Preoperative serum ST2 level predicts acute kidney injury after adult cardiac surgery

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ABSTRACT

Objective: The purpose of this study was to evaluate the relationship between preoperative levels of serum soluble ST2 (ST2) and acute kidney injury (AKI) after cardiac surgery. Previous research has shown that biomarkers facilitate the prediction of AKI and other complications after cardiac surgery.

Methods: Preoperative ST2 proteins were measured in 1498 patients undergoing isolated coronary artery bypass graft surgery at 8 hospitals participating in the Northern New England Biomarker Study from 2004 to 2007. AKI severity was defined using the Acute Kidney Injury Network (AKIN) definition. Preoperative ST2 levels were measured using multiplex assays. Ordered logistic regression was used to examine the relationship between ST2 levels and levels of AKI severity.

Results: Participants in this study showed a significant association between elevated preoperative ST2 levels and acute kidney risk. Before adjustment, the odds of patients developing AKIN stage 2 or 3, compared with AKIN stage 1, are 2.43 times higher (95% confidence interval, 1.86-3.16; $P < .001$) for patients in the highest tercile of preoperative ST2. After adjustment, patients in the highest tercile of preoperative ST2 had significantly greater odds of developing AKIN stage 2 or 3 AKI (odds ratio, 1.99; 95% confidence interval, 1.50-2.65; $P < .001$) compared with patients with AKIN stage 1.

Conclusions: Preoperative ST2 levels are associated with postoperative AKI risk and can be used to identify patients at higher risk of developing AKI after cardiac surgery. (J Thorac Cardiovasc Surg 2018;156:1114-23)

Preoperative ST2 levels and risk of acute kidney injury after cardiac surgery.

Central Message

The development of AKI after cardiac surgery is associated with increased morbidity and mortality. ST2 has been investigated in improving preoperative AKI risk forecasting.

Perspective

Acute kidney injury is a common complication of cardiac surgery and is associated with significant morbidity and mortality. A timely diagnosis would allow for earlier intervention and could improve patient outcomes. Our findings suggest that preoperative ST2 levels are associated with AKI and could potentially be used to identify patients at the highest risk of developing AKI in cardiac surgery.

See Editorial Commentary page 1124.

The development of acute kidney injury (AKI) after cardiac surgery is associated with increased morbidity and mortality. AKI is a common postoperative complication occurring in up to 40% of adult patients who undergo

cardiac surgery.¹⁻³ Identifying patients at increased risk of AKI is important to take preventative measures and counsel patients on potential outcomes after cardiac surgery. Previous research has examined risk factors

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Abbreviations and Acronyms

AKI	= acute kidney injury
AKIN	= Acute Kidney Injury Network
CABG	= coronary artery bypass graft
CHF	= chronic heart failure
CI	= confidence interval
NNE	= Northern New England
NNECDSG	= Northern New England Cardiovascular Disease Study Group
NT-proBNP	= N-terminal prohormone of brain natriuretic peptide
ROC	= receiver operating characteristic
ST2	= serum soluble ST2

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associated with the occurrence of postoperative AKI, largely focusing on preoperative factors,⁴⁻⁷ but also including perioperative risks such as transfusion requirements, bleeding, and low cardiac output.^{1,4-12} Preexisting renal dysfunction, hypertension, diabetes, and other cardiovascular comorbidities have traditionally identified patients at increased risk of AKI after surgery.^{1,4-12}

A sensitive and specific marker of AKI risk could improve risk stratification, potentially identify patients who will benefit from greater care management before surgery, and alert clinicians to individuals who will need earlier interventions to prevent AKI. Although clinical and demographic variables have provided predictive value in identifying these patients, the additional use of specific serum biomarkers might further improve our ability to identify patients at risk of AKI.

Serum soluble ST2 (ST2) is a member of the interleukin-1 receptor family of proteins, which play an important role in the regulation of immune and inflammatory response in the body. In the heart, ST2 has a biological role in the immunological process and is directly involved in a cardiac signaling pathway. Elevated levels of ST2 have been associated with myocardial infarction and volume overloaded hearts and might have a direct, adverse effect on kidney function.¹³⁻¹⁵ Soluble ST2 is an emerging biomarker that has been shown to predict adverse outcomes and death in individuals with established heart failure.¹⁶ ST2 has been investigated in risk stratification of mortality and offers promise in improving preoperative

AKI risk forecasting.^{17,18} The aim of this study was to determine the strength of the ST2 association with AKI after adjusting for traditional risk markers in adults who undergo cardiac surgery.

