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Do High Sensitivity Troponin and Natriuretic Peptide Predict Death or Serious Cardiac Outcomes After Syncope?

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Abstract

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Author contributions:

CLC is the responsible corresponding author. CLC, BCN, TAG, REW had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. CLC,TAG, REW, ANY, SEV, DHA, AB, CWB, JMC, DBD, JEH,BAN, DKN, MNS, KAS, ABS, STW, BCS had substantial contribution to the manuscript including responsibility for concept, data collection, manuscript development, review and final approval.

Presentations:

This work was presented at the American College of Emergency Physicians Scientific Assembly, October 2018.

Objective: An estimated 1.2 million annual emergency department (ED) visits for syncope/near syncope occur in the United States. Cardiac biomarkers are frequently obtained during the ED evaluation, but the prognostic value of index high-sensitivity troponin (hscTnT) and Natriuretic Peptide (NT-proBNP) are unclear. The objective of this study was to determine if hscTnT and NT-proBNP drawn in the ED are independently associated with 30-day death/serious cardiac outcomes in adult patients presenting with syncope.

METHODS: A pre-specified secondary analysis of a prospective, observational trial enrolling participants ≥ age 60 presenting with syncope, at 11 United States hospitals, was conducted between 4/2013 and 9/2016. Exclusions included seizure, stroke, transient ischemic attack, trauma, intoxication, hypoglycemia, persistent confusion, mechanical/electrical invention, prior enrollment, or predicted poor follow-up. Within 3 hours of consent, hscTnT and NT-proBNP were collected and later analyzed centrally using Roche Elecsys Gen 5 STAT® and 2010 Cobas® respectively. Primary outcome was combined 30-day all-cause mortality and serious cardiac events. Adjusting for illness severity, using multivariate logistical regression analysis, variations between primary outcome and biomarkers were estimated, adjusting absolute risk associated with ranges of biomarkers using Bayesian Markov Chain Monte Carlo methods.

RESULTS: The cohort included 3,392 patients; 367 (10.8%) experienced the primary outcome. Adjusted absolute risk for the primary outcome increased with hscTnT and NT-proBNP levels. HscTnT levels ≤ 5 ng/L were associated with a 4% (95%CI: 3–5%) outcome risk; hscTnT >50 ng/L, a 29% (95%CI: 26–33%) risk. NT-proBNP levels ≤ 125 ng/L were associated with a 4% (95%CI: 4–5%) risk; NT-proBNP > 2000 ng/L a 29% (95%CI: 25–32%) risk. Likelihood ratios and predictive values demonstrated similar results. Sensitivity analyses excluding ED index serious outcomes demonstrated similar findings.

CONCLUSION: HscTnT and NT-proBNP are independent predictors of 30-day death and serious outcomes in older ED patients presenting with syncope.

Introduction:

There are over 1.2 million annual events of syncope/near syncope in the United States leading to an emergency department (ED) visit, resulting in 440,000 annual admissions[1] and $2.4 billion in yearly hospital costs.[2] Despite the high incidence and associated costs of syncope/near syncope, there are currently no effective prediction tools to identify older patients (age ≥60 years) who may be at risk for subsequent short-term death or serious cardiac events.[3,4]

High-sensitivity troponin and natriuretic peptides are very accurate markers of myocardial dysfunction, structural heart disease, and long-term cardiac death.[5,6] Cardiac biomarkers are frequently obtained during the ED evaluation for syncope/near syncope, but the prognostic value of high-sensitivity troponin (hscTnT) and natriuretic peptide (NT-proBNP) measurements in the presentation of syncope/near syncope are unclear.

Preliminary work suggests these biomarkers may be important in syncope/near syncope risk prediction.[7–12] However, cardiac biomarkers have not been uniformly measured in these pilot studies, and this may have introduced testing bias due to illness severity. The 2017 American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm

Society (HRS) Syncope Guidelines state: “The ability of troponin and natriuretic peptide measurement to influence clinical decision making or patient outcome is unknown.”[13]

This study sought to assess the association of hscTnT and NT-proBNP with composite 30-day all-cause mortality and serious cardiac outcomes after an ED evaluation for syncope/near syncope and their prognostic value. We hypothesize that these biomarkers have independent predictive value, after adjustment for symptoms, co-morbidities, physician risk assessment, and electrocardiogram (ECG) abnormalities.

Methods:

Study Design

We performed a preplanned secondary analysis of a multi-site prospective observational cohort study (NCT01802398). The study enrolled older adults (≥60 years of age) at 11 United States EDs who presented with the primary chief complaint of syncope or near syncope as confirmed by the treating physician. The study ended upon attaining enrollment goals. The study, including the biomarker blood draws, was approved by the institutional review boards at all sites. Written informed consent was obtained from subjects or their legally authorized representative. Data reported were preplanned analyses of biomarker measurements drawn during the initial index visit enrollment of the patient, within three hours of consent, and later analyzed at a central laboratory.

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Study Setting and Population

Eligible patients were screened and enrolled at 11 United States EDs between April 28, 2013 and September 21, 2016. Patient inclusion criteria for eligibility were age ≥60 years presenting with a chief complaint of syncope or near syncope as determined by the treating physician. Participating subjects agreed to have blood drawn for biomarkers. Syncope was defined as a transient loss of consciousness with loss of postural tone followed by spontaneous and complete recovery. Near syncope was defined as the sensation of imminent loss of postural tone without loss of consciousness. For this preplanned analysis, patientswere only included if they had a biomarker result available.

