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Improving The Prediction Of Long-term Readmission And Mortality Using A Novel Biomarker Panel

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Abstract

Objective.—Several short-term readmission and mortality prediction models have been developed using clinical risk factors or biomarkers among patients undergoing coronary artery bypass graft (CABG) surgery. The use of biomarkers for long-term prediction of readmission and mortality is less well understood. Given the established association of cardiac biomarkers with short-term adverse outcomes, we hypothesized that 5-year prediction of readmission or mortality may be significantly improved using cardiac biomarkers.

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Materials and Methods.—Plasma biomarkers from 1,149 patients discharged alive after isolated CABG surgery from eight medical centers were measured in a cohort from the Northern New England Cardiovascular Disease Study Group (NNE) between 2004 and 2007. We assessed the added predictive value of a biomarker panel with a clinical model against the clinical model alone and compared the model discrimination using the area under the receiver operating characteristic (AUROC) curves.

Results.—In our cohort, 461 (40%) patients were readmitted or died within 5 years. Long-term outcomes were predicted by applying the STS ASCERT clinical model with an AUROC of 0.69. The biomarker panel with the clinical model resulted in a significantly improved AUROC of 0.74 (p-value<0.0001). Across 5 years, the hazard ratio for patients in the second to fifth quintile predicted probabilities from the biomarker augmented STS ASCERT model ranged from 2.2 to 7.9 (p-values<0.001).

Conclusions.—We report that a panel of biomarkers significantly improved prediction of long-term readmission or mortality risk following CABG surgery. Our findings suggest biomarkers help clinical care teams better assess the long-term risk of readmission or mortality.

Keywords

CABG; biomarkers; risk prediction; cardiac surgery

Introduction

Hospital readmission after coronary artery bypass graft surgery (CABG) is common and is often associated with increased mortality. The 30-day all-cause readmission rate among CABG patients exceeds 17%.¹ Readmitted CABG patients have a 10-fold higher likelihood of experiencing in-hospital mortality compared to their non-readmitted counterparts.² Prior studies have documented improved prediction of readmission or mortality when using biomarkers collected during the index admission, including: soluble suppression of tumorigenicity 2 (ST2), Galectin-3, N-terminal pro-brain natriuretic peptide (NT-proBNP), Cystatin-C, Interleukin-6 (IL-6), and Interleukin-10 (IL-10).^{3–6}

The pathophysiological mechanisms underpinning the association between biomarkers and readmission or mortality have been previously described.^{3,4,7–10} For instance, soluble ST2 is a protein up-regulated by cardiac myocytes in response to mechanical strain. Its transmembrane and cellular forms have cardioprotective properties when binding with interleukin-33, and soluble ST2 downregulates the process acting like a scavenger receptor.^{11,12} Galectin-3, produced by activated cardiac macrophages, may be directly involved in impairing cardiac function and predictive of readmission and death.¹³ Upregulation of NT-proBNP occurs in direct response to myocardial injury and other heart failure issues.¹⁴ It has been demonstrated that elevated levels of NT-proBNP and ST2 are associated with increased risk of one-year mortality.¹⁵ Cystatin-C, the cysteine proteinase inhibitor, has been established over the previous decade as a biomarker for heart failure risk with a measurable association at increasing levels and has been associated, alone and along with a panel of other biomarkers, with mortality from 30 days and up to 5 years.^{16,17}

Novel and clinically available biomarkers are likely significant predictors of readmission and mortality and have the potential to improve risk models.^{8,18}

There is a growing interest in the clinical utility of biomarkers in predicting long-term cardiovascular outcomes.^{1,2} Biomarkers have significant predictive value in heart failure (HF) and may also be used to identify patients at the highest risk of readmission and subsequent death after CABG. However, few studies have evaluated the relationship between cardiac biomarkers and hospital readmission or mortality in CABG patients, particularly for long-term prediction. We hypothesize that the addition of a pre and postoperative biomarker panel to clinical characteristics can help delineate higher risk patients and their potential long-term outcomes and complications following CABG.

