the ICU.[16]

Measurements

Serum creatinine was measured at the pre-operative visit and daily up to post-operative day 3 (all patients) or 5 (ICU patients) as part of clinical practice. Sites used isotope dilution mass spectrometry–calibrated or the Jaffé method to measure serum creatinine. Estimated glomerular filtration rate was calculated using the serum creatinine–based CKD Epidemiology Collaboration (CKD-EPI) equation.[17] CysC was measured from the study specimens collected at the pre-operative visit and daily until post-operative day 5, using plasma samples that had not undergone additional freeze-thaw cycles.

Outcomes

The primary outcome was time to mortality after discharge. Mortality was ascertained as previously described[1] and analyzed at the Institute for Clinical Evaluative Sciences. Range of follow-up time was 2–5 years. In this study, individuals who experienced in-hospital mortality were excluded (N=20) from the total enrolled population of 1219 as we were interested in long term prognosis. Individuals with missing blood creatinine or cysC measurements were also excluded (N=68) for a final sample size of 1131 individuals with all biomarker measurements available for the analysis of change from pre-op to peak (Appendix Figure 1).

Statistical Analysis

The association between changes in filtration markers and time to mortality was examined using Cox proportional hazards regression with robust sandwich variance estimators (accounting for clustering within centers). We used Schoenfeld residuals to confirm the proportional hazards assumption. For each filtration marker, cysC and creatinine, the percentage change was calculated for two time periods: pre-op to 6 hours post-op, and pre-op to peak within 3 days post-op. To allow comparisons between changes in cysC and creatinine levels, we calculated the relative increases in each marker from baseline (<0%, 0–

25%, ≥ 25%) and compared risk for their associations with the mortality endpoint. These thresholds were chosen based on the distribution of changes in cysC and creatinine in TRIBE.[14] These three categories were chosen to be able to compare the substantial number of individuals who had a post-operative decline in filtration markers separately from those who experienced post-operative increases. The primary analysis examined models of each biomarker separately.

In model 1, we adjusted for age (per year), sex, white race, center, cardiopulmonary bypass time > 120 minutes, non-elective surgery, pre-op eGFR, diabetes, hypertension, center, heart failure, myocardial infarction, pre-op urine albumin to creatinine ratio, and type of surgery (CABG alone or valve repair alone versus both). A second adjusted model included model 1 plus eGFRcr or eGFRcys for creatinine change and cysC change analyses, respectively. Model 2 for combined changes in both filtration markers adjusted for pre-operative eGFR.

All analyses were performed in SAS (version 9.3; SAS Institute, Cary, NC) and R 2.15.0 (R Foundation for Statistical Computing, Vienna, Austria) software). Small cell counts are only presented for data collected by TRIBE-AKI study and not from Institute for Clinical Evaluative Sciences data holdings.

Results

Baseline Characteristics

Among 1131 participants who survived hospitalization and had complete creatinine and cysC measurements, those in the highest category of change in blood cysC were more likely to be older, have hypertension, and have albuminuria ≥ 300 mg/g compared with persons with smaller changes (Table 1). These trends were paralleled in those in the highest category of change in serum creatinine (Appendix Table 1). Individuals in the highest category of change in either cysC or creatinine were also more likely to have longer perfusion times, cross-clamp times, and hospitalization lengths of stay.

At the first post-operative time point (between 0–6 hours), 120 individuals (10%) had an increase in serum creatinine of ≥ 25% while only 21 (2%) had a ≥ 25% increase in cystatin (Figure 1). Conversely, twice as many individuals experienced any decrease in cysC (range of change −0.6 to 0) immediately post-operatively (N=938, or 84%) than experienced a decrease in creatinine (N= 552, or 47%) (Figure 1). During the first 3 days of hospitalization, twice as many patients had a peak rise in creatinine ≥ 25% (N=359, or 30%) as had a ≥ 25% peak rise in cysC (N=174, 15%) (Figure 2). As in the period from 0–6 hours, the number of patients whose postoperative values never exceeded baseline (i.e. experienced a reduction from baseline level) was two-fold higher when measured by cysC (N=508, or 45%, range of change −0.57 to 0) than by creatinine (N=248, or 21%) (Figure 2). These proportions were similar between groups treated on- and off-cardiopulmonary bypass (Appendix Figures 2 and 3).