We excluded patients who presented with seizure, stroke, transient ischemic attack (TIA), head trauma, intoxication from drugs or alcohol, or hypoglycemia as the presumptive cause of symptoms. We further excluded patients with persistent confusion relative to baseline mental status and those who required medical or electrical interventions (e.g., intravenous glucose, defibrillation) to restore consciousness. Patients with prior enrollment were also excluded. To minimize attrition, we excluded patients unlikely to complete follow-up,

including those who lacked phone access, lacked a permanent address, or did not speak either English or Spanish.[14] Patients or those with legally authorized representatives who were unable or unwilling to provide informed consent or follow-up information were also excluded.

Study Protocol

Consistent with published research reporting guidelines pertaining to syncope risk-stratification[15], all participating patients underwent a standardized evaluation, including history, physical exam, and an initial 12-lead ECG. Physician risk assessment was obtained from the treating physician immediately after consent. The physician risk assessment had a range from 0% to 100% and served as a surrogate for the treating physician's subjective level of concern regarding the potential for 30-day death or serious cardiac outcomes. Serum samples were collected for hscTnT and NT-proBNP within 3 hours of consent, and these were sent to and analyzed at a central laboratory (University of Rochester, Rochester, NY). These results were not available to the treating physicians. Clinical testing at the participating hospitals was at the sole discretion of the clinical providers, and patient disposition was unaffected by this protocol. Research personnel collected objective information about age, gender, and triage vital signs from the ED electronic medical record and symptom data directly from the patients or their legally authorized representatives. The treating physician provided information about co-morbidities, exam findings and physician risk assessment. All 12-lead ECGs were interpreted by a study physician both locally and at the coordinating center.

All local patient records were reviewed for subsequent hospital visits, serious cardiac outcomes, and death within 30-days of the index ED visit by site physician investigators. Follow up phone calls performed by the coordinating center at 30 days identified additional medical visits and 30 day serious outcomes. Medical records were obtained and reviewed by the coordinating center for these visits. Site investigators and the coordinating center were blinded to central laboratory biomarker results.

Serious cardiac outcomes were dichotomized as occurring during the index emergency department visit or after.

To assess inter-rater reliability of chart review, records for the first 5 sequentially enrolled patients at each of the 10 external sites (excluding the coordinating center) were independently reviewed by local research staff and the coordinating center. The specific number of charts chosen for this review was restricted by availability of research staff resources. All 5 serious cardiac outcomes in the training set were identified by local site reviewers.

Key Outcome Measures

The primary composite outcome included all-cause mortality and serious cardiac events at 30-days. We defined serious cardiac events apriori. These included: sustained ventricular arrhythmia (>30 seconds) or symptomatic ventricular tachycardia; sinus pause ≥3 seconds; third-degree or Mobitz II atrioventricular block; symptomatic supraventricular tachycardia pacemaker/defibrillator malfunctions; symptomatic bradycardia (heart rate ≤40 beats per

minute); myocardial infarction as defined by the universal definition[16]; a new diagnosis of severe aortic stenosis (area ≤0.9 cm^2), severe pulmonary hypertension, hypertrophic cardiomyopathy, or atrial mass causing outflow obstruction; aortic dissection, and pulmonary embolism. Symptomatic was defined as the "simultaneous occurrence of dizziness, lightheadedness, hypotension (systolic blood pressure <90 mm Hg), or syncope with an arrhythmia on ECG monitoring."[8] Atrial fibrillation, atrial flutter, paroxysmal atrial tachycardia and supraventricular tachycardia were all included in the category of supraventricular tachycardia if symptomatic. Research staff coded serious cardiac events as identified during or after the index ED visit.

To address potential bias introduced by "obvious" cardiac conditions identified during the ED evaluation, we analyzed a secondary outcome that included all-cause mortality and serious cardiac events at 30-days that were not identified during the index ED evaluation.

Independent Predictors and Covariates

Our independent predictors were the measurements of hscTnT and NT-proBNP (Elecsys, Roche Diagnostics). The hscTnT assay used was the Roche Elecsys Gen 5 STAT® which has a lower detectable limit of 5 ng/L and a US reference 99th percentile cutoff limit of 19 ng/L for hscTnT.[17] The NT-proBNP assay used was the Roche Elecys 2010 Cobas®, with recommended use of a 125ng/L lower limit of normal for patients under 75 years and 450 ng/L for patients over 75 years. We report both. Covariates included demographic characteristics and potentially confounding co-morbidities. In a previous meta-analysis, we identified potential predictors of serious outcomes including age, cardiac co-morbidities, a complaint of dyspnea, hypotension (ED triage systolic blood pressure <90mmHG), and initial ECG abnormalities.[18] These were used as covariates. Additional covariates also included disposition and initial physician risk assessment.

An abnormal initial ECG was defined by the presence of non-sinus rhythms (including paced rhythms), sinus tachycardia >100 beats/min, multiple premature ventricular complexes (≥2), sinus bradycardia (≤40 beats/min), ventricular hypertrophies, short PR-segment intervals (<100 ms), axis deviations, first-degree blocks (>200 ms), complete bundle branch blocks, Brugada patterns, Wolff-Parkinson-White Syndrome patterns, bifascicular block (both complete right bundle branch block and left axis deviation), abnormal QRS duration (>120 ms), abnormal QTc prolongations (>450 ms), or Q/ST/T-segment abnormalities suggestive of acute or chronic ischemia. The supervising physicians' initial risk assessments were measured as a percentage estimate for 30-day death or serious cardiac events.