METHODS**Cohort, Northern New England Biomarker Study**

This study expands on the experience of the Northern New England Cardiovascular Disease Study Group (NNECDSG), a regional collaborative consortium founded in 1987. The NNECDSG captures all coronary revascularizations and/or valve procedures in northern New England including 8 medical centers in Vermont, New Hampshire, and Maine. All hospitals in this consortium submit data on cases with validation of procedure numbers and mortality conducted every 2 years. The NNECDSG registry contains data on patient characteristics, procedural indications, clinical variables, and in-hospital outcomes. Data are periodically validated to ensure that all procedures and end points included in the registry have been accurately assessed. The Northern New England (NNE) Biomarker Study is an initiative designed to assess the role of biomarkers in cardiac surgery.¹⁹

Patient, procedural, and outcome data were collected from patients who underwent isolated coronary artery bypass graft (CABG) surgery at 8 hospitals participating in the NNE Biomarker Study from 2004 to 2007 (n = 1690). For the present study, the sample included patients who underwent emergent, urgent, and nonurgent CABG surgeries. Those who underwent CABG incidental to heart valve repair or replacement, resection of a ventricular aneurysm, or other surgical procedure were not included. We excluded any patients who had preoperative renal failure (n = 17). Only patients who had outcome data and whose biomarker levels collected were retained in the final analyses (n = 1498). The Committee for the Protection of Human Subjects at Dartmouth College (institutional review board) approved this study for the prospective cohort with patient consent as well as the linkage of readmission and mortality events.

AKI

The primary outcome of this study was the development of AKI after cardiac surgery. The change in the last serum creatinine level before sternotomy and highest postoperative serum creatinine level before discharge were used to classify the stage of AKI. AKI stages were defined by the Acute Kidney Injury Network (AKIN) definitions as follows: AKIN stage 1: 0.3 or 50% increase in serum creatinine level from baseline; AKIN stage 2: a twofold increase in serum creatinine; and AKIN stage 3: a threefold or 0.5 increase if the baseline serum creatinine level was at least 4.0 (mg/dL), or new dialysis-dependent renal failure. Because of the small proportion of patients in AKIN stage 2 and 3, we bundled stage 2 or 3 patient outcomes in this report. Urine output was not recorded in this prospective cohort.

Soluble ST2

Preoperative levels of soluble ST2 was the main exposure of interest for this study. Blood samples were preoperatively collected before incision at each participating site in a 10-mL serum tube. Preoperative biomarker levels were measured using custom-made multiplex enzyme linked immunosorbent assays (Meso Scale Discovery, Rockville, Md). Blood was allowed to clot at room temperature for 20 minutes to separate out the red blood cells; the tubes were centrifuged at 3500 rpm for 20 minutes, and the sera stored at the respective medical centers below -80°C until transportation on dry ice to the Laboratory for Clinical and Biomedical Research in Colchester, Vermont where they were stored at -80°C until measurement. Frozen serum was analyzed at a central laboratory, at the same time for biomarker measurement. Biomarkers were linked to the

TABLE 1. Patient characteristics and postoperative AKI occurrence

Characteristic	AKIN Stage			P value
	No AKIN (n = 972)	Stage 1 (n = 447)	Stage 2 or 3 (n = 79)	
Age*	64.0 ± 10.0	67.6 ± 9.9	71.0 ± 9.5	.464
Female sex	231 (23.8%)	100 (22.4%)	21 (26.6%)	.680
BMI*	29.2 ± 5.2	30.3 ± 5.9	30.5 ± 7.1	.464
BSA, m ² *	2.0 ± 0.2	2.1 ± 0.3	2.0 ± 0.3	.464
Smoker	253 (26.1%)	72 (16.1%)	15 (19.0%)	<.001
Atrial fibrillation	51 (5.2%)	40 (9.0%)	9 (11.4%)	.008
CHF	82 (8.4%)	51 (11.4%)	20 (25.3%)	<.001
Last preoperative serum creatinine*	1.1 ± 1.0	1.1 ± 0.4	1.4 ± 0.7	.464
Diabetes	319 (32.8%)	189 (42.3%)	39 (49.4%)	<.001
Ejection fraction <40%	82 (8.9%)	57 (13.2%)	14 (18.9%)	.004
Hypertension	780 (80.2%)	365 (81.8%)	63 (80.8%)	.779
IABP preoperative	31 (3.2%)	22 (4.9%)	8 (10.1%)	.006
Previous MI				
No	580 (59.7%)	229 (51.2%)	33 (41.8%)	.016
<24 h preoperatively	15 (1.5%)	8 (1.8%)	2 (2.5%)	
>24 h and <7 d preoperatively	172 (17.7%)	97 (21.7%)	18 (22.8%)	
>7 d and <365 d preoperatively	82 (8.4%)	53 (11.9%)	13 (16.5%)	
>365 d preoperatively	123 (12.7%)	60 (13.4%)	13 (16.5%)	
Vascular disease	238 (24.5%)	138 (30.9%)	33 (41.8%)	<.001
Unstable angina	533 (55.3%)	245 (55.4%)	47 (59.5%)	.769
COPD	121 (12.4%)	61 (13.6%)	14 (17.7%)	.375
Left main, ≥50% stenosis	324 (33.3%)	148 (33.1%)	36 (45.6%)	.079
Previous CABG	17 (1.8%)	10 (2.3%)	7 (9.1%)	<.001
Previous PCI	197 (20.3%)	75 (16.8%)	22 (27.9%)	.051
Priority				
Emergent	15 (1.5%)	10 (2.2%)	4 (5.1%)	.244
Urgent	657 (67.6%)	303 (67.8%)	54 (68.4%)	
Nonurgent	300 (30.9%)	134 (30.0%)	21 (26.6%)	
Received pRBC units	283 (29.2%)	229 (51.2%)	60 (76.0%)	<.001
Number of pRBC units given preoperatively				
0	955 (98.5%)	433 (96.9%)	79 (100.0%)	.359
1	4 (0.4%)	5 (1.1%)	0 (0.0%)	
2	7 (0.7%)	7 (1.6%)	0 (0.0%)	
3 or more	4 (0.4%)	2 (0.5%)	0 (0.0%)	

