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Biomarker predictors of cardiac hospitalization in chronic heart failure: a recurrent event analysis

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Abstract

Background—Identification of heart failure (HF) patients at risk for hospitalization may improve care and reduce costs. We evaluated nine biomarkers as predictors of cardiac hospitalization in chronic HF.

Methods and Results—In a multicenter cohort of 1512 chronic HF outpatients, we assessed the association between 9 biomarkers and cardiac hospitalization using a recurrent events approach. Over a median follow-up of 4 years, 843 participants experienced one or more hospitalizations (total 2178 hospitalizations). BNP and TnI exhibited the strongest associations with risk of hospitalization [HR 3.8 (95% CI 2.9-4.9) and HR 3.3 (95% CI 2.8-3.9); third vs. first tertile]. sFlt-1 exhibited the next strongest association [HR 2.8 (95% CI 2.4-3.4)], followed by ST2 [HR 2.3 (95% CI 2.0-2.8)] and creatinine [HR 1.9 (1.6-2.4)]. Within ischemic/nonischemic subgroups, BNP and TnI remained most strongly associated. Except for creatinine, hazard ratios for all biomarkers studied were smaller within the ischemic subgroup, suggesting greater importance of cardio-renal interactions in decompensation of ischemic HF.

Conclusion—While BNP and TnI exhibited the strongest associations with hospitalization, etiology-dependent associations for the remaining biomarkers suggest etiology-specific mechanisms for HF exacerbation. sFlt-1 exhibited a strong association with cardiac hospitalization, highlighting its potential role as a biomarker of HF morbidity.

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Introduction

Heart failure (HF) hospitalizations are a major public health burden in the United States, accounting for over 1 million hospital admissions annually (1, 2). Numerous prior studies have used clinical factors and circulating biomarkers to develop predictors of adverse clinical events in HF (reviewed in (3)), the vast majority of which have focused on ‘terminal’ events such as ventricular assist device (VAD) placement, cardiac transplantation, and death (3). With respect to HF hospitalization, models have been developed primarily to predict time-to-first hospitalization alone or as a component of a composite terminal event (4). Although these approaches are highly relevant, they do not consider the possibly repeated nature of hospitalizations that are typical of chronic HF patients (5). As HF progresses, the highest-risk patients often experience a series of hospitalizations. These ‘recurrent’ events are not only burdensome to the patient but also result in a significant cost to the health care system, accounting for more than \$17 billion in annual spending (1, 2, 5). To address these high costs, the US Center for Medicare and Medicaid Services (CMS) and the Patient Protection and Affordable Care Act established public reporting guidelines and instituted financial penalties for centers with high rates of HF readmissions (6, 7). Improved identification of patients at high risk for hospitalization would allow for subsequent targeting of appropriate interventions thereby decreasing costs and improving patient morbidity.

As heart failure progresses, abnormalities accumulate in multiple physiologic systems. We have previously shown that assessing a panel of biomarkers that quantifies these abnormalities can improve prediction of terminal events in HF outpatients (8). Here we sought to determine the association between each of these biomarkers and risk of one or more cardiac hospitalizations. We tested the following nine biomarkers and associated pathways: high-sensitivity C-reactive protein (hsCRP) [inflammation], uric acid and myeloperoxidase (MPO) [oxidative stress], B-type natriuretic peptide (BNP) [neurohormonal activation], soluble fms-like tyrosine kinase receptor-1 (sFlt-1) and placental-like growth factor (PLGF) [vascular remodeling], troponin I (TnI) [myocyte injury], soluble toll-like receptor-2 (ST2) [myocyte stress], and creatinine [renal function] with risk of cardiac hospitalization in a multicenter cohort of 1,512 ambulatory HF patients. Our modeling approach assessed risk of one or more cardiac hospitalizations while accounting for the competing risk of terminal events. We also assessed whether biomarker associations differed according to HF etiology.