Associations of acute post-operative filtration marker changes with long-term mortality

Among 1131 participants, 127 patients died at a median of 2.8 years of follow-up. The absolute risk of long-term mortality was similar between groups with ≥ 25% increase in

cysC and creatinine at the 0–6 hour time point (66.3 versus 79.5 per 1000 patient-years, p= 0.17) (Table 2). The group with a 0–25% increase in cysC (death rate 35/1000 patient-years) had a lower absolute mortality rate than the group with a decrease in cysC (death rate 51/1000 patient-years, $p < 0.01$), while those who experienced a drop in post-operative serum creatinine had similar absolute mortality compared to those who had 0–25% increase (48 versus 55 per 1000 patient-years, p=0.59). In multivariable analyses, increases in either cysC or creatinine were not significantly associated with long-term mortality in either categorical or continuous analyses.

Associations of peak filtration marker changes within 3 days post-operatively with long-term mortality

Individuals with a cysC increase ≥ 25% measured from pre-operative to peak levels had an absolute rate of death (88/1000 person-years) (N=174), whereas individuals in the highest category of creatinine change had a lower rate (80/1000 person-years; $p < 0.01$) (N=359) (Table 3). In contrast to the non-significant associations at the first post-operative time point (above), those with a ≥ 25% peak rise in cysC or creatinine had a higher risk for mortality (Table 3), even after adjustment for pre-operative eGFR. Participants with peak cysC rise of 0–25% had similar rates of mortality as those with <0% change (47 versus 45 per 1000 patient-years, p=0.84). The associations of each marker as continuous linear variables demonstrated a more linear association between creatinine and mortality than cystatin C.

Associations of peak changes in both filtration markers with long-term mortality

Consideration of both filtration markers in conjunction appeared to give similar prognostic value relative to either marker alone. Those with an elevation ≥ 25% in cysC but not creatinine had a significantly increased risk of mortality (N=60) (Table 4), while the converse group (increase in creatinine but not cysC) did not (N=233). When both cysC and creatinine increased by ≥ 25% (N=114), mortality risk was nearly two-fold higher compared to the group that experienced < 25% rise in both (Table 4).

Additional analyses

We evaluated six potential interactions of clinical characteristics with the association of filtration marker changes and long-term survival, including diabetes, type of surgery (elective versus non-elective; CABG or valve alone versus combined), cardiopulmonary bypass (CPB) time, heart failure, and myocardial infarction. The length of CPB time had significant interactions with each filtration marker (p=0.03 for each), but in opposite directions. The association of an elevation ≥ 25% in cysC was weaker when CPB time was >120 minutes (HR 1.02 (95% CI 0.48–2.18)) versus when CPB time was <120 [HR 2.13 (1.73–2.63)]. In contrast, the association for an elevation ≥ 25% in creatinine was stronger when CPB was >120 [HR 2.02 (95% CI 0.85–4.83)] versus < 120 [HR 1.5 (95% CI 0.97–2.32)].

Discussion

AKI is an important risk factor for mortality in cardiac surgery patients. Use of creatinine alone to define AKI has been criticized for being delayed, insensitive, and non-specific. In

this analysis, we demonstrated that a greater proportion of individuals experienced a decrease in cysC immediately post-operatively than a decrease in creatinine, shifting the associations with AKI and mortality. Although elevations ≥ 25% were less common by cysC than by creatinine, the highest category of peak change in cysC was associated with a higher absolute risk of death than that measured by the highest category of change in creatinine.