AKIN, Acute Kidney Injury Network; BMI, body mass index; BSA, body surface area; CHF, congestive heart failure; IABP, intraoperative balloon pump; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; pRBC, packed red blood cell.

*Mean ± SD.

NNECDSG cohort to conduct the preoperative risk model. Biomarkers were evaluated as continuous variables, log-transformation, and terciles.

Statistical Analysis

We evaluated the ST2 measurements to determine the association with the primary outcome (AKI) using univariate and ordered logistic regression. Postoperative outcomes were compared using the χ^2 tests, and continuous data were compared using the analysis of variance test with the Bonferroni correction. The NNE clinical mortality model was used for risk adjustment.²⁰ To evaluate the association of the biomarker

with AKI outcomes, we divided the cohort into terciles on the basis of ST2 values, where the lowest tercile is the reference group. We included indicator variables for the middle and highest terciles. We used mean imputation replacement method for missing values of continuous variables in the NNE clinical model and assumed that missing values of indicator variables were 0. All biomarker values below the assay's lower quantitative limit were assigned the lower limit of detection. The performance of the risk model was assessed by measuring the total area under the receiver operating characteristic curve (ROC; or c-statistic). Standard errors and 95% confidence intervals (CIs) were estimated for the c-statistic using a bootstrap method. Model discrimination analyses were performed on various

TABLE 2. Patient and patient characteristics according to terciles of preoperative ST2

Characteristic	First tercile	Second tercile	Third tercile	P value
Age*	64.4 ± 10.2	65.6 ± 9.7	66.0 ± 10.5	.464
Female sex	165 (32.1%)	104 (20.1%)	92 (18.2%)	<.001
BMI*	29.3 ± 5.1	30.2 ± 5.8	29.6 ± 5.7	.464
BSA, m ² *	2.0 ± 0.3	2.1 ± 0.3	2.0 ± 0.3	.464
Smoker	138 (26.9%)	99 (19.2%)	111 (21.9%)	.027
Atrial fibrillation	24 (4.7%)	31 (6.0%)	48 (9.5%)	.025
CHF	36 (7.0%)	37 (7.2%)	86 (17.0%)	<.001
Last preoperative serum creatinine*	1.1 ± 1.4	1.1 ± 0.5	1.3 ± 1.0	.464
Diabetes	152 (29.6%)	194 (37.5%)	223 (44.1%)	<.001
Ejection fraction <40%	39 (8.0%)	50 (10.0%)	70 (14.7%)	.012
Hypertension	408 (79.4%)	425 (82.4%)	405 (80.2%)	.461
IABP preoperatively	8 (1.6%)	16 (3.1%)	39 (7.7%)	<.001
Previous MI				
No	328 (63.8%)	299 (57.8%)	240 (47.4%)	<.001
<24 h preoperative	3 (0.6%)	6 (1.2%)	16 (3.2%)	
>24 h and <7 d preoperative	89 (17.3%)	87 (16.8%)	115 (22.7%)	
>7 d and <365 d preoperative	38 (7.4%)	48 (9.3%)	65 (12.8%)	
>365 d preoperative	56 (10.9%)	77 (14.9%)	70 (13.8%)	
Vascular disease	116 (22.6%)	138 (26.7%)	162 (32.0%)	.001
Unstable angina	290 (57.2%)	277 (54.0%)	280 (55.8%)	.644
COPD	59 (11.5%)	60 (11.6%)	80 (15.8%)	.150
Left main, ≥50% stenosis	186 (36.2%)	168 (32.5%)	167 (33.0%)	.282
Previous CABG	14 (2.7%)	12 (2.3%)	9 (1.8%)	.580
Previous PCI	99 (19.3%)	21.5%	18.6%	.110
Priority				
Emergent	7 (1.4%)	10 (1.9%)	13 (2.6%)	.002
Urgent	366 (72.1%)	318 (61.5%)	358 (70.8%)	
Nonurgent	141 (27.4%)	189 (36.6%)	135 (26.7%)	
Received pRBC units	160 (31.1%)	181 (35.1%)	239 (47.2%)	<.001
Number of pRBC units given preoperatively				
0	509 (99.0%)	511 (99.2%)	486 (96.0%)	.001
1	2 (0.4%)	1 (0.2%)	6 (1.2%)	
2	3 (0.6%)	2 (0.4%)	9 (1.8%)	
3 or more	0 (0.0%)	1 (0.2%)	5 (1.0%)	