Methods

Study Population

The Penn Heart Failure Study (PHFS) is a National Heart, Lung and Blood Institute-sponsored multicenter cohort study of outpatients with chronic HF recruited from referral centers at the University of Pennsylvania (Philadelphia, PA), University Hospitals/Case Medical Center (Cleveland, OH), and the University of Wisconsin (Madison, WI) (8). The primary inclusion criterion is a clinical diagnosis of HF as determined by a HF specialist. The exclusion criteria are a non-cardiac condition resulting in an expected survival of less than six months as judged by the treating physician, or if patients are unwilling or unable to

provide consent. The resultant cohort consists of outpatients with predominantly chronic systolic HF and spans a full spectrum of HF severity, ranging from mild to severe disease requiring advanced therapies. All PHFS participants provide written, informed consent. Participating institutional review boards approved the PHFS protocol.

Biomarker Assays

Biomarker levels were measured from plasma obtained at the time of study entry and banked at -80°C until time of assay, as previously described (8). sFlt-1, PIGF, and MPO were measured using prototype ARCHITECT chemiluminescent microparticle-based immunoassays (Abbott Laboratories, Abbott Park, IL). BNP, TnI, hsCRP, uric acid, and creatinine were measured using standard ARCHITECT immunoassays (Abbott Laboratories, Abbott Park, IL). The TnI assay used has a lower limit detection of 5 ng/L with a coefficient of variation 10%. ST2 was measured via a high-sensitivity sandwich monoclonal immunoassay (Presage ST2 Assay, Critical Diagnostics, San Diego, CA).

Follow-up and Outcome Ascertainment

PHFS participants were followed prospectively from time of study entry. Adverse events including cardiac hospitalization and the occurrence of any terminal event (all-cause mortality, cardiac transplantation, and VAD placement) were ascertained through patient contact and verified through death certificates, medical records, or contact with patients' families by research personnel. Cardiac hospitalization was defined as a hospitalization for any cardiac etiology. Research personnel, blinded to biomarker levels, adjudicated cardiac versus non-cardiac hospitalization at the time of data acquisition using source documents from the medical record.

Participants were followed until the occurrence of any terminal event or administrative censoring. If a participant was hospitalized, then follow-up continued until the occurrence of a next hospitalization, and so on, until the end of follow-up. Participants who were alive and free of cardiac transplantation or VAD placement at the end of follow-up were censored. Thus, cardiac hospitalization was treated as a recurrent event, in that participants remained at risk for hospitalization throughout follow-up, regardless of the number of hospitalizations incurred, until the occurrence of a terminal event or censoring. Participants with a VAD placement prior to study entry were excluded from the analysis.

Statistical Methods

Characteristics of study participants at enrollment were summarized using standard descriptive statistics and compared between participants with ischemic and non-ischemic HF etiology. A non-parametric, recurrent event survival curve was used to summarize the survival distribution for cardiac hospitalization (9); a standard Kaplan-Meier curve was used for the composite terminal event of all-cause death, cardiac transplantation, or VAD placement. Recurrent event models were used to determine the association between each biomarker and risk of cardiac hospitalization, which may have occurred more than once for each participant. To facilitate the comparison of associations across biomarkers, each biomarker was categorized according to tertiles of its distribution. Because hospitalization fundamentally alters the risk of death, and because hospitalization cannot occur after death,

proper analysis of hospitalization risk requires consideration of informative censoring due to competing terminal events. A joint frailty model was used to accommodate informative censoring by all-cause death, cardiac transplantation, or VAD placement (10). The joint frailty model formulates a time-to-event model for risk of hospitalization and a time-to-event model for risk of any terminal event; an unobserved latent variable (or, frailty) is used to formulate a dependence structure between the two time-to-event models. Adjustment variables were selected *a priori* and included age, sex, race (Caucasian, African American, or other), and HF etiology (ischemic or non-ischemic). Additional analyses were stratified by HF etiology. In post-hoc analyses, we compared the risk of subsequent cardiac hospitalization between groups defined by biomarkers that exhibited the strongest associations in adjusted models. All analyses were completed using R 2.15.2 (R Development Core Team, Vienna, Austria), including the survrec and frailtypack extension packages (11).