Materials and Methods

Study Population: Northern New England Biomarker Study

The Northern New England (NNE) Biomarker Study is an initiative designed to assess the role of biomarkers in cardiac surgery.^{11–15} This study uses datasets from eight medical centers in Vermont, New Hampshire and Maine in the NNE Cardiovascular Study Group. Patients undergoing CABG surgery at any of eight participating hospitals were prospectively enrolled into the NNE Biomarker Study from 2004 to 2007 (N = 1,690). We excluded 39 patients who experienced in-hospital deaths, resulting in a total of 1,651 patients. Of the remaining patients, 1,149 individuals had all preoperative and postoperative biomarkers for inclusion in our modeling analysis. The Committee for the Protection of Human Subjects at Dartmouth College approved this study.

Primary Outcome: Long-term Survival or Readmission

The study outcome is all-cause readmission or mortality within 5 years following CABG surgery. The sample is restricted to patients who had at least 5 years of complete follow-up. A composite endpoint was used due to the limited number of events. This outcome was measured among patients who were discharged alive after isolated CABG surgery, therefore excluding in-hospital mortality from the study outcome.

Readmission and mortality status were ascertained through the national death index and state all-payer claims. The NNE cohort was linked to state all-payer in-patient claims using name, sex, social security number, date of birth, and residence at the time of surgery. Maine and Vermont completed linkage internally before releasing the data. We used probabilistic linking for New Hampshire all-payer in-patient claims. We achieved complete ascertainment for Vermont, and Maine.

Biomarker Data Collection

Pre and postoperative biomarkers ST2, Galectin-3, NT-proBNP, Cystatin-C, IL-6, and IL-10 were the main exposures of interest in this study. We collected biomarker samples preoperatively prior to incision at each participating site and the postoperative samples (10mL) were collected approximately 24 hours after patient surgery. Pre and postoperative biomarkers were measured using custom made multiplex ELISA assays (Meso Scale

Discovery, Rockville, MD). Blood samples were stored at room temperature for 20 minutes to allow clotting and separation. Tubes were centrifuged at 3500 rpm for 20 minutes. Resulting sera samples were stored at the respective medical centers below -80°C until transportation on dry ice to the University of Vermont Laboratory for Clinical and Biochemical Research in Colchester, Vermont. Samples were then stored at -80°C until measurement where they were analyzed for measurement.

Statistical Analysis

Patient, clinical, and procedural characteristics were compared using chi-square tests and continuous data were compared between groups using the student's t-test or Wilcoxon Rank-Sum tests, when appropriate. A multivariable logistic regression model was fit to measure the association between pre and postoperative biomarkers and a composite endpoint of readmission or mortality. Adjustment was carried out using covariates used in the American College of Cardiology Foundation-Society of Thoracic Surgeons (STS) Collaboration on the Comparative Effectiveness of Revascularization Strategy (ASCERT) Long-Term Survival Probability Calculator.¹⁹ This model corrects for age, sex, body mass index, preoperative intra-aortic balloon pump, preoperative myocardial infarction, prior CABG, prior percutaneous intervention, smoking status, atrial fibrillation, unstable angina, history of congestive heart failure, ejection fraction, left main stenosis $> 50\%$, hypertension, diabetes, vascular disease, COPD, preoperative serum creatinine, and emergent and urgent priority status.

The biomarker panel included in the augmented model were pre and postoperative biomarkers ST2, Galectin-3, NT-proBNP, Cystatin-C, IL-6, and IL-10. Patients were stratified by pre-and postoperative biomarker levels by tercile. Readmission was evaluated using a competing risks regression accounting for mortality. The discriminating ability of the regression model was assessed by the C-statistic, which is the area under the receiver operating characteristic (AUROC) curve.¹⁶ The net reclassification index (NRI) was also calculated.

Kaplan-Meier and Cox proportional hazard regression techniques were used to conduct a time-to-event analysis. Patients were categorized into quintiles of predicted risk from the augmented model. We assessed the model's discriminative ability by plotting predicted risk of readmission or mortality. We conducted a sensitivity analysis to determine any collinearity among the biomarkers (Appendix Table 1). All analyses were conducted using Stata 14.1 (College Station, TX).