BMI, Body mass index; BSA, body surface area; CHF, congestive heart failure; IABP, intraoperative balloon pump; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; pRBC, packed red blood cell. *Mean ± SD.

biomarker cut points and serum creatinine values >2 and >1.2 mg/dL to determine an optimal cut point. This process provided sensitivity, specificity, positive predictive values, and negative predictive values for the models.

Secondary Analyses

We sought to adjust for previously studied clinical factors associated with postoperative AKI. We created an additional multivariable model on the basis of the NNE mortality model but adjusted for the following additional covariates: chronic heart failure (CHF), diabetes, lower ejection fraction (<40%), preoperative intra-aortic balloon pump, previous myocardial infarction, vascular disease, previous CABG surgery, and packed red blood cell units received in postoperative AKIN stage 2 to 3

occurrence group. We repeated our logistic and ordered logistic regression analyses using this augmented model.

We also compared the incremental value of ST2 with standard serum creatinine values, adjusting for the NNE preoperative clinical mortality model. We analyzed models first excluding serum creatinine level variables, then including preoperative serum creatinine levels >2 mg/dL and >1.2 mg/dL, and finally including both measures of serum creatinine and ST2 levels. We used the test of equality of ROC areas to assess differences in model performance.

Finally, we created an alternative final multimarker model including preoperative biomarker N-terminal prohormone of brain natriuretic peptide (NT-proBNP) values as well as preoperative ST2, in addition to the base NNE clinical mortality model, to assess the predictive power using a combination of cardiac biomarkers. We compared model performance

using the test of equality of ROC areas. All analyses were conducted using Stata 13.1 (StataCorp, College Station, Tex).

RESULTS

Overall, 525 patients (35.1%) developed AKI within AKIN-defined stage 1 (29.8%) and stage 2 to 3 (5.3%). Patient and procedural characteristics according to AKI outcome are summarized in Table 1. Patient and procedural characteristics according to ST2 terciles are summarized in Table 2. ST2 sample measurements ranged from 0.96 to 94.66 ng/mL with a median (quartile 1 to quartile 3) value of 3.82 ng/mL (2.87-5.17 ng/mL). Patients with higher preoperative serum ST2 were more likely to be older and male, to be a smoker, to have congestive heart failure (CHF), diabetes, peripheral vascular disease, and were more likely to have had previous CABG surgery. There was a significant association between elevated preoperative ST2 levels and development of AKI ($P < .001$). For patients in the lowest tercile of ST2, 22.5% experienced stage 1 AKI compared with 35.6% in the highest biomarker tercile. Similarly, for patients in the highest tercile, 4.1% were classified as stage 3 AKI compared with 1.0% in the lowest tercile. There was a stepwise result of risk of postoperative AKI and elevated preoperative ST2 after cardiac surgery (Figure 1). The distribution of continuous ST2 and association with AKI is represented as a kernel density plot in Figure 2.

Table 3 shows the crude and adjusted results for the AKI risk model and preoperative ST2 biomarker terciles. Before adjustment, the odds of patients developing postoperative AKIN stage 2 or 3, compared with AKIN stage 1, were 2.43 times higher (95% CI, 1.86-3.16; $P < .001$) for patients in the highest tercile of preoperative ST2. After adjustment, patients in the highest tercile had 1.99 greater odds of developing AKIN stage 2 or 3 AKI (95% CI, 1.50-2.65; $P < .001$), compared with developing AKIN stage 1.