Data Analysis

This study protocol proposed 3,330 completed enrollments (3,700 patients with a 10% attrition rate) to identify associations between predictors and the primary outcomes with an adjusted odds ratio of 1.5 or greater. We used chi-square tests to test association of the outcome with discrete predictors and logistic regression to test for association of the outcome with continuous variable predictors, with hscTnT and NT-proBNP on the log scale to check for univariate association with the outcomes. Unadjusted associations between the

outcome and hscTnT and NT-proBNP were visually assessed using smoothing splines. Tabled values of hscTnT and NT-proBNP quantiles (20%, 68%, 77%, 90%, 96%, and 99%) were rounded to the closest easily conceptualized values.

To assess the independent association of hscTnT and NT-proBNP with the primary outcome, we performed multivariate logistic regression using complete case data. The model included all covariates along with hscTnT and NT-proBNP. We explored multiple approaches (linear, categorical, log-transform) to parameterize the continuous independent variables. Log transform of hscTnT and NT-proBNP values provided the best fit models based on Akaike information criterion. We assessed for interaction effects between the two biomarkers. In sensitivity analysis, we performed multiple imputations with the MICE package for missing data to include all observations in regression models.[19]

We found adjusted odds ratio for specific values of hscTnT and NT-proBNP, compared to reference values of 5 ng/mL and 125png/mL, respectively, and we then calculated adjusted odds ratios and their 95% confidence intervals using coefficient estimates and 95% interval endpoints from the multiply-imputed logistic regression model. We used a p value of 0.05 as statistically significant. Given the observational nature of the study, the alpha was not adjusted for multiple comparisons. We assumed a linear relationship between the log-odds of an event and the logs of hscTnT and NT-proBNP with all other variables held constant.

We estimated the adjusted absolute risk of the primary outcome for intervals bounded by the quantiles described above. We first calculated the risk of an event for each subject, and then averaged the values across subjects in the particular range. The risk we calculated for an individual patient is the adjusted probability of an event controlling for other covariates. HscTnT and NT-proBNP were entered as continuous covariates and logged before analysis.

We then ran a multivariate logistic regression, including all variables from the main model on each imputed data set. Each imputed data set had an associated estimated vector of coefficients, $\hat{\beta}$, and an estimated variance-covariance matrix Σ for those coefficients. From those we calculated the average of the estimates and the marginal covariance matrix across imputations, denoted $\bar{\beta}$ and $\bar{\Sigma}$.

Using patients with complete data, we performed a Bayesian analysis using Markov Chain Monte Carlo (MCMC) to calculate the predicted probabilities of a 30-day serious cardiac outcome or death for each patient. In each iteration of MCMC, we sampled a vector, $\beta(i)$, which followed a multivariate normal distribution with mean $\bar{\beta}$ and covariance matrix $\bar{\Sigma}$. We then calculated the predicted probability for each patient using the inverse logit function,

$$\hat{p} = \frac{\exp\left(X^T \beta^{(i)}\right)}{1 + \exp\left(X^T \beta^{(i)}\right)},$$

where X^T represents the predictors for the given patient. At each iteration, we calculated the average risk of an event across people within each interval of hscTnT and NT-proBNP. We analyzed individual site of enrollment as a fixed effect and found no appreciable differences.

Therefore, in the interest of simplicity, we have not reported site specific breakdowns in the data results.

We repeated all analyses for the secondary outcome of serious 30-day events occurring after the index ED evaluation. All data analyses were performed in R version 3.2.3.[20]

It is our belief that collinearity and outliers are not generally a problem with this type of data collection, therefore, we did not perform post-regression diagnostics on our model.

Results:

We studied 3,392 patients who had available biomarker data (Figure 1);367 (10.8%) patients experienced the primary outcome. Characteristics of the study cohort are described in Table 1, and type and timing of serious events are presented in Table 2. Some patients experienced multiple outcomes. The mean age of participants was 72.8 ±9.0 years. No significant sex or race/ethnicity differences were noted between those with and without serious outcomes.. Cardiac co-morbidities, dyspnea, hypotension, and abnormal ECG were associated with serious events ($p<0.01$). The majority of patients (80%) were admitted to the hospital. Only 20 % of patients were discharged directly from the ED.

Values of cardiac biomarkers were greater in patients who experienced the primary outcome (hscTnT, median [IQR] ng/mL: 22 [10, 51] ng/mL vs. 11 [6, 22] ng/mL; NT-proBNP median [IQR] ng/mL: 776 [244, 2175] ng/mL vs. 210 [82, 620] ng/mL. Table 1 and Appendix Figures 1 and 2 illustrate that the probability of serious outcomes increases with increasing values of both hscTnT and NT-proBNP. We illustrated likelihood ratios and negative/positive predictive values at multiple cut points for both biomarkers (Table 3).

In multivariate logistic regression analysis (Table 4), hscTnT and NT-proBNP measurements were independently predictive of outcomes ($p<0.0001$). These results were robust to multiple imputation for missing data (Appendix Table 1). We did not find evidence of an interaction effect between hscTnT and NT-proBNP. (Appendix Table 2) Either cardiac marker was useful in predicting the outcome even if the other marker was already included as a predictor.

For both hscTnT and NT-proBNP, increasing values were associated with greater adjusted absolute risk (Table 5) and odds ratio (Table 6) for the primary outcome. For example, a hscTnT value of ≤ 5 pg/mL was associated with an absolute risk of 4% (95CI: 3–5%), whereas a hscTnT value of >50 ng/L was associated with an absolute risk of 29% (95CI: 26–33%). A NT-proBNP value of ≤125 ng/L was associated with an absolute risk of 4% (95CI: 4–5%), whereas a NT-proBNP value of >2000 ng/L was associated with an absolute risk of 29% (95CI: 25–32%). There were 434 patients (13%) who had hscTnT ≤ 5 pg/mL and NT-proBNP value of ≤ 125 ng/L; the estimated adjusted risk for the primary outcome was 3% (95CI 3–4%).