Results:

Patient, clinical, and procedural characteristics by 5-year readmission or mortality status is described in Table 1. Out of the 1,149 patients included in the study, 40.1% ($n = 461$) experienced readmission or mortality within 5-years after surgery. Patients who experienced readmission or mortality by 5-years were significantly older and were more likely to have a history of myocardial infarction, lower ejection fraction values, atrial fibrillation, congestive heart failure, and higher BMI compared to patients without an event.

Patient clinical conditions and biomarker distributions are described in Tables 2 and 3. We found that preoperative clinical conditions CHF, renal failure, emergent status, prior MI, smoking status, and the use of an intra-aortic balloon pump are significantly associated with pre and postoperative biomarkers. We also found that postoperative clinical conditions intubation, atrial fibrillation, inotropic support and increased creatinine levels are also significantly associated with elevated biomarkers.

Long-term Readmission or Mortality

Preoperative—1,149 patients had complete pre and postoperative biomarkers and were included in the predictive modeling analysis. Before adjustment, elevated preoperative levels of ST2, Galectin-3, Cystatin-C, NT-proBNP, IL-6 and IL-10 demonstrated significantly greater odds of readmission or mortality 5-years following surgery. After adjustment, CABG patients with preoperative levels of NT-proBNP in the third tercile were 59% more likely to experience readmission or mortality compared to patients within the first tercile of NT-proBNP levels (OR 1.59, 95 % CI 1.02, 2.46) (Table 4).

Postoperative—Before adjustment, elevated postoperative levels of ST2, Galectin-3, Cystatin-C, NT-proBNP, IL-6 and IL-10 were significantly associated with greater odds of readmission or mortality 5-years after surgery. After adjustment, CABG patients with postoperative levels of Cystatin-C in the third tercile were 84% more likely to experience readmission or mortality compared to patients within the lowest tercile of Cystatin-C levels (OR 1.84, 95 % CI 1.15, 2.95) (Table 4)

Figure 1 illustrates the added statistically significant predictive value of the augmented clinical model with the biomarker panel (AUROC of 0.74; 95%CI: 0.71–0.76) compared to the clinical model alone ($p = <0.001$). This finding suggests the biomarkers significantly improve the ability to discriminate between adults with and without readmission or mortality at 5-years. The added predictive value of preoperative and postoperative biomarkers was additionally supported by a NRI value of 0.07 (p -value: 0.007).

We plotted quintiles of predicted values from the augmented model using Kaplan-Meier and Cox's proportional hazards regression. (Figure 2). Across 5 years, the hazard ratio for patients in the second to fifth quintile predicted probabilities from the biomarker augmented STS ASCERT model ranged from 2.2 to 7.9 (p -values <0.001).

Discussion

Hospital readmission after CABG surgery is common and often correlated with increased mortality. In addition to clinical and demographic variables, theoretical and empirical evidence suggests that biomarkers offer additional utility in predicting readmission and mortality events. Our findings demonstrate that elevated levels of pre and postoperative NT-proBNP, ST2, IL-6, IL-10, Cystatin-C and Galectin-3 are associated with increased risk of long-term readmission or mortality following CABG surgery. After controlling for established confounders, CABG patients with elevated preoperative NT-proBNP and postoperative Cystatin-C levels remained significantly more likely to experience readmission or mortality than patients with normal biomarker levels. The addition of a pre and

postoperative biomarker panel (ST2, Galectin-3, Cystatin-C, NT-proBNP, IL-6 and IL-10) with the modified STS ASCERT clinical model resulted in significantly improved prediction of readmission or mortality 5 years after CABG surgery.