Our preoperative model resulted in a ROC of 0.66 (95% CI, 0.63-0.69), summarized in Table 4. In our augmented model, the addition of clinical factors CHF, diabetes, ejection fraction, preoperative intra-aortic balloon pump, previous myocardial infarction, vascular disease, previous

FIGURE 1. The association of elevated preoperative ST2 levels and patients who developed acute kidney injury (AKI) after cardiac surgery. ST2, Serum soluble ST2; AKIN, Acute Kidney Injury Network.

FIGURE 2. Kernel density plot of continuous serum soluble ST2 (ST2) measurements and acute kidney injury (AKI). AKIN, Acute Kidney Injury Network.

CABG surgery, and packed red blood cell use to our preoperative model resulted in an improved ROC of 0.66 to 0.68 for preoperative ST2 terciles ($P = .013$; 95% CI, 0.65-0.71). When we included postoperative ST2 values to the augmented model, our model improved significantly from ROC 0.66 to 0.72 ($P = .002$; 95% CI, 0.68-0.75; Table 4).

We did not observe any significant difference in comparing the predictive ability of our preoperative model when we included preoperative serum creatinine >2 mg/dL and serum creatinine >1.2 mg/dL. We also did not observe any difference in model prediction when we excluded serum creatinine levels. These models are listed in Tables 5 and 6. We compare the discriminatory power of preoperative serum creatinine and ST2 in predicting postoperative AKI in Tables 7 and 8. Postoperative characteristics and complications by terciles of ST2 and AKI status are described in Tables E1 and E2.

In our alternative final model, the addition of NT-proBNP resulted in an ROC improvement to 0.68 ($P < .001$). We see

TABLE 3. Unadjusted and adjusted ordered logistic regression models with preoperative ST2 measurements and association with AKI severity

ST2	Unadjusted		Adjusted*	
	OR (95% CI)	P value	OR (95% CI)	P value
Continuous	1.02 (1.00-1.04)	.015	1.02 (1.00-1.03)	.042
Natural log	1.76 (1.45-2.14)	<.001	1.57 (1.29-1.91)	<.001
Terciles				
1	REF		REF	
2	1.76 (1.34-2.30)	<.001	1.63 (1.22-2.16)	.001
3	2.43 (1.86-3.16)	<.001	1.99 (1.50-2.65)	<.001

ST2, Serum soluble ST2; OR, odds ratio; CI, confidence interval; REF, reference.

*Model adjusts for variables included in the NNE mortality model.

TABLE 4. Augmented ordered regression model evaluating preoperative ST2 measurements and development of acute kidney injury after cardiac surgery

ST2	Base NNE mortality model	Augmented NNE model*		Augmented NNE model with postoperative values	
	C-statistic (95% CI)	C-statistic (95% CI)	P value†	C-statistic (95% CI)	P value†
Continuous	0.66 (0.63-0.69)	0.66 (0.63-0.69)	.252	0.67 (0.64-0.71)	.221
Natural log	0.66 (0.63-0.69)	0.67 (0.65-0.70)	.013	0.69 (0.65-0.72)	.031
Terciles	0.66 (0.63-0.69)	0.68 (0.65-0.71)	.013	0.69 (0.66-0.72)	.030

ST2, Serum soluble ST2; NNE, Northern New England; CI, confidence interval. *Augmented NNE mortality model includes clinical factors: CHF, previous MI, preoperative IABP, and postoperative pRBC units received. †ROC comparison with NNE base model.

the inclusion of NT-proBNP significantly improves the discrimination of AKI preoperatively. Results from this model are listed in Table 6. The distribution of cases, according to hospital, are shown in Figure 3.

DISCUSSION

In this cohort study of adult patients who underwent cardiac surgery we showed a significant association of the protein soluble biomarker ST2 and postoperative AKI. The odds of patients developing postoperative AKIN stage 2 or 3, compared with AKIN stage 1, was nearly 2 times greater for patients in the highest tercile of preoperative ST2. To our knowledge, we are the first to show a significant association of elevated levels of ST2 as a prognostic indicator of AKI after cardiac surgery.

Recent research has shown that natriuretic peptides are particularly useful as diagnostic markers of heart failure and for the risk-stratification of patients.¹³ ST2 is independent of natriuretic peptide levels and thus might add additional predictive value that is not conflated with natriuretic peptide values. Soluble ST2 is a novel indicator

of fibrosis that reflects cardiac dysfunction such as remodeling or postinjury scarring.^{14,15} ST2 is also a recognized biomarker that signals the presence and severity of adverse cardiac events including myocardial infarction, acute coronary syndrome, and worsening heart failure. Aldous et al reported that for patients with a primary outcome of death, heart failure, acute myocardial infarction, arrhythmia, or stroke, all had statistically higher median values of ST2 compared with those who did not have events.²¹

Transient increase of ST2 has been reported after myocardial infarction in mice subjected to coronary artery ligation.²² Increased levels of ST2 have been reported in the circulation of patients 1 day after acute myocardial infarction and correlated positively with creatine kinase.²² Additionally, studies have shown that high baseline levels of ST2 predicted congestive heart failure and mortality in patients with acute myocardial infarction at 30 days. To our knowledge, our study is the first to establish ST2 as an independent predictor of AKI among CABG patients in a large cohort of cardiac surgery patients.