We found that increasing values of cardiac biomarkers were associated with adjusted absolute risk for 30-day serious events identified only after the index ED visit (Table 7). We

illustrated likelihood ratios and negative/positive predictive values at multiple cut points for both biomarkers after excluding events found during the index ED visit (Table 8).

Discussion:

In this multi-center cohort of older adults presenting to the ED with syncope/near syncope, both hscTnT and NT-proBNP levels were found to be independent predictors of 30-day death and serious cardiac events. Increasing values of both biomarkers corresponded with greater risk of adverse events. These findings are robust to multiple sensitivity analyses, and they are valid for risk prediction in patients without an apparent cardiac cause after the initial ED evaluation. These biomarkers have independent predictive power. To our knowledge, this is the largest study to date that has standardized collection of hscTnT and NT-proBNP in patients with syncope. Our findings suggest that these biomarkers could be helpful in syncope/near syncope risk stratification in older adults.

A systematic review of 11 studies assessing biomarker use in syncope/near syncope concluded that “there is modest predictive value for high-sensitivity troponin and natriuretic peptides for major cardiac adverse cardiovascular events.”[12] However, these conclusions were tempered by limitations of prior studies, including small sample sizes, single center populations, and non-standardized data collection of potential confounding variables. Our study design specifically addresses these methodological challenges and confirms the independent predictive value of these biomarkers.

Prior syncope/near syncope risk stratification studies have been criticized for including patients with serious events identified during the ED evaluation.[21] Patients with dangerous medical conditions identified in the ED require treatment rather than risk stratification, and inclusion of such patients may result in optimistically biased estimates of association between predictors and outcomes. In sensitivity analyses, we found that both hscTnT and NT-proBNP were independent predictors of 30-day serious cardiac outcomes and death even after omitting events identified during the index ED visit. This is important in determining which patients are at risk of serious outcomes and death even when an ED evaluation does not find a significant cause for the syncope or near syncope.

Elevated hscTnT and NT-proBNP have been shown in previous studies to be predictive of long term cardiac events, and hscTnT has strongly correlated with NT-proBNP in the same studies.[22,23,24] Syncope/near syncope may be the presenting event for these cardiac comorbidities and therefore portend increased risk of serious events. An abnormal serum concentration of hscTnT has been found to be an independent predictor of adverse outcome and risk of cardiac event in patients with hypertrophic cardiomyopathy.[25] Elevation of hscTnT and NT-proBNP have been shown to be predictive of future cardiac events such as acute myocardial infarction, pulmonary embolus and acute decompensated heart failure.[26,27,28,29,30] This prior literature provides a conceptual foundation for why elevations of hscTnT and NT-proBNP in syncope/near syncope may be useful in predicting further cardiac events.

A major clinical challenge is identifying which patients presenting with syncope/near syncope would benefit most from hospital admission, observation or discharge with outpatient follow-up. In our cohort, the majority of patients (79.5%) were admitted. HscTnT and NT-proBNP may help identify patients at low risk of subsequent short-term events who could be discharged. Likelihood ratios and predictive values confirm this (Table 3,8). After excluding patients who have obvious cardiac pathology after ED evaluation, cardiac biomarkers were able to identify patients with ≤ 2% risk of serious outcomes at 30-days (Table 7). This finding may inform shared decision making and disposition choices. The ability to safely discharge these patients may save unnecessary admissions and cost. This is an important finding in our study.

We found that hscTnT and NT-proBNP are independent predictors of short term 30-day risk. These findings should be combined with other clinical data, such as known cardiac disease, historical elements, and findings on the 12-lead ECG to assess which patients can safely be discharged home after a syncopal event. Our findings can be used to inform the development of a comprehensive risk scoring system. To our knowledge, none of the published risk tools include these biomarkers.

Limitations:

Our study does have limitations. We used data from a single blood draw, and it is possible that serial biomarker testing may provide additional prognostic information.

Our study focused on older adults, as adverse outcomes and health service use are concentrated in this population. Our results will need to be verified in younger cohorts.[31, 32]

We analyzed NT-proBNP values, and these results may not be generalizable to other natriuretic peptide assays. However, multiple studies in other disease states suggest that BNP and NT-proBNP are functionally interchangeable.[33]

We did not code symptomatic supraventricular tachycardias into specific subgroups (e.g. atrial fibrillation, atrial flutter, paroxysmal supraventricular tachycardia), which limits the ability to assess the clinical significance of these arrhythmias..

Finally, the hscTnT assay was approved for clinical use in the United States in 2017, and this assay may not be currently available in many EDs. However, we believe that many EDs in the United States will convert to high sensitivity cardiac troponin assays in the near future.

Conclusions:

In older adults who presented to the ED for evaluation of syncope/near syncope, elevated hscTnT and NT-proBNP levels are independent predictors of 30-day mortality and serious cardiac events. These biomarkers may be helpful in risk stratification and clinical decision making. Future clinical decision aids should consider the incorporation of these biomarkers.