The current study, along with previous studies, have linked elevated NT-proBNP biomarkers to adverse outcomes after CABG surgery.^{4,20} Preoperative NT-proBNP has been found to be associated with lower postoperative functional class, perioperative myocardial infarction, short- and long-term mortality.^{21–23} Viholm et al. discovered elevated levels of preoperative NT-proBNP to be associated with 5-year mortality after CABG surgery, which reflect the current study findings.²³ After adjustment, the current study did not find a significant association between postoperative NT-proBNP and 5-year readmission or mortality. This relationship has been identified in the literature with the outcomes of 1-year readmission and 1-year mortality after CABG surgery.^{4,21}

Cystatin-C is an established biomarker used among heart failure patients to predict the risk of short- and long-term all-cause mortality and rehospitalization.^{24–26} Cystatin-C is also a novel renal function measure sensitive at detecting acute renal insufficiency.^{15,27} Although less is known about the use of Cystatin-C in predicting adverse events after CABG surgery, a few studies have observed this relationship because decreased kidney function is associated with adverse cardiovascular outcomes.^{27,28} Estimated glomerular filtration rates calculated from Cystatin-C levels have been found to be independently associated with acute renal insufficiency in diabetic patients and long-term mortality after CABG surgery.^{27,28} Future studies that observe the predictive ability of the Cystatin-C biomarker in forecasting renal function and the impact on survival among CABG surgical patients are warranted.

The use of multiple biomarkers or a biomarker panel may assist clinical care teams with discharge planning, readiness and in evaluating the risk of long-term readmission or mortality. As novel biomarker assays become routinely available in clinical laboratories, the integration of novel biomarker risk information into prediction algorithms for readmission, mortality, and other endpoints will become more seamless.

Study Strengths and Limitations

This is an observational study of regional data that used a multicenter, prospective cohort to demonstrate the added value of pre and postoperative cardiac biomarkers in predicting long-term readmission and mortality following CABG. This study benefited from observing a relatively large sample of CABG patients over a long follow-up period (i.e., 5 years). Although regional datasets can impact generalizability of study findings, homogeneous demographics could reduce the impact of potential confounding bias.

Despite a major strength of the study being the use of six pre and postoperative biomarkers, the panel did not include all biomarkers shown to have an epidemiologic relationship with adverse outcomes among CABG patients. Amin et al, found early elevated Troponin-I levels to be significantly associated with 4-year death or reinfarction after CABG surgery.²⁹ Beller et al. also found preoperative Troponin-I levels to be associated with adverse outcomes (including mortality) following CABG, but this association was nullified after STS risk

adjustment.³⁰ If Troponin-I was observed in the current study, we would have likely found a significant association between the biomarker and readmission or mortality but this relationship would likely be attenuated after adjusting for the modified STS ASCERT clinical model.

Another study limitation is the age of the dataset, which cannot be addressed via design or analytic methods. Although this analysis occurred eight years after study follow-up, our rates of readmission or mortality were comparable to other studies with more recently collected data.^{31–34} Lella et al reported that 36% of patients experienced rehospitalization or mortality approximately 14 months after CABG or valve procedures. Chang et al pulled data from three multicenter trials that followed CABG patients for an average of 4.3 years and found that 38.3% experienced all-cause mortality or repeat revascularization. A systematic review of randomized control trials found that 9.2% of patients experienced 5-year all-cause mortality after hospital discharge following CABG surgery.³⁵ Hu et al reported the rate of 5-year readmission due to major adverse cardiac events after CABG surgery to be 30.1%. Our composite endpoint of 5-year all-cause readmission or death after CABG surgery was 40%, similar to other peer reviewed publications.

Conclusion

The addition of novel biomarkers to the clinical models highlights an important signal between biomarker activity and time to readmission or mortality. Our findings indicate that these biomarkers can be used to identify patients at increased risk of readmission and death after CABG; therefore, biomarkers may facilitate strategies of personalized medicine in patients undergoing cardiac surgery.

Acknowledgments and Disclosures

Our authors have nothing to disclose.

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Data Availability:

De-identified data can be made available upon request, contingent on user obtaining required approval and a data use agreement with the nncdsg.org

Appendix

Table 1.