TABLE 5. Assessing the incremental value of preoperative and postoperative ST2 and serum creatinine in predicting postoperative AKI

Model statistics	C-statistic (95% CI)	Comparison with NNE mortality model without serum creatinine variables		Comparison with NNE mortality model		Comparison with NNE mortality model with serum creatinine variables		
		P value	IDI (95% CI)	P value	IDI (95% CI)	P value	IDI 95% CI	P value*
Preoperative continuous	0.66 (0.63-0.69)	.066	0.01 (0.00-0.02)	.180	0.00 (0.00-0.01)	.152	0.00 (0.00-0.01)	.269
Postoperative continuous	0.70 (0.67-0.73)	.000	0.06 (0.04-0.08)	.001	0.05 (0.03-0.06)	.000	0.05 (0.03-0.06)	.269
Pre- to postoperative absolute difference	0.70 (0.66-0.73)	.000	0.06 (0.04-0.07)	.001	0.05 (0.03-0.06)	.000	0.05 (0.03-0.06)	.269
Preoperative natural log	0.67 (0.65-0.70)	.004	0.02 (0.01-0.03)	.011	0.01 (0.01-0.02)	.000	0.01 (0.01-0.02)	.269
Postoperative natural log	0.70 (0.67-0.73)	.000	0.06 (0.04-0.07)	.001	0.05 (0.03-0.06)	.000	0.05 (0.03-0.06)	.269
Pre- to postoperative log difference	0.68 (0.64-0.71)	.025	0.03 (0.02-0.04)	.089	0.02 (0.01-0.03)	.000	0.02 (0.01-0.03)	.269
Preoperative terciles	0.68 (0.65-0.71)	.005	0.02 (0.02- 0.03)	.014	0.02 (0.01-0.02)	.000	0.01 (0.01-0.02)	.269
Postoperative terciles	0.69 (0.66-0.73)	.001	0.05 (0.03-0.06)	.004	0.04 (0.02-0.05)	.000	0.03 (0.02-0.05)	.269
Pre- to postoperative terciles	0.69 (0.66-0.72)	.002	0.04 (0.03-0.06)	.009	0.03 (0.02-0.04)	.000	0.03 (0.02-0.04)	.269
Pre- to postoperative log difference terciles	0.68 (0.65-0.71)	.014	0.03 (0.02-0.04)	.053	0.02 (0.01-0.02)	.000	0.02 (0.01-0.02)	.269

CI, Confidence interval; NNE, Northern New England; IDI, integrated discrimination improvement. *ROC comparison against base model.

TABLE 6. A multimarker model that includes preoperative ST2 and NT-proBNP biomarkers in improving prediction of postoperative AKI

Preoperative ST2	Base model	Base model with preoperative ST2 and preoperative NT-proBNP		
	C-statistic (95% CI)	C-statistic (95% CI)	P value†	P value*
Continuous	0.66 (0.63-0.69)	0.68 (0.65-0.70)	.000	.000
Natural log	0.66 (0.63-0.69)	0.69 (0.66-0.72)	.001	.039
Terciles	0.66 (0.63-0.69)	0.69 (0.66-0.71)	.002	.091

ST2, serum soluble ST2; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; CI, confidence interval. *P value (ROC comparison against base model with preoperative ST2 biomarker). †P value (ROC comparison against base model only).

Therefore, our study continues to extend the predictive ability of ST2 from exclusively cardiovascular outcomes to renal functioning outcomes. Future investigations should continue to explore the association between ST2 with cardiovascular as well as renal outcomes at the cellular level to determine the ways in which ST2 interacts with the kidney (Video 1).