Previously we showed that pre-operative cysC was more sensitive than pre-operative creatinine for predicting AKI[15] and improved risk discrimination. Subsequently, we showed that cysC identified a subgroup of AKI patients with a higher risk of adverse events during hospitalization.[14] Our current manuscript suggests that although a higher change in cystatin C is associated with a higher absolute risk of death, the association with long-term mortality after hospital discharge is only apparent in the group with change ≥ 25%. In the prior study, there were only 20 in-hospital deaths, limiting our statistical power to evaluate risk for this outcome. The in-hospital mortality rate was clearly highest for those who had both creatinine and cysC rise ≥ 25% during hospital. This paper extends our findings by allowing us to evaluate longer term mortality. The apparent lower sensitivity of post-operative cysC for detecting AKI in TRIBE appears to be due to an acute drop in cysC during the operation; presumably, this is from administration of intravenous fluids or a different effect of coronary bypass on cysC compared to creatinine. CysC is extracellular[12] and has a smaller volume of distribution compared to creatinine,[13] making the half-life of cysC approximately 1/3 as long as that of creatinine.[18] Thus, loss of fluid from the intravascular space to the interstitium during CPB may affect cysC and creatinine differently. Finally, although cysC production rate is thought to be stable, the temperature change experienced during surgery may affect gene expression.[19] A decrease in cysC measured immediately after cardiac surgery has been noted previously. In a study by Koyner et al, plasma cysC dropped in the first six hours following cardiac surgery to a greater degree than creatinine, although creatinine also decreased.[20] In a study by Abu-Omar, among 60 individuals undergoing CABG, 30 who were treated off-pump had a drop in mean serum cysC on post-operative day 2.[21] However, the on-pump group did not experience this decrease, and a similar study of patients undergoing valve replacement on cardiopulmonary bypass had an increase in cysC on day 2.[10] Our study demonstrates that the acute decrease in cysC is much more pronounced than in creatinine. Our comparison between on- and off-pump shows no difference between groups, suggesting that the use of cardiopulmonary bypass pump is the not the mechanism inflicting this change.

Our findings are interesting for several reasons. The assessment of peak post-operative changes in both cysC and creatinine may allow identification of the highest risk group for mortality following surgical hospitalization. Although an ideal predictive biomarker would allow measurement and intervention prior to an AKI-producing insult, cysC adds utility by identifying a subset of AKI patients who are at higher long-term risk. Over the last decade, definitions of AKI have become sensitive and consequently minor bumps in serum creatinine elevations are increasingly prone to false positive diagnoses due to laboratory and biological variations. Our research may identify patients with early AKI by combining minor elevations in creatinine and cysC to conserve sensitivity of diagnosis while preserving the long term attributable mortality risk. Unlike many novel AKI biomarkers, cysC is already approved for use in the U.S. and can be easily integrated into clinical care. On the

other hand, cysC may be more susceptible to changes in volume status than creatinine. The results of our interaction analysis for cardiopulmonary bypass time are provocative and may support different mechanisms of cysC and creatinine shifts during surgery. These findings will need to be validated and accounted for to interpret changes in cysC during hospitalization.

Our study has several strengths. To our knowledge, this is the largest multicenter study to date to compare cysC and creatinine and to assess the combined use of both filtration markers in an assessment of post-operative AKI and mortality risk. Blood measurements of cysC and creatinine were obtained at multiple time points and data were rigorously collected. The follow-up time to mortality is also long for a cardiac surgery cohort. The population represented in TRIBE-AKI is diverse and should be generalizable to other high-risk cardiac surgery patients. Our study also has a few limitations. Blood cysC and creatinine were measured in two separate blood samples drawn at the same time point in most, but not all, patients, although the variability in time was minimized by protocol. Nevertheless, the number of individuals who had a decrease in cysC compared to those with a decrease in creatinine is much larger than in other studies. Although data for receiving dialytic support are being collected in this cohort, there were not enough events to evaluate end-stage renal disease outcomes in this study. Finally, we recognize the limitations of categorizing variables (for example, cardiopulmonary bypass time) rather than including them as continuous variables in all analyses.