Correlation matrix of biomarkers

Preoperative						
	ST2	Galectin-3	NT-proBNP	IL-6	Cystatin-C	IL-10
ST2	1.00					

Galectin-3	0.071	1.00				
NT-proBNP	0.236	0.144	1.00			
IL-6	0.193	0.069	0.322	1.00		
Cystatin-C	0.169	0.231	0.339	0.236	1.00	
IL-10	0.191	0.133	0.182	0.208	0.179	1.00
Postoperative						
	ST2	Galectin-3	NT-proBNP	IL-6	Cystatin-C	IL-10
ST2	1.00					
Galectin-3	0.071	1.00				
NT-proBNP	0.236	0.144	1.00			
IL-6	0.193	0.069	0.322	1.00		
Cystatin-C	0.169	0.231	0.339	0.236	1.00	
IL-10	0.191	0.133	0.182	0.208	0.179	1.00

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Figure 1.

Receiver Operating curve comparison for the base clinical model (dotted line) vs the model augmented with the biomarker panel (solid line) to predict readmissions and mortality. The augmented model had a statistically significant added predictive value compared to the clinical model alone (p value: <0.001).

Figure 2.

Kaplan-Meier survival curve for the augmented biomarker panel model split into quintiles of predicted probabilities. Across 5 years, the hazard ratio for patients in the second to fifth quintile predicted probabilities from the biomarker augmented STS ASCERT model ranged from 2.2 to 7.9 (p-values<0.001).

Table 1.

Characteristics of patients who have undergone coronary artery bypass graft surgery (n = 1,149).

	5-year Readmission or Mortality		P value
	Yes N (%)	No N (%)	
Overall	461	688	
Age (mean, SD)	65.0 (9.8)	66.7 (9.9)	0.003
Female	115 (44.6)	143 (55.4)	0.098
Body Mass Index (mean, SD)	29.8 (5.7)	29.5 (5.3)	0.333
COPD	77 (55.0)	63 (45.0)	<0.001
Last pre-operative serum creatinine (mean, SD)	1.2 (0.63)	1.1 (0.54)	0.042
Low ejection fraction (EF < 40%)	68 (15.4)	67 (10.1)	0.038
Hypertension	377 (40.5)	554 (59.5)	0.543
Diabetes	203 (44.0)	235 (34.2)	<0.001
Left Main Stenosis 50%	163 (45.2)	198 (54.9)	0.019
Prior Myocardial Infarction			
None	233 (37.1)	395 (62.9)	
< 24 hr preop	5 (27.8)	13 (72.2)	
>24 hr & < 7 day	91 (39.1)	142 (60.9)	
> 7 day & < 365	56 (50.0)	56 (50.0)	
> 365	76 (48.1)	82 (51.9)	0.015
Prior PCI	20 (51.3)	19 (48.7)	0.148
Atrial fibrillation	44 (58.7)	31 (41.3)	<0.001
Preoperative IABP	17 (44.7)	21 (55.3)	0.555
Prior CABG	13 (54.2)	11 (45.8)	0.156
Operative status			
Emergent	6 (35.3)	11 (64.7)	
Urgent	336 (41.8)	467 (58.2)	
Non-urgent	119 (36.2)	210 (63.8)	0.193
Unstable angina	267 (40.8)	388 (59.2)	0.609
Congestive Heart Failure (NYHA-IV)	78 (60.9)	50 (39.1)	<0.001
Smoker	114 (46.2)	133 (53.9)	0.030
Number of diseased vessels			
1	35 (36.5)	61 (63.5)	
2	164 (39.4)	252 (50.6)	
3	257 (41.7)	359 (58.3)	0.308

SD standard deviation, *COPD* chronic obstructive pulmonary disease, *PCI* percutaneous intervention, *IABP* intra-aortic balloon pump, *CABG* coronary artery bypass graft, *NYHA-IV* New York Heart Association-Class IV

Table 2.