Comment

Most renal and AKI risk models are static and do not currently consider biomarkers other than creatinine.^{23,24}

Changes in serum creatinine commonly lag behind important clinical changes, making it a suboptimal marker. Although previously overlooked, small changes in serum creatinine and renal dysfunction—which exhibit a dose-dependent effect on mortality, morbidity, length of stay, readmissions, and costs associated with adult cardiac surgery—are increasingly scrutinized and studied.²⁵⁻³⁰ The importance of renal dysfunction as a postoperative complication is emphasized by the fact that acute renal failure has the highest rate of failure to rescue of the major complications associated with CABG surgery.³¹

TABLE 7. Comparing the discriminatory power of preoperative serum creatinine, various cut points of preoperative serum soluble ST2, and postoperative serum soluble ST2 in the prediction of postoperative AKI

	PPV	NPV	Sensitivity	Specificity
Preoperative continuous	30.77	64.85	0.76	99.07
Postoperative continuous	57.94	67.30	18.16	92.74
Pre- to postoperative absolute difference	59.50	67.36	17.91	93.29
Preoperative natural log	43.33	65.23	4.94	96.50
Postoperative natural log	56.00	67.62	20.90	90.96
Pre- to postoperative log difference	59.09	64.95	3.23	98.77
Preoperative above median	—	64.89	0.00	100.00
Postoperative above median	—	64.49	0.00	100.00
Above median of pre- to postoperative absolute difference	—	64.49	0.00	100.00
Above median of pre- to postoperative log difference	—	64.49	0.00	100.00
Preoperative terciles	—	64.89	0.00	100.00
Postoperative terciles	—	64.49	0.00	100.00
Terciles of pre- to postoperative absolute difference	—	64.49	0.00	100.00
Terciles of pre- to postoperative log difference	—	64.49	0.00	100.00
Preoperative quartiles	—	64.89	0.00	100.00
Postoperative quartiles	52.13	70.00	36.57	81.51
Quartiles of pre- to postoperative absolute difference	51.44	69.67	35.57	81.51
Quartiles of pre- to postoperative log difference	—	64.49	0.00	100.00
Preoperative quintiles	—	64.89	0.00	100.00
Postoperative quintiles	52.65	68.76	29.60	85.34
Quintiles of pre- to postoperative absolute difference	52.23	68.61	29.10	85.34
Quintiles of pre- to postoperative log difference	—	64.49	0.00	100.00
Preoperative serum creatinine >2.0	69.70	65.67	4.37	98.97
Preoperative serum creatinine >1.2	—	64.89	0.00	100.00

PPV, Positive predictive value; NPV, negative predictive value.

TABLE 8. Assessing the incremental value of preoperative ST2 and serum creatinine in predicting postoperative AKI

	Base model	Comparison with NNE mortality model without any serum creatinine variables			Comparison with NNE mortality model		
	ROC (95% CI)	P value	IDI	IDI 95% CI	P value	IDI	IDI 95% CI
NNE mortality model without serum creatinine variables	0.66 (0.63-0.68)						
NNE mortality model	0.66 (0.63-0.69)	.213	0.01	0.00 to 0.01			
NNE mortality model with serum creatinine variables	0.66 (0.63-0.69)	.105	0.01	0.00 to 0.02	.302	0.00	0.00 to 0.00

ST2, serum soluble ST2; AKI, acute kidney injury; NNE, Northern New England; ROC, receiver operating characteristic; CI, confidence interval; IDI, integrated discrimination improvement.

Biomarkers offer considerable promise in AKI risk detection and assessment. Biomarkers might allow for earlier use of mitigation tactics (such as avoidance or delay of surgery, alteration in hemodynamic goals, and avoidance of potentially nephrotoxic medications). Personalized medicine might allow the physician to provide a better therapy for patients in terms of efficiency, safety, and treatment length to reduce the associated costs. Biomarker sampling should be used routinely to improve identification of patients at higher risk of AKI before cardiac surgery. Patient care management modifications can be made subsequent to patient stratification, including modifying perfusion practices and timing of surgery, can reduce the risk of AKI. Formal risk prediction of patients who undergo CABG surgery using a routinely assessed biomarker, along with routinely collected clinical information, has been shown to be cost-effective.³²

Biomarkers for AKI risk assessment have been categorized as renal, cardiac, or general, and might be found in blood or urine.³³ Cardiac biomarkers such as troponin and brain natriuretic peptide have been

investigated and used to enhance preoperative risk assessment (including AKI).^{34,35} Similarly, the novel cardiac biomarker ST2 is a blood protein, which acts as a decoy receptor for interleukin-33 and is increased in myocardial infarction and volume-overloaded hearts.³⁶ ST2 has been investigated in risk stratification of mortality independent of brain natriuretic peptide and offers promise in improving preoperative AKI risk forecasting. On the basis of our study, the combination of NT-proBNP and ST2 proves to be a helpful adjunct to existing risk models to identify individuals who are likely to develop post-cardiac surgery AKI.

The primary strength of this study is the large sample size comprised of patients who underwent cardiac surgery at multiple hospitals across Maine, Vermont, and New Hampshire. Studies on preoperative biomarker levels and prediction of AKI has been previously conducted with small cohorts, in single-center settings, with a lack of defined, explicit outcomes.²¹ We leveraged the NNECDSG registry for this study, which is comprehensive in the patient and procedural data that it contains. The completeness and

FIGURE 3. Distribution of number of cases according to hospital.