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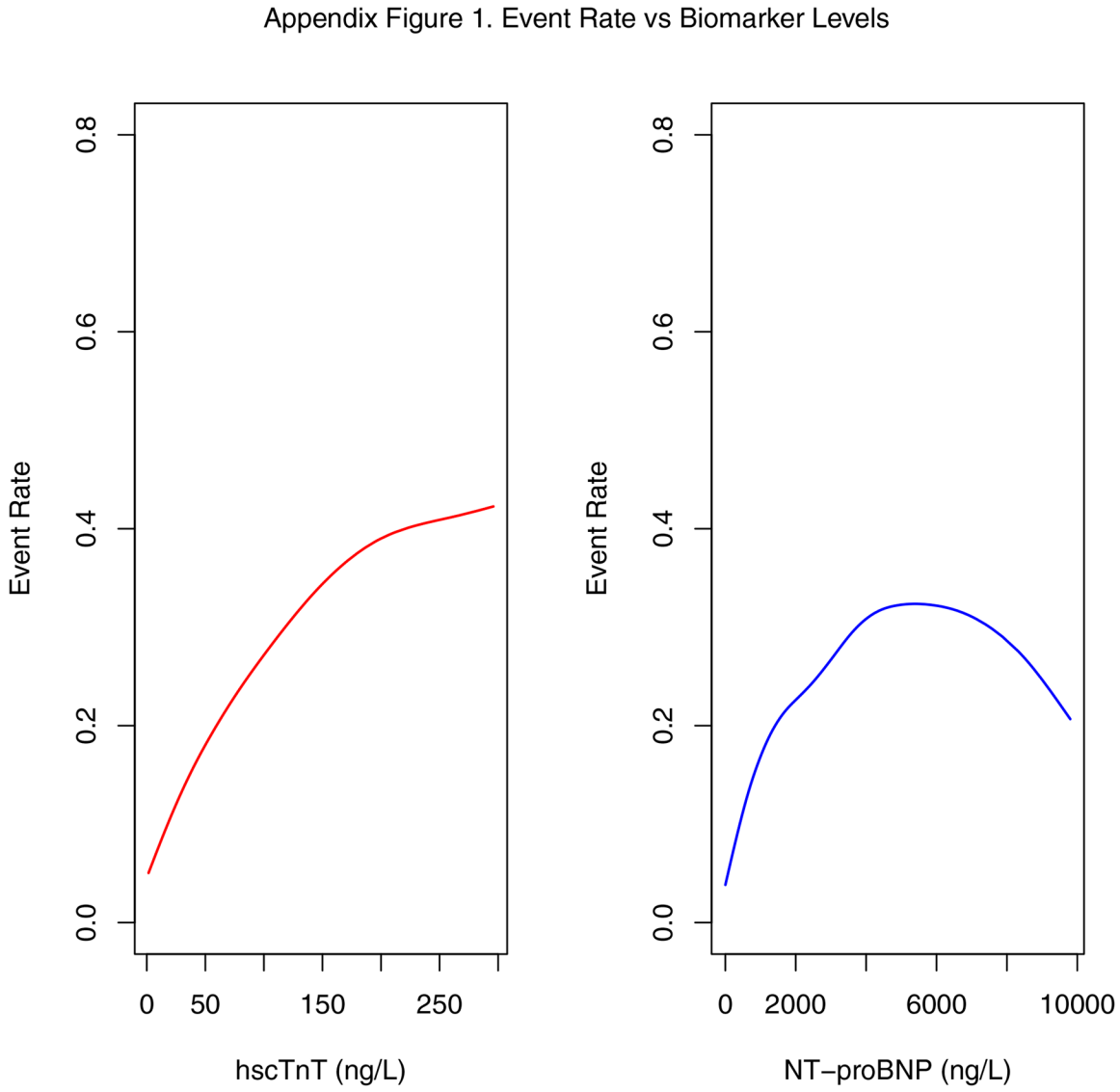
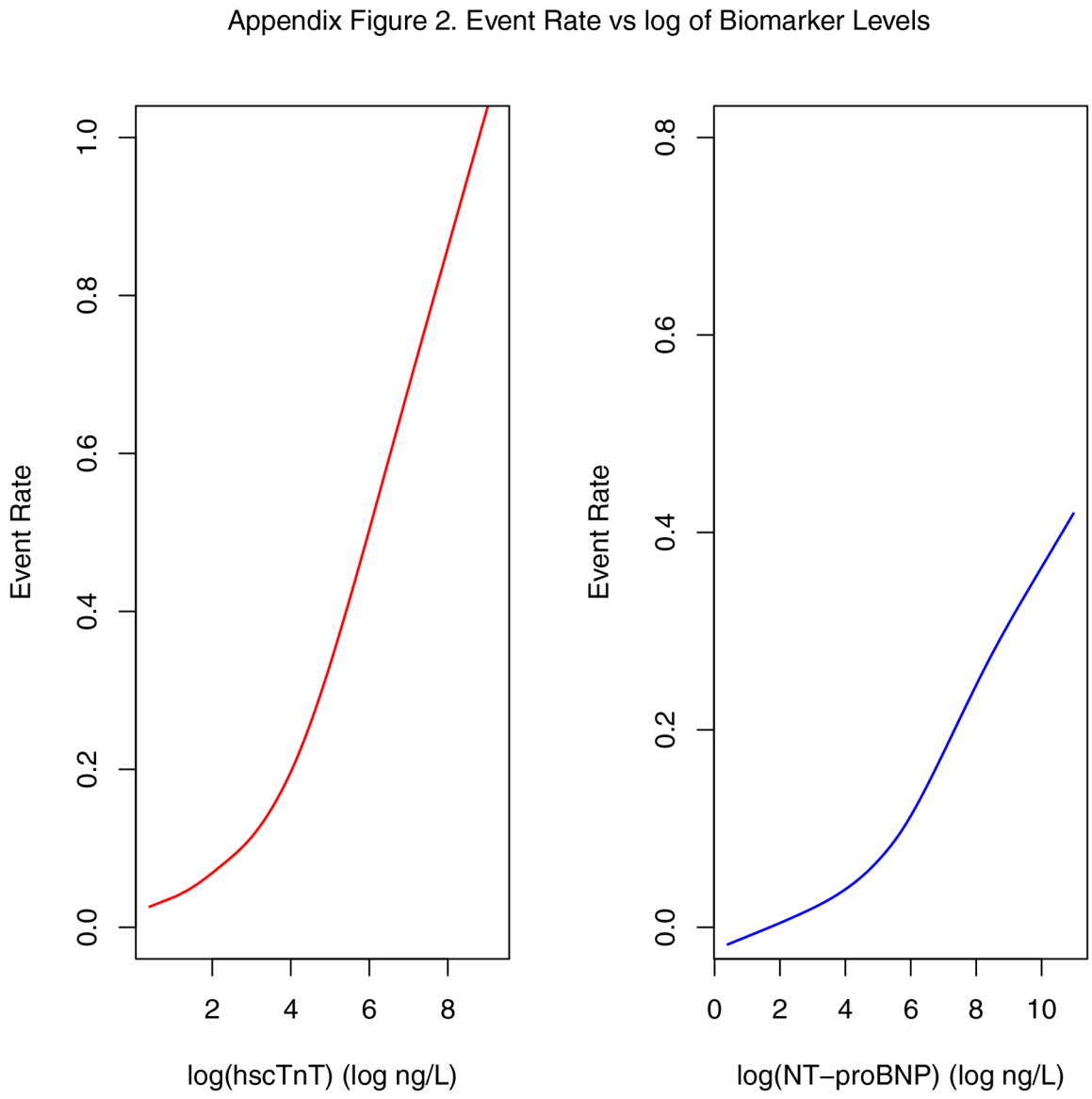
Conflict of Interest Disclosure:

CLC's institution has received grant funding from the National Heart, Lung, and Blood Institute of the National Institutes of Health. CLC's institution has received contract funding from Radiometer and Ortho Scientific for industry-initiated research. TAG's institution has received grant funding from the National Heart, Lung, and Blood Institute of the National Institutes of Health. REW's institution has received grant funding from the National Heart, Lung, and Blood Institute of the National Institutes of Health. ANY's institution has received grant funding from the National Heart, Lung, and Blood Institute of the National Institutes of Health. SEM's institution has received grant funding from the National Heart, Lung, and Blood Institute of the National Institutes of Health. DHA's institution has received grant funding from the National Heart, Lung, and Blood Institute of the National Institutes of Health institution and has received contract funding for industry-initiated research from Roche. AB's institution has received grant funding from the National Heart, Lung, and Blood Institute of the National Institutes of Health. AB's institution has received contract funding f from Radiometer and Ortho Scientific for industry-initiated research. CWB's institution has received grant funding from the National Heart, Lung, and Blood Institute of the National Institutes of Health. CWB has received funding personally from Roche for consulting. JMC institution has received grant funding from the National Heart, Lung, and Blood Institute of the National Institutes of Health. DBD institution has received grant funding from the National Heart, Lung, and Blood Institute of the National Institutes of Health. DBD has received funding personally from Roche for consulting and DBD's institution has received contract funding from Novartis, Ortho Scientific, and Roche for industry-initiated research institutional research. JEH's institution has received grant funding from the National Heart, Lung, and Blood Institute of the National Institutes of Health and JEH's institution has received contract funding from Alere, Siemens, Roche and Trinity for industry-initiated research institutional research. DKN's institution has received grant funding from the National Heart, Lung, and Blood Institute of the National Institutes of Health. DKN has received funding personally from Roche for consulting. MNS institution has received grant funding from the National Heart, Lung, and Blood Institute of the National Institutes of Health. KAS's institution has received grant funding from the National Heart, Lung, and Blood Institute of the National Institutes of Health. ABS's institution has received grant funding from the National Heart, Lung, and Blood Institute of the National Institutes of Health. ABS has received funding personally from Siemens and Quidel for consulting. STW's institution has received grant funding from the National Heart, Lung, and Blood Institute of the National Institutes of Health. BCS has received grant funding from the National Heart, Lung, and Blood Institute of the National Institutes of Health. BCS has received funding personally from Medtronic for consulting and received diagnostic testing platforms for this study from Roche.

Appendix



Appendix Figure 1.
Event Rate vs Biomarker Levels



Appendix Figure 2.
Event Rate vs log of Biomarker Levels

Appendix Table 1.

Multivariate Model of 30-Day Outcomes, Multiple Imputation for Missing Data

Variable	Estimate	t-value	p-value	95% CI	Missing Values
Age (10yrs)	−0.221	−3.206	0.001	(−0.356, −0.086)	0
Male Gender	−0.013	−0.105	0.917	(−0.256, 0.230)	0
Black	−0.225	−1.194	0.233	(−0.594, 0.144)	0
Other Race	−0.083	−0.219	0.827	(−0.824, 0.659)	0
Congestive Heart Failure	−0.205	−1.221	0.222	(−0.534, 0.124)	3

Variable	Estimate	t-value	p-value	95% CI	Missing Values
Coronary Artery Disease	−0.282	−2.043	0.041	(−0.552, −0.011)	3
Arrhythmia	0.721	5.646	<.001	(0.471, 0.972)	3
Dyspnea	0.410	3.079	0.002	(0.149, 0.671)	78
Hypotension	0.219	1.293	0.196	(−0.113, 0.55)	21
Abnormal Electrocardiogram	0.349	2.483	0.013	(0.073, 0.624)	60
Physician Risk Assessment	0.015	4.323	<.001	(0.008, 0.022)	90
Log(hscTnT)	0.388	5.876	<.001	(0.259, 0.518)	96
Log(NT-proBNP)	0.250	4.896	<.001	(0.150, 0.350)	0

* CI=Confidence intervals

Appendix Table 2.