Results

Baseline Characteristics

Summaries of baseline characteristics and biomarker levels of the 1512 participants in the study cohort are shown in Table 1, both in the overall cohort and according to etiology of the cardiomyopathy (ischemic and non-ischemic). The mean age of the overall cohort was 56 years (SD, 15 years), 66% were male, 74% were Caucasian, and 22% were African American. Seventy six percent had NYHA II/III symptoms, 30% had an ischemic etiology, and the average ejection fraction (EF) was 33%. Guideline-based therapies were highly prevalent (87% ACE inhibitors or ARBs, 88% beta blockers, 35% aldosterone antagonists). On average, participants with ischemic cardiomyopathy were more likely to be older, male, Caucasian, have a greater burden of cardiovascular risk factors, higher NYHA class, lower glomerular filtration rates, and lower ejection fractions than non-ischemic participants. Median levels of BNP, PIGF, SFlt-1, hsCRP, ST2, creatinine, uric acid, and percentage of participants with detectable troponin were higher in the ischemic subgroup.

Cardiac Hospitalizations

Follow-up time was a median of 4.0 years and a maximum of 8.9 years. 843 participants (55.8%) experienced one or more cardiac hospitalizations, for a total of 2178 hospitalizations: 347 participants experienced 1 hospitalization, 193 experienced 2, 112 experienced 3, 77 experienced 4, and 114 experienced 5 or more. 669 participants (44.2%) were never hospitalized. Median survival free from cardiac hospitalization was 3.9 years in the overall cohort (Figure 1a). 453 participants (30.0%) experienced a terminal event of death, cardiac transplantation, or VAD placement (Figure 1b). Among participants who subsequently experienced death, cardiac transplantation, or VAD placement, median survival free from cardiac hospitalization was 2.6 years (Figure 1c). Analysis of *a priori* selected covariates showed that ischemic etiology was an independent predictor of hospitalization (HR 1.3, 95% CI 1.1-1.5), as was male gender (HR 1.3, 95% CI 1.1-1.6), African American race (HR 1.5, 95% CI 1.3-1.8), and increasing age.

Associations between Biomarkers and Risk of Cardiac Hospitalization

Among all participants, several biomarkers were significantly associated with risk of cardiac hospitalization (Table 2). BNP and TnI exhibited the strongest associations in both adjusted and unadjusted models. Among the remaining biomarkers, all but PIGF showed statistically significant associations with risk of cardiac hospitalization in both the adjusted and unadjusted models, albeit with smaller hazard ratios than TnI or BNP. Furthermore, all biomarkers showed a dose-response relationship, with larger hazard ratios with increasing tertile of plasma biomarker level.

The strength of association between individual biomarkers and risk of cardiac hospitalization showed interesting differences by HF etiology (Figure 2). Among participants with non-ischemic HF, the biomarkers that exhibited the strongest associations with a HR > 2 when comparing the third to first tertile were: BNP (HR 4.1), TnI (HR 3.5), sFlt-1 (HR 3.2) and ST2 (HR 2.8). These findings implicate neurohormonal activation, myocyte necrosis, vascular remodeling, and myocyte stress as precursors of cardiac hospitalization in non-ischemic HF. In the ischemic subgroup, BNP (HR 3.2) and TnI (HR 2.7) showed the strongest associations, but the magnitudes of the hazard ratios were smaller than in nonischemics. Creatinine (HR 2.7) showed the third-strongest association with cardiac hospitalization in the ischemic subgroup, which differed substantially from the association in non-ischemics (HR 1.8). This finding suggests a greater importance for cardio-renal interactions as a precursor to hospitalization in ischemic HF.

Because BNP and TnI showed the strongest associations overall and in both subgroups, we explored their combined association with cardiac hospitalization. After stratifying the overall cohort by levels of BNP (dichotomized at the median of 173 pg/mL) and TnI (dichotomized as detectable versus not), risk of cardiac hospitalization increased with elevation of either BNP or TnI and further increased in participants with elevations in both (Table 3).