Associations between preoperative clinical conditions and biomarker distributions

	CHF	p value	Renal failure	P	Priority (Emergent)		Prior MI		Smoker (Y)		IABP	
Preoperative												
ST2		<0.001		<0.001		0.154	158 (30.3)	<0.001	59 (23.9)	0.001		0.004
2 v 1	30 (23.4)		6 (17.1)		6 (35.3)		208 (39.9)		90 (36.4)		10 (25.0)	
3 v 1	69 (53.9)		24 (68.6)		5 (29.4)						23 (57.5)	
Gal3		<0.001		<0.001		0.134		0.467		0.327		0.095
2 v 1	34 (26.6)		4 (11.4)		3 (17.7)		164 (31.5)		79 (32.0)		19 (47.5)	
3 v 1	65 (50.8)		23 (65.7)		4 (23.5)		177 (34.0)		76 (30.8)		8 (20.0)	
IL-6		<0.001		<0.001		<0.001		<0.001		0.110		<0.001
2 v 1	32 (25.0)		8 (22.9)		8 (47.1)		158 (30.3)		88 (35.6)		7 (17.5)	
3 v 1	74 (57.8)		25 (71.4)		8 (47.1)		234 (44.9)		90 (36.4)		32 (80.0)	
IL-10		<0.001		0.066		<0.001		<0.001		0.004		0.057
2 v 1	38 (29.7)		12 (34.3)		3 (17.7)		166 (31.9)		75 (30.4)		14 (35.0)	
3 v 1	62 (48.4)		17 (48.6)		8 (47.1)		219 (42.0)		68 (27.5)		19 (47.5)	
NT-proBNP		<0.001		<0.001		0.001		<0.001		0.519		<0.001
2 v 1	20 (15.6)		6 (17.1)		6 (35.3)		170 (32.6)		89 (36.0)		12 (30.0)	
3 v 1	103 (80.5)		27 (77.1)		8 (47.1)		244 (46.8)		76 (30.8)		24 (60.0)	
Cystatin-C		<0.001		<0.001		0.667		0.002		0.326		0.240
2 v 1	33 (25.8)		1 (2.9)		6 (35.3)		159 (30.5)		78 (31.6)		13 (32.5)	
3 v 1	81 (63.3)		32 (91.4)		4 (23.5)		201 (38.6)		75 (30.4)		9 (22.5)	
Postoperative												
ST2		<0.001		<0.001		0.001		<0.001		0.001		0.001
2 v 1	40 (31.3)		6 (17.1)		6 (35.3)		173 (33.2)		80 (32.4)		16 (40.0)	
3 v 1	63 (49.2)		25 (71.4)		7 (41.2)		202 (38.8)		62 (25.1)		21 (52.5)	
Gal3		<0.001		<0.001		0.023		0.725		0.223		0.972
2 v 1	35 (27.3)		7 (20.0)		2 (11.8)		167 (32.1)		87 (35.2)		14 (35.0)	
3 v 1	65 (50.8)		23 (65.7)		5 (29.4)		178 (34.8)		71 (28.7)		13 (32.5)	
IL-6		0.994		0.567		0.025		0.062		0.159		0.037
2 v 1	42 (32.8)		12 (34.3)		4 (23.5)		178 (34.2)		71 (28.7)		13 (32.5)	

	CHF	p value	Renal failure	P	Priority (Emergent)		Prior MI		Smoker (Y)		IABP	
3 v 1	43 (33.6)		14 (40.0)		8 (47.1)		187 (35.9)		93 (37.7)		20 (50.0)	
IL-10		0.008		0.213		0.744		0.003		0.158		0.661
2 v 1	43 (33.6)		13 (37.1)		5 (29.4)		186 (35.7)		83 (33.6)		12 (30.0)	
3 v 1	56 (43.8)		15 (42.9)		6 (35.3)		188 (36.1)		71 (28.7)		16 (40.0)	
NT-proBNP		<0.001	5 (14.3)	<0.001		0.117		<0.001		<0.00		0.206
2 v 1	33 (25.8)		28 (80.0)		3 (17.7)		170 (32.6)		72 (29.2)	1	13 (32.5)	
3 v 1	87 (68.0)				6 (35.3)		214 (41.1)		67 (27.1)		18 (45.0)	
Cystatin-C		<0.001		<0.001		0.010		<0.001		0.001	5 (12.5)	0.016
2 v 1	32 (25.0)		1 (2.9)		9 (52.9)		168 (32.3)		84 (34.0)			
3 v 1	85 (66.4)		31 (88.6)		4 (23.5)		202 (38.8)		60 (24.3)		18 (45.0)	

Table 3.