In conclusion, in a large population of adult cardiac surgery patients with high risk for AKI, individuals with the elevations in both cysC and creatinine had a higher overall risk for mortality than those with elevations in only one filtration marker. Use of both cysC and creatinine in the post-operative period may help to differentiate those at highest risk for poor outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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List of abbreviations

cysC	cystatin C
TRIBE-AKI	Translational Research Investigating Biomarker Endpoints for Acute Kidney Injury
eGFRcr	glomerular filtration rate estimated from creatinine
eGFRcys	glomerular filtration rate estimated from cystatin C
eGFR	estimated glomerular filtration rate

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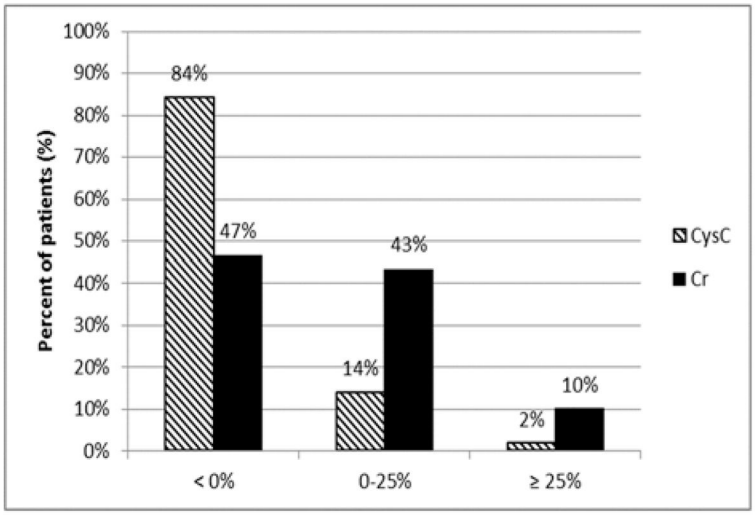

Figure 1.
Relative changes from preoperative values of CysC and Cr to 6 hours post cardiac surgery.

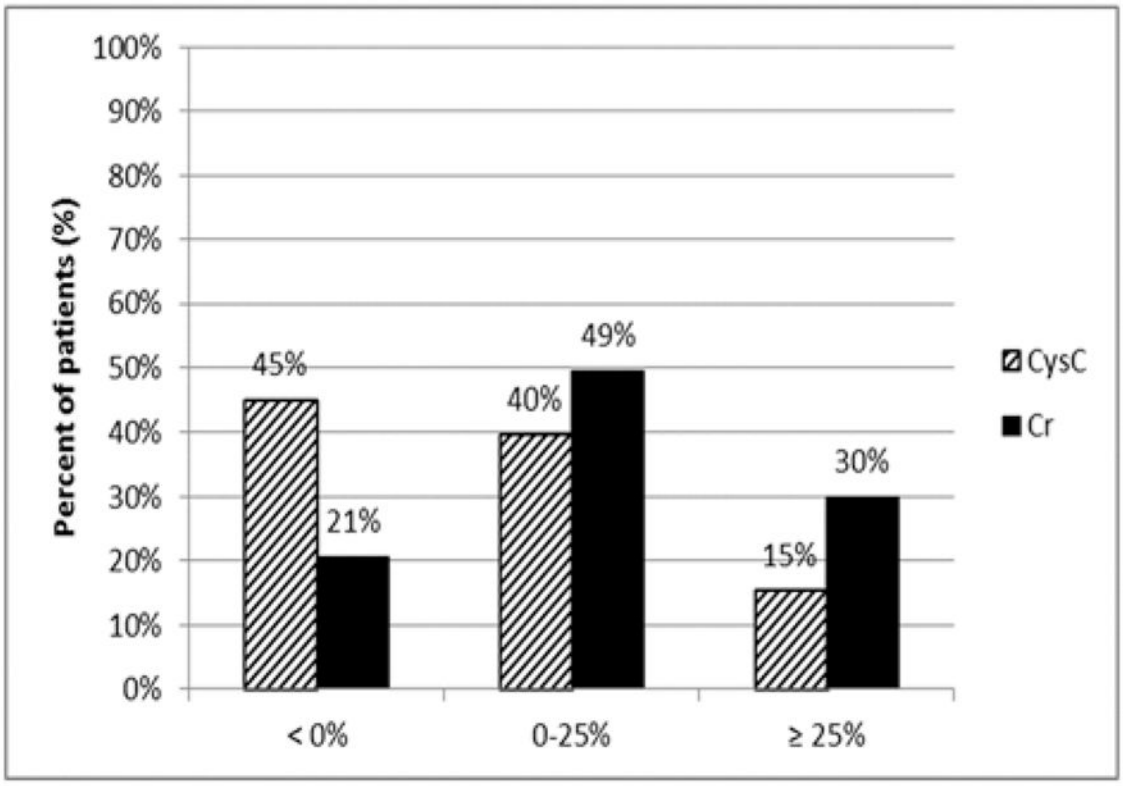

Figure 2.
Relative changes from preoperative values of CysC and Cr to peak post cardiac surgery.