Preoperative Serum ST2 Levels Predicts Acute Kidney Injury After Adult Cardiac Surgery

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VIDEO 1. The video provides a brief synopsis of the ST2 AKI findings, importance, and recommendations for surgical care teams how to act upon elevated ST2 levels known before cardiac surgery. Video available at: [https://www.jtcvs.org/article/S0022-5223\(18\)30940-1/fulltext](https://www.jtcvs.org/article/S0022-5223(18)30940-1/fulltext).

quality of the data help ensure that adequate adjustment was performed.

AKI is a frequent postoperative complication and occurs in up to 40% of adults after cardiac surgery, with 1% to 5% needing dialysis, in whom the mortality rate reaches 80%.³⁷ The development of AKI after cardiac surgery has been well studied in the past and is associated with poor outcomes and elevated mortality in patients. Although our data are from 2004 to 2007, AKI after cardiac surgery remains highly prevalent.³⁸ Improved prediction of postoperative AKI should be of great interest to cardiac surgeons, caregivers, and patients, because it might allow for improved care management for patients.

Several limitations should be considered in the interpretation of our data. First, we lacked detailed information on some conditions known to affect the incidence of AKI including cardiopulmonary bypass times, hemodynamics, or the use of inotropic and vasoactive drugs in the perioperative period. Therefore, residual confounding of the demonstrated association of ST2 with AKI cannot be excluded. The association we showed after adjusting for many known risk markers of AKI and the remaining effect size suggest that these unavailable variables would be unlikely to explain the full effect we observed. Second, we also used creatinine-based definitions for AKI, which are relatively insensitive and nonspecific in the period directly after injury to the kidney. Finally, the multiple imputation method used to address missing data might influence the overall composition and performance of the model.

CONCLUSIONS

This study showed a significant relationship between protein-soluble biomarker ST2 and AKI severity in patients who undergo cardiac surgery. Our findings suggest that preoperative ST2 levels are associated with AKI and could potentially be used to identify patients at the highest risk of developing AKI in cardiac surgery.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: acute kidney injury, ST2, cardiac surgery, biomarkers

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FIGURE E1. Patient flow diagram. *NNE*, Northern New England; *AKI*, acute kidney injury.

TABLE E1. Postoperative complications according to terciles of preoperative ST2

Complication	First tercile	Second tercile	Third tercile	<i>P</i> value*
Length of stay†	7 (6, 10)	7 (6, 10)	8 (6, 13)	.000
Stroke intra- or postoperatively	0.39%	2.50%	2.90%	.007
Transient ischemic attack postoperatively	0.58%	0.19%	0.19%	.445
Return to OR for bleeding	1.74%	0.77%	1.93%	.252
Mediastinitis/sternal dehisc requiring repeat surgery				
No	100.00%	98.84%	98.46%	.104
Yes, in-hospital	0.00%	0.96%	1.16%	
Yes, postdischarge	0.00%	0.19%	0.39%	
Postoperative leg wound infection	0.19%	1.16%	1.35%	.108
Postoperative pneumonia	0.97%	2.50%	3.47%	.026
New postoperative atrial fibrillation	18.22%	22.16%	22.78%	.149
Low output failure intra-/postoperative	4.13%	6.67%	8.46%	.018
	6.98%	7.32%	17.76%	<.001

OR, Odds ratio; *dehisc*, dehiscence. *Nonparametric test of trend was used for the continuous variable. †Median (25th percentile, 75th percentile).

TABLE E2. Postoperative characteristics according to AKI status

Characteristic	No AKI	AKI	P value*
Status at discharge	0.31%	4.18%	<.001
Length of stay†	7 (5, 10)	9 (7, 14)	.000
Stroke intra- or postoperatively	1.23%	2.85%	.025
Transient ischemic attack postoperatively	0.41%	0.19%	.478
Return to OR for bleeding	1.03%	2.28%	.054
Mediastinitis/Sternal dehisc requiring repeat surgery			
No	99.59%	98.10%	.005
Yes, in-hospital	0.21%	1.71%	
Yes, post-discharge	0.21%	0.19%	
Postoperative leg wound infection	0.51%	1.71%	.022
Pneumonia postoperatively	0.82%	4.94%	<.001
New postoperative atrial fibrillation	16.15%	30.42%	<.001
Low output failure intra/postoperatively	4.30%	9.25%	<.001

AKI, Acute kidney injury; OR, odds ratio; *dehisc*, dehiscence. *Nonparametric test of trend was used for the continuous variable. †Median (25th percentile, 75th percentile).