Associations between postoperative clinical conditions and biomarker distributions

	Intubation	p value	Atrial fibrillation	p value	Inotropic support ¹	p value	Creatinine difference (pre to post op) ²	p value
Preoperative								
ST2		0.035		0.190		<0.001		<0.001
2 v 1	10 (29.4)		89 (35.7)		135 (30.7)		77 (33.9)	
3 v 1	18 (52.9)		89 (35.7)		180 (40.9)		108 (47.6)	
Gal3		0.683		0.032		0.835		<0.001
2 v 1	9 (26.5)		89 (35.7)		143 (32.5)		71 (31.3)	
3 v 1	13 (38.2)		94 (37.8)		151 (34.3)		103 (45.4)	
IL-6		0.020		0.793		<0.001		<0.001
2 v 1	11 (32.4)		87 (34.9)		161 (36.6)		73 (32.2)	
3 v 1	18 (52.9)		82 (32.9)		173 (39.3)		100 (44.1)	
IL-10		0.275		0.183		0.927		0.017
2 v 1	14 (41.2)		95 (38.2)		150 (34.1)		74 (32.6)	
3 v 1	13 (38.2)		80 (32.1)		146 (33.2)		92 (40.5)	
NT-proBNP		0.820		0.103		<0.001		<0.001
2 v 1	11 (32.4)		89 (35.7)		121 (27.5)		68 (30.0)	
3 v 1	13 (38.2)		91 (36.6)		205 (46.6)		118 (52.0)	
Cystatin-C		0.735		0.013		0.055		<0.001
2 v 1	9 (26.5)		84 (33.7)		146 (33.2)		48 (21.2)	
3 v 1	12 (35.3)		98 (39.4)		161 (36.6)		141 (62.1)	
Postoperative								
ST2		0.005		0.060		<0.001		<0.001
2 v 1	8 (23.5)		96 (38.6)		132 (30.0)		73 (32.2)	
3 v 1	20 (58.8)		84 (33.7)		183 (41.6)		121 (53.3)	
Gal3		0.893		0.009		0.667		<0.001
2 v 1	10 (29.4)		75 (30.1)		152 (32.3)		59 (26.0)	
3 v 1	12 (35.3)		103 (41.4)		144 (32.7)		125 (55.1)	
IL-6		0.205		0.022		0.778		<0.001
2 v 1	8 (23.5)		92 (37.0)		141 (32.1)		68 (30.0)	
3 v 1	16 (47.1)		92 (37.0)		148 (33.6)		103 (45.4)	
IL-10		0.018		0.008		0.093		<0.001
2 v 1	13 (38.2)		84 (33.7)		142 (32.3)		65 (28.6)	
3 v 1	17 (50.0)		100 (40.2)		163 (37.1)		115 (50.7)	
NT-proBNP		0.055		0.025		<0.001		<0.001
2 v 1	13 (38.2)		82 (32.9)		146 (33.2)		61 (26.9)	
3 v 1	16 (47.1)		99 (39.8)		192 (43.6)		144 (63.4)	
Cystatin-C		0.965		0.001		<0.001		<0.001
2 v 1	11 (32.4)		91 (36.6)		130 (29.6)		37 (16.3)	

	Intubation	p value	Atrial fibrillation	p value	Inotropic support¹	p value	Creatinine difference (pre to post op)²	p value
3 v 1	12 (35.3)		99 (39.8)		176 (40.0)		174 (76.7)	

¹ Any inotropic support within 4 hours post-operatively

² A 50% increase in preoperative to postoperative creatinine levels

Table 4.