Discussion

While numerous prior studies have evaluated a multitude of biomarkers in HF populations, these studies have focused on the outcome of death or another terminal event such as cardiac transplantation and/or VAD placement, and have not focused on hospitalization as a primary outcome. Rather, hospitalizations were included either as a secondary outcome or as part of a composite hospitalization and terminal event outcome in a time-to-first-event analysis. This approach, while standard among clinical trials, does not take into account the multiple hospitalizations experienced by HF patients over time and so does not fully represent the patients' overall experience with their disease. Moreover, in a time-to-first analysis, all patients contribute equally to the analysis regardless of the number of hospitalizations incurred, thereby creating a disconnect between the included data and the patients' true burden of disease (5). In addition, death and hospitalization are competing risk events, because hospital admission fundamentally alters the risk of death and admission cannot occur after death (12). Heidenreich et al. showed divergent trends in rates of rehospitalization and mortality, which demonstrates the limitations of viewing hospitalization as simply a surrogate marker for mortality (13). Rising health care costs and

increasing focus on quality performance measures further underscore the relevance of HF hospitalization as an important clinical endpoint (6). To our knowledge, our study is the first multi-biomarker study of chronic heart failure to evaluate hospitalization as the primary outcome, to include recurrent hospitalizations in our analyses, and to properly account for competing risks.

We tested a panel of nine biomarkers that span several biological processes and have been previously implicated in HF pathophysiology. Among these candidate biomarkers, BNP and TnI exhibited the strongest association with risk of cardiac hospitalization overall and in both the ischemic and non-ischemic subgroups. BNP and TnI have been shown to associate independently with morbidity and mortality across a wide breadth of HF severity (14–21) and to have an additive ‘dose response’ effect, with stronger associations seen with elevations of both biomarkers over each biomarker alone (22, 23). Our study extends this consistent finding to a recurrent event framework regarding risk of cardiac hospitalization.

As shown in Figure 2, nearly all biomarkers showed weaker associations in the ischemic compared to the nonischemic subgroup. Because HF is a heterogeneous disorder it seems likely that within any HF population there would be subgroups within which biomarkers provide more, or less, information about the risk of incident events. In our cohort, comparison of the ischemic versus nonischemic subgroups in Table 1 shows that ischemic HF patients have a higher prevalence of comorbid conditions such as hypertension, diabetes, and dyslipidemia. We speculate that these comorbid conditions influence biomarker levels independently of HF and as a result dampen associations between many biomarker levels and outcomes to a greater extent in ischemic HF.

By contrast, creatinine, a well-established marker of renal function and prognosis in HF patients (24, 25), exhibited a stronger association in the ischemic subgroup, suggesting a greater impact of cardiorenal interactions as a precursor to hospitalization in ischemic HF. The precise biological mechanisms for this finding are unclear. However, it is likely that intrinsic primary renal disease is more prevalent in ischemic HF due to shared etiologic factors, such as diabetes and hypertension, which contribute to both coronary artery disease and to renal dysfunction. As shown in Table 1, hypertension and diabetes were more common among patients with ischemic heart disease in our cohort, and baseline creatinine levels were on average higher. We speculate that the population of patients with HF tends to have worse intrinsic renal function and further renal embarrassment is therefore more likely and more indicative of subsequent decompensation.

We note that sFlt-1, a marker of vascular remodeling that is not commonly studied in HF populations, showed a strong association with risk of hospitalization in the overall cohort and especially so in the non-ischemic subgroup. sFlt-1 is a soluble anti-angiogenic factor that binds to and sequesters vascular endothelial growth factor (26). Profound elevations in sFlt-1 that accompany pregnancy may cause excessive impairment of angiogenesis, leading to microvascular loss in the heart and peripartum cardiomyopathy (27). Our findings support the hypothesis that excessive sFlt-1 contributes to HF decompensation, as evidenced by a higher likelihood of hospitalization. It is also noteworthy that sFlt-1 had stronger associations in both subgroups than did the clinically approved biomarker ST2, which