Multivariate Model of 30-Day Outcomes, Interactions Between Cardiac Biomarkers

Variable	Estimate	Std. Error	z value	Pr(>|z|)
Age (10yrs)	−0.246	0.074	−3.314	0.001
Male Gender	−0.031	0.132	−0.233	0.816
Black	−0.212	0.200	−1.059	0.289
Other Race	−0.084	0.406	−0.206	0.837
Congestive Heart Failure	−0.265	0.177	−1.494	0.135
Coronary Artery Disease	−0.294	0.145	−2.021	0.043
Arrhythmia	0.760	0.135	5.628	0.000
Dyspnea	0.438	0.139	3.154	0.002
Hypotension	0.288	0.176	1.641	0.101
Abnormal Electrocardiogram	0.400	0.149	2.683	0.007
Physician Risk Assessment	0.016	0.004	4.147	0.000
Log(hscTnT)	0.674	0.224	3.006	0.003
Log(NT-proBNP)	0.374	0.119	3.144	0.002
Log(hscTnT) * *Log(NT-proBNP)*	−0.040	0.033	−1.219	0.223

* AIC: 1802, AUC: 0.7752

† n=3043 complete cases

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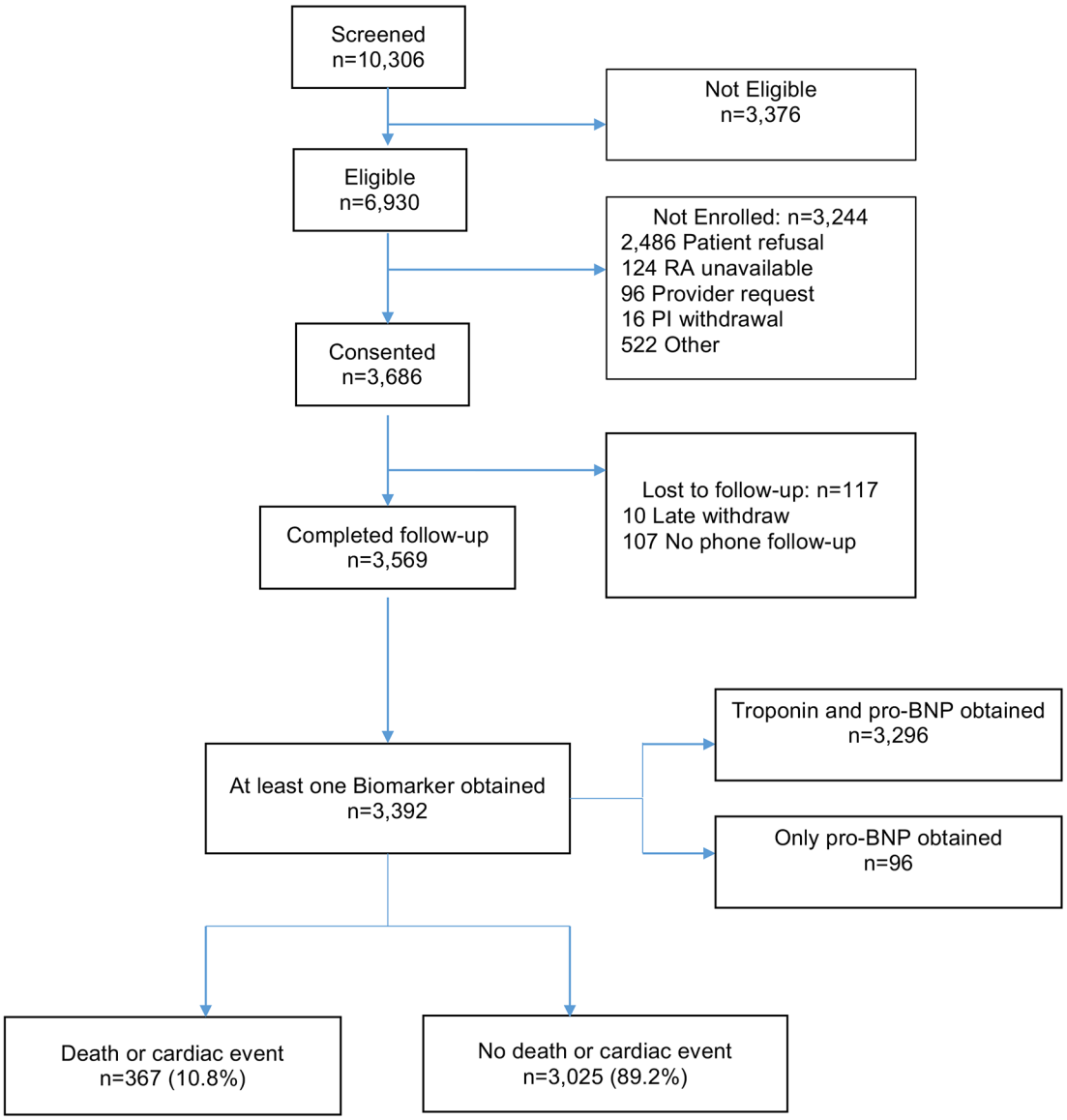

Figure 1.
Study Cohort, Central Figure

Table 1.