Table 1

Baseline characteristics by peak change in cystatin C

	Peak Change in Cystatin C			
	< 0% (n = 508)	**0–25% (n=449)**	**≥ 25% (n = 174)**	**P value**
Demographics				
Age at the time of surgery, years	72 (9.9)	71 (10.2)	71 (9.9)	0.013
Male	335 (66%)	316 (70%)	123 (71%)	0.265
White Race	475 (94%)	421 (94%)	161 (93%)	0.854
Medical History				
Diabetes	167 (33%)	205 (46%)	68 (39%)	0.0003
Hypertension	389 (77%)	356 (79%)	147 (84%)	0.085
Ejection fraction <35% or grade 3 or 4 left ventricular function	49 (10%)	47 (10%)	18 (10%)	0.908
Previous myocardial infarction	134 (26%)	120 (27%)	35 (20%)	0.201
Pre-op plasma creatinine (mg/dL)	1.07 (0.32)	1.07 (0.33)	1.16 (0.41)	0.047
Pre-op eGFR Plasma Creatinine	67 (19)	69 (19)	65 (21)	0.023
Pre-op eGFR Cystatin C	67 (22)	72 (24)	69 (27)	0.003
Pre-op eGFR Cr-Cys C	67 (20)	71 (21)	67 (23)	0.005
Urine Albumin to Creatinine				
≤10.0	208 (41%)	154 (34%)	47 (27%)	
10–30	163 (32%)	125 (28%)	51 (29%)	
30–300	116 (23%)	142 (32%)	59 (34%)	
≥ 300	21 (4%)	28 (6%)	17 (10%)	
Operative Characteristics				
Elective Surgery	426 (84%)	353 (79%)	122 (70%)	0.0004
CABG	251 (49%)	224 (50%)	75 (43%)	0.11
CABG & Valve	103 (20%)	111 (25%)	39 (22%)	
Valve	154 (30%)	114 (25%)	60 (34%)	
Off-pump	61 (12%)	44 (10%)	8 (5%)	0.031
Re-do surgery	9 (2%)	8 (2%)	2 (1%)	0.846
Perfusion Time (minutes)	106.71 (57.54)	113.4 (56.55)	132.63 (68.6)	0.0003
Cross Clamp Time (minutes)	72.41 (43.19)	76.89 (41.53)	90.69 (50.35)	0.001
Postoperative Complications				
Clinical AKI (>100% or dialysis)	9 (2%)	13 (3%)	26 (15%)	<0.0001
Oliguria in first day	5 (1%)	6 (1%)	4 (2%)	0.433
Percentage Change in Plasma Creatinine	0.09 (0.22)	0.19 (0.25)	0.51 (0.52)	<0.0001
Percentage Change in Plasma Cystatin C	−0.12 (0.08)	0.11 (0.07)	0.49 (0.31)	<0.0001
Diuretics (first 3 days post-op)	274 (54%)	299 (67%)	130 (75%)	<0.0001
ICU length of stay (days)	2.66 (4.76)	2.96 (5.52)	4.99 (15.86)	0.023
Hospital length of stay (days)	7.99 (8.37)	7.83 (6.8)	10.95 (18.18)	0.004

Table 2

Risk of Death by Percentage Change from Pre-operative to 0–6 hours Post Cardiac Surgery