assesses an IL-33 mediated stress-response pathway that affects myocardial function (28). Among the remaining biomarkers, several have been assessed extensively in HF populations and have become established markers of prognosis, including uric acid, MPO, and hsCRP (29–33). These biomarkers showed significant association with risk of hospitalization overall and in both subgroups, but the strength of these associations was substantially weaker than that for the biomarkers discussed above. This finding suggests that oxidative stress and inflammation may be less important to assess in predicting likelihood of cardiac hospitalization in chronic HF. PIGF did not exhibit a significant association after adjustment for covariates.

Our study has several relevant strengths and limitations. This was a large cohort study with participants recruited from HF referral centers with broad inclusion criteria. As a result, the study cohort represents a broad spectrum of HF disease severity, and the population is diverse with 44% female and 26% non-Caucasian. However, we acknowledge that certain subgroups, such as non-ischemic HF, may be over-represented, and others, such as the elderly, maybe under-represented. In particular, we have a very small proportion (< 8%) of patients with HF and preserved ejection fraction and are unable to assess the association between biomarkers and risk of hospitalization in this subgroup. We did not evaluate serial measures of biomarkers, which have been previously shown to associate with adverse outcomes (14, 18, 34), and our panel included only select biomarkers that were chosen to represent a specific biologic processes. It is plausible that additional markers that were not evaluated, such as high-sensitivity troponin or galectin-3, could have stronger associations. Future discovery of relevant biomarkers using unbiased approaches such as metabolomics and proteomics may yield further advances. Finally, we focused on association models rather than on the evaluation of risk-prediction models using receiver operating characteristic curves or risk reclassification analyses. There are currently no available statistical methods to build a multi-marker risk score and evaluate its prediction accuracy for a recurrent event that may be censored by a competing terminal event.

These findings may influence clinical care by allowing clinicians to better predict HF patients at higher risk of hospitalization. Reducing HF hospitalizations and early readmissions has been a focus of recent payment reform. Whether changing HF therapy or implementing disease management strategies will influence either the levels of biomarkers or the risk of hospitalization is unknown and will require further study.

In summary, we found that while BNP and troponin exhibited the strongest association with risk of cardiac hospitalization, the strength of the associations between the remaining biomarkers varied by HF etiology. sFlt-1 exhibited a stronger association than several well-established biomarkers, highlighting its potential role as a biomarker for HF morbidity. Further studies are needed to determine the optimal biomarkers involved in HF disease progression, as well as to develop statistical methods to quantify prediction accuracy in the setting of recurrent events and competing risks.

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Disclosures:

Drs. Ky and Cappola are co-inventors on a pending patent for use of sFlt-1 as a cardiac biomarker.

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Number at risk

1512 1331 1233 1106 766 558 396 170 39

Figure 1.

Probability of incident cardiac hospitalization for all participants (A) and probability of all-cause death, cardiac transplantation, or VAD placement for all participants (B). Probability of incident cardiac hospitalization stratified by the subsequent occurrence of all-cause death, cardiac transplantation, or VAD placement during follow-up (C).

Figure 2.

Associations between biomarkers and risk of cardiac hospitalization according to second vs. first and third vs. first tertile for each biomarker distribution, among participants with ischemic and nonischemic heart failure etiology; estimates adjusted for age, gender, and race (Caucasian, African American, or other)

Table 1

Characteristics of study participants at enrollment; summaries presented as n (%) unless noted otherwise