Association between biomarkers and readmission or mortality 5-years after surgery.

	Unadjusted		Adjusted*	
	<i>OR (95% CI)</i>	<i>P-value</i>	<i>OR (95% CI)</i>	<i>P-value</i>
Preoperative				
ST2				
Tercile 2 vs 1	1.13 (0.85 – 1.51)	0.396	1.07 (0.77 – 1.48)	0.677
Tercile 3 vs 1	1.48 (1.10 – 1.97)	0.009	0.92 (0.65 – 1.31)	0.652
Galectin-3				
Tercile 2 vs 1	1.01 (0.75 – 1.35)	0.964	0.93 (0.63 – 1.37)	0.720
Tercile 3 vs 1	1.71 (1.27 – 2.29)	<0.001	1.55 (0.96 – 2.49)	0.074
NT-proBNP				
Tercile 2 vs 1	1.85 (1.37 – 2.50)	<0.001	1.53 (1.09 – 2.16)	0.014
Tercile 3 vs 1	2.53 (1.87 – 3.42)	<0.001	1.59 (1.02 – 2.46)	0.039
Cystatin-C				
Tercile 2 vs 1	1.10 (0.82 – 1.49)	0.523	0.73 (0.51 – 1.04)	0.077
Tercile 3 vs 1	2.43 (1.81 – 3.25)	<0.001	1.03 (0.65 – 1.62)	0.910
IL-6				
Tercile 2 vs 1	1.38 (1.03 – 1.86)	0.033	0.98 (0.70 – 1.38)	0.898
Tercile 3 vs 1	1.87 (1.40 – 2.51)	<0.001	1.01 (0.69 – 1.48)	0.954
IL-10				
Tercile 2 vs 1	1.31 (0.97 – 1.75)	0.070	1.17 (0.85 – 1.62)	0.331
Tercile 3 vs 1	1.37 (1.02 – 2.83)	0.036	1.05 (0.73 – 1.49)	0.803
Postoperative				
ST2				
Tercile 2 vs 1	1.31 (0.98 – 1.75)	0.069	1.01 (0.72 – 1.42)	0.954
Tercile 3 vs 1	1.52 (1.14 – 2.04)	0.005	0.98 (0.67 – 1.42)	0.910
Galectin-3				
Tercile 2 vs 1	1.15 (0.86 – 1.55)	0.343	1.04 (0.70 – 1.54)	0.848
Tercile 3 vs 1	1.75 (1.31 – 2.34)	<0.001	1.04 (0.63 – 1.71)	0.872
NT-proBNP				
Tercile 2 vs 1	1.27 (0.95 – 1.71)	0.113	1.02 (0.72 – 1.43)	0.928
Tercile 3 vs 1	2.06 (1.54 – 2.77)	<0.001	0.97 (0.63 – 1.49)	0.904
Cystatin-C				
Tercile 2 vs 1	1.43 (1.05 – 1.93)	0.021	1.26 (0.88 – 1.81)	0.208
Tercile 3 vs 1	2.96 (2.20 – 3.99)	<0.001	1.84 (1.15 – 2.95)	0.011
IL-6				
Tercile 2 vs 1	1.10 (0.82 – 1.47)	0.535	0.96 (0.69 – 1.33)	0.790
Tercile 3 vs 1	1.53 (1.14 – 2.04)	0.004	1.23 (0.86 – 1.77)	0.247
IL-10				
Tercile 2 vs 1	1.26 (0.94 – 1.68)	0.124	1.04 (0.74 – 1.45)	0.831
Tercile 3 vs 1	1.36 (1.01 – 1.82)	0.041	1.04 (0.72 – 1.50)	0.831

* Adjusted for age, sex, body mass index, preoperative intra-aortic balloon pump, preoperative myocardial infarction, prior CABG, prior percutaneous intervention, smoking status, atrial fibrillation, unstable angina, history of congestive heart failure, ejection fraction, left main stenosis > 50%, hypertension, diabetes, vascular disease, COPD, preoperative serum creatinine, and emergent and urgent priority status.

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