Filtration marker		N	Filtration marker Range	Death Rate†	HR (95% CI)	
					Model 1	Model 2
Cys C	< 0%	938	−0.6 to 0	50.9	1.0 (referent)	1.0 (referent)
	0% to 25%	155	0 to 0.25	34.8	0.70 (0.56, 0.87)	0.78 (0.64, 0.94)
	≥ 25%	21	0.25 to 0.90	66.3	1.25 (0.34, 4.68)	1.52 (0.38, 6.0)
	Continuous				0.47 (0.21, 1.03)	0.81 (0.54, 1.20)
Cr	< 0%	552	−0.5 to 0	48.6	1.0 (referent)	1.0 (referent)
	0% to 25%	515	0 to 0.25	55.3	1.12 (0.76, 1.66)	1.15 (0.78–1.69)
	≥ 25%	120	0.25 to 1.13	79.5	1.36 (0.77, 2.39)	1.43 (0.80, 2.53)
	Continuous				2.09 (0.82, 5.33)	2.37 (0.93, 6.01)

†Mortality Rate per 1000 patient years adjusted for site

Model 1: Age (per year), sex, white race, cardiopulmonary bypass time > 120 minutes, non-elective surgery, diabetes, hypertension, center, Heart Failure (HF), Myocardial Infarction (MI), Pre-op urine albumin to creatinine ratio, and Type of surgery (CABG or valve vs. all others).

Model 2: For models with Cys C, Model 1 + pre-op eGFR by CysC.

For models with Cr, Model 1 + pre-op eGFR by Cr

Table 3

Risk of Death by Percentage Change from Pre-operative to Peak Post Cardiac Surgery

Filtration marker		N	Filtration marker Range	Death Rate†	HR (95% CI)	
					Model 1	Model 2
Cys C	< 0%	508	−0.57 to 0	47.1	1.0 (referent)	1.0 (referent)
	0% to 25%	449	0 to 0.25	44.7	0.84 (0.71, 0.99)	0.89 (0.75, 1.04)
	≥ 25%	174	0.25 to 2.23	87.9	1.52 (0.99, 2.34)	1.5 (1.07, 2.24)
	Continuous				1.53 (0.60, 3.86)	1.57 (0.70, 3.52)
Cr	< 0%	248	−0.42 to 0	38.0	1.0 (referent)	1.0 (referent)
	0% to 25%	592	0 to 0.25	47.1	1.22 (0.82, 1.81)	1.25 (0.84, 1.86)
	≥ 25%	359	0.25 to 3.5	80.5	1.79 (1.01, 3.16)	1.83 (1.03, 3.23)
	Continuous				2.06 (1.21, 3.51)	2.08 (1.24, 3.51)

†Mortality Rate per 1000 patient years adjusted for site

Model 1: Age (per year), sex, white race, cardiopulmonary bypass time > 120 minutes, non-elective surgery, diabetes, hypertension, center, Heart Failure (HF), Myocardial Infarction (MI), Pre-op urine albumin to creatinine ratio, and Type of surgery (CABG or valve vs. all others).

Model 2: For models with Cys C, Model 1 + pre-op eGFR by CysC.

For models with Cr, Model 1 + pre-op eGFR by Cr

Table 4

Association of Changes in both Cystatin C and Creatinine with Mortality after Discharge

Change in Kidney Marker	N	Death Rates†	Unadjusted (95% CI)	Adjusted HR (95% CI) Model 1	Adjusted HR Model 2
Both < 25%	724	39.9	1.0 (referent)	1.0 (referent)	1.0 (referent)
CysC < 25%; Cr ≥ 25%	233	73.8	1.85 (1.21, 2.83)	1.54 (0.99, 2.39)	1.50 (0.96, 2.34)
CysC ≥ 25%; Cr < 25%	60	91.7	2.3 (1.19, 4.44)	2.16 (1.07, 4.36)	2.20 (1.09, 4.47)
Both ≥ 25%	114	90.4	2.28 (1.36, 3.82)	1.83 (1.06, 3.15)	1.79 (1.03, 3.1)

†Mortality Rate per 1000 patient years adjusted for site

Model 1: Age (per year), sex, white race, cardiopulmonary bypass time > 120 minutes, non-elective surgery, diabetes, hypertension, center, Heart Failure (HF), Myocardial Infarction (MI), Pre-op urine albumin to creatinine ratio, and Type of surgery (CABG or valve vs. all others).

Model 2: Model 1 + Pre-op eGFR by Cys C