	All participants n=1512	Ischemic etiology n = 454	Non-ischemic etiology n=1058	p [*]
Demographic characteristics				
Age, years, mean (SD)	56(15)	63 (10)	53 (15)	< 0.001
Male	1001 (66)	375 (83)	626 (59)	< 0.001
Race				< 0.001
Caucasian	1124(74)	394 (87)	730 (69)	
African American	332 (22)	41(9)	291 (28)	
Other	56(4)	19(4)	37(3)	
Medical history and risk factors				
History of hypertension	883 (58)	299 (66)	584 (55)	< 0.001
History of diabetes	443 (29)	196 (43)	247 (23)	< 0.001
Tobacco use				< 0.001
Current	137 (9)	36(8)	101(10)	
Former	808 (54)	317(70)	491 (47)	
Never	557 (37)	101 (22)	456 (44)	
Hypercholesterolemia	753 (50)	319(70)	434(41)	< 0.001
Heart failure characteristics				
NYHA functional classification				< 0.001
I	258(17)	48(11)	210 (20)	
II	691 (46)	198 (44)	493(47)	
III	446 (30)	160 (35)	286 (27)	
IV	113(7)	47(10)	66(6)	
Ischemic etiology	454 (30)	-	-	-
Cardiac resynchronization therapy	377 (25)	170 (37)	207 (20)	< 0.001
Defibrillator	635 (42)	286 (63)	349 (33)	< 0.001
Medication use				
ACE inhibitors or ARBs	1316(87)	403 (89)	913(86)	0.22
Aldosterone antagonists A	508 (34)	189(42)	319(30)	< 0.001
Aspirin	822 (54)	361 (80)	461 (44)	< 0.001
Beta-blockers	1328 (88)	410(90)	918(87)	0.065
Digoxin	586 (39)	228 (50)	358 (34)	< 0.001
Diuretics	1184(78)	389 (86)	795 (75)	< 0.001
HMG CoA reductase inhibitors	753 (50)	361 (80)	392 (37)	< 0.001
Clinical measures, mean (SD)				
Body mass index, kg/m ²	30 (7.2)	30(5.9)	30 (7.7)	0.11
Systolic blood pressure, mmHg	114(20)	111(19)	115(21)	< 0.001
Diastolic blood pressure, mmHg	70 (12)	68(11)	71 (12)	< 0.001
eGFR, ml/min/1.73 m ²	84 (32)	74 (29)	88 (33)	< 0.001
Sodium, mEq/L	139(3.4)	139(3.8)	139(3.2)	0.009

	All participants n=1512	Ischemic etiology n = 454	Non-ischemic etiology n=1058	p [*]
Ejection fraction, %	33 (17)	28(13)	36(18)	< 0.001
Biomarkers, median (IQR)				
BNP, pg/mL	173 (47, 579)	353(131,849)	120 (33, 44)	< 0.001
PIGF, pg/mL	18.7(15.1,22.9)	21.2(17.5,25.3)	17.6(14.4,21.7)	< 0.001
sFlt-1, pg/mL	309 (260, 379)	320 (268, 387)	302 (255, 376)	0.002
hsCRP, mg/L	0.35(0.14,0.90)	0.40(0.16, 1.04)	0.33(0.14,0.82)	0.018
MPO, pmol/L	137 (95, 227)	138(96, 232)	137 (95,224)	0.65
ST2, ng/mL	27.4 (20.0, 40.5)	31.8(22.4,48.7)	25.4(19.0,37.3)	< 0.001
TnI				< 0.001
Detectable, n (%)	975 (64)	371 (82)	604 (57)	
TnI, ng/L, median (IQR) **	20 (10, 40)	20(10,30)	20 (10, 40)	
Creatinine, mg/dL	0.92 (0.76, 1.25)	1.07(0.82, 1.44)	0.87(0.74, 1.15)	< 0.001
Uric acid, mg/dL	6.9(5.7,8.8)	7.5(6.1,9.4)	6.8(5.4,8.5)	< 0.001

* P values obtained from two-sample t-tests, Wilcoxon rank-sum tests, or chi-squared tests comparing characteristics between participants with ischemic and non-ischemic etiology

** Among those participants with a detectable troponin I

SD, standard deviation; IQR, 25th and 75th percentile; NYHA, New York Heart Association; ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; PIGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase receptor-1; hsCRP, high-sensitivity C-reactive protein; MPO, myeloperoxidase; ST2, soluble toll-like receptor-2; TnI, troponin I

Table 2

Associations between biomarkers and risk of cardiac hospitalization according to second vs. first and third vs. first tertile for each biomarker distribution

	Unadjusted model HR (95% CI)	P	Adjusted Model* HR (95% CI)	P
BNP				
80-377 vs. < 80 pg/mL	2.0(1.7,2.4)	< 0.001	2.0(1.6,2.6)	< 0.001
377 vs. < 80 pg/mL	3.8(3.2,4.5)	< 0.001	3.8(2.9,4.9)	< 0.001
TnI				
5 - 20 vs. < 5 ng/L	2.0(1.7,2.4)	< 0.001	2.0(1.6,2.4)	< 0.001
20 vs. < 5 ng/L	3.4(2.9,4.1)	< 0.001	3.3 (2.8, 3.9)	< 0.001
sFlt-1				
274–346 vs. < 274 pg/mL	1.5(1.2, 1.7)	< 0.001	1.4(1.2, 1.7)	< 0.001
346 vs. < 274 pg/mL	3.0(2.5,3.6)	< 0.001	2.8(2.4,3.4)	< 0.001
ST2				
22.4–35.0 vs. < 22.4 ng/mL	1.3(1.1,1.5)	0.005	1.3(1.1, 1.6)	0.002
35.0 vs. < 22.4 ng/mL	2.4 (2.0, 2.9)	< 0.001	2.3 (2.0, 2.8)	< 0.001
Creatinine				
0.80–1.11 vs. < 0.80 mg/dL	1.5(1.3, 1.8)	< 0.001	1.4(1.2, 1.7)	< 0.001
1.11 vs. < 0.80 mg/dL	2.2(1.8,2.6)	< 0.001	1.9(1.6,2.4)	< 0.001
Uric acid				
6.1–8.1 vs. < 6.1 mg/dL	1.4(1.1, 1.6)	< 0.001	1.3(1.1,1.5)	0.009
8.1 vs. < 6.1 mg/dL	2.0(1.7,2.4)	< 0.001	1.9(1.6,2.2)	< 0.001
hsCRP				
0.20–0.61 vs. < 0.20 mg/L	1.2(1.0, 1.4)	0.030	1.2 (0.99, 1.4)	0.065
0.61 vs. < 0.20 mg/L	1.9(1.6,2.3)	< 0.001	1.8(1.5,2.1)	< 0.001
MPO				
109–182 vs. <109pmol/L	1.2(1.0, 1.5)	0.016	1.2(1.0, 1.5)	0.022
182 vs. <109pmol/L	1.4(1.2, 1.7)	< 0.001	1.4(1.2, 1.7)	< 0.001
PIGF				
16.2–21.3 vs. < 16.2 pg/mL	0.95(0.80, 1.1)	0.55	0.91(0.77, 1.1)	0.30
21.3 vs. < 16.2pg/mL	1.2(1.0, 1.5)	0.022	1.2(0.96, 1.4)	0.12

* Adjusted model includes age, gender, race (Caucasian, African American, or other), and heart failure etiology (ischemic or non-ischemic)

HR, hazard ratio; CI, confidence interval; BNP, B-type natriuretic peptide; TnI, troponin I; sFlt-1, soluble fms-like tyrosine kinase receptor-1; ST2, soluble toll-like receptor-2; hsCRP, high-sensitivity C-reactive protein; MPO, myeloperoxidase; PIGF, placental growth factor

Table 3

Unadjusted hazard ratios for incident cardiac hospitalization comparing groups defined by BNP (dichotomized at median) and troponin (dichotomized as detectable vs. not)

TnI	BNP < 173 pg/mL N; HR (95% CI); P	173 pg/mL N; HR (95% CI); P
Not detectable	434; Referent	103; 2.3 (1.7, 3.1); < 0.001
Detectable	322; 2.3 (1.8, 2.8); < 0.001	653; 4.1 (3.4, 4.9); < 0.001

N, sample size in each group; HR, hazard ratio, CI, confidence interval; BNP, B-type natriuretic peptide; TnI, troponin I