Cohort Characteristics

Variable	Overall Cohort (N=3392)	30-Day Event (n=367)	No 30-Day Events (n=3025)	p-value
Demographics				
Age, years (SD)	72.8 (9.0)	73.34 (9.0)	72.7 (9.0)	0.184
Male Gender, n (%)	1765 (52.0)	210 (57.2)	1555 (51.4)	0.04
Race, n (%)				0.575
White	2824 (83.7)	313 (85.5)	2511 (83.5)	
Black	443 (13.1)	44 (12.0)	399 (13.3)	
Other	105 (3.1)	9 (2.5)	96 (3.2)	
Co-Morbidities				
Congestive Heart Failure, n (%)	428 (12.6)	76 (20.7)	352 (11.6)	<0.001
Coronary Artery Disease, n (%)	920 (27.1)	120 (32.7)	800 (26.5)	0.014
Arrhythmia, n (%)	766 (22.6)	157 (42.8)	609 (20.2)	<0.001
Dyspnea, n (%)	710 (21.4)	114 (32.0)	596 (20.1)	<0.001
Hypotension, n (%)	362 (10.7)	61 (16.8)	301 (10.0)	<0.001
Abnormal ECG, n (%)	1842 (55.3)	261 (73.1)	1581 (53.1)	<0.001
Physician Risk Assessment, Mean, % (SD)	9.09 (13.04)	15.11 (18.80)	8.35 (11.93)	<0.001 *
Disposition—Admitted, n (%)	2637 (79.5)	338 (96.0)	2299 (77.5)	<0.001
Cardiac Biomarkers				
hscTnT (N=3296)				
hscTnT > 19 ng/L, n (%)	1052 (31.9)	196 (55.4)	856 (29.1)	<0.001
hscTnT, median [IQR]	12 [6, 24]	22 [10, 51]	11 [6, 22]	<0.001 *
NTpro-BNP (N=3392)				
NT-proBNP > 125 ng/L, n (%)	2244 (66.2)	324 (88.3)	1920 (63.5)	<0.001
NT-proBNP, median [IQR] ng/L	240 [88, 742]	776 [244, 2175]	210 [82, 620]	<0.001 *

*Logistic regression used on log transformed continuous variables,

†SD=Standard Deviation,

‡IQR=Interquartile Range

Table 2.

Type and Timing of 30-Day Outcomes

Outcome	All Outcomes n (%)*	Identified in ED n (%)	Identified after ED n (%)
Death			
Cardiac	14 (0.4)	0 (0.0)	14 (0.4)
Non-Cardiac/Unknown	27 (0.8)	0 (0.0)	27 (0.8)
Arrhythmia			
Ventricular Arrhythmia	8 (0.2)	4 (0.1)	4 (0.1)
Symptomatic Supraventricular Tachycardia	145 (4.3)	103 (3.0)	42 (1.2)
Sick sinus	21 (0.6)	7 (0.2)	14 (0.4)
Mobitz II/Complete Heart Block	12 (0.4)	7 (0.2)	5 (0.1)
Symptomatic Bradycardia	42 (1.2)	32 (0.9)	10 (0.3)
Pacemaker/ICD Malfunction	1 (0.0)	0 (0.0)	1 (0.0)
Myocardial Infarction	67 (2.0)	40 (1.2)	27 (0.8)
New Diagnosis of:			
Severe Aortic Stenosis	13 (0.4)	2 (0.1)	11 (0.3)
Outflow Obstruction	1 (0.0)	0 (0.0)	1 (0.0)
Severe Pulmonary Hypertension	20 (0.6)	3 (0.1)	17 (0.5)
Aortic Dissection	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary Embolism	33 (1.0)	24 (0.7)	9 (0.3)

*Denominator is entire cohort (N=3,392).

†Some people experienced more than one outcome

Table 3:

Diagnostic Yield for 30-day Serious Events by hscTnT and NT-proBNP cutoffs

hscTnT							**NT-proBNP**						
Cut Point	Sensitivity (95% CIs)	Specificity (95% CIs)	NPV (95% CIs)	PPV (95% CIs)	LR+ (95% CIs)	LR-(95% CIs)	Cut Point	Sensitivity (95% CIs)	Specificity (95% CIs)	NPV (95% CIs)	PPV (95% CIs)	LR+ (95% CIs)	LR-(95% CIs)
5	0.924, (0.891, 0.949)	0.219, (0.204, 0.235)	0.960, (0.942, 0.973)	0.125, (0.112, 0.138)	1.18, (1.14, 1.23)	0.35, (0.24, 0.50)	125	0.883, (0.845, 0.914)	0.365, (0.348, 0.383)	0.963, (0.950, 0.973)	0.144, (0.130, 0.160)	1.39, (1.33, 1.46)	0.32, (0.24, 0.43)
19	0.554, (0.500, 0.606)	0.709, (0.692, 0.725)	0.930, (0.918, 0.940)	0.186, (0.163, 0.211)	1.90, (1.71, 2.12)	0.63, (0.56, 0.71)	450	0.646, (0.594, 0.695)	0.692, (0.675, 0.708)	0.941, (0.931, 0.951)	0.203, (0.180, 0.227)	2.09, (1.91, 2.30)	0.51, (0.45, 0.59)
25	0.446, (0.394, 0.500)	0.798, (0.783, 0.812)	0.923, (0.912, 0.933)	0.210, (0.181, 0.241)	2.21, (1.93, 2.53)	0.69, (0.63, 0.76)	850	0.471, (0.419, 0.524)	0.802, (0.787, 0.816)	0.926, (0.915, 0.936)	0.224, (0.195, 0.255)	2.38, (2.09, 2.71)	0.66, (0.60, 0.73)
50	0.251, (0.207, 0.300)	0.923, (0.912, 0.932)	0.911, (0.900, 0.921)	0.281, (0.232, 0.334)	3.24, (2.61, 4.04)	0.81, (0.76, 0.86)	2000	0.264, (0.220, 0.313)	0.913, (0.903, 0.923)	0.911, (0.900, 0.921)	0.270, (0.225, 0.319)	3.05, (2.48, 3.75)	0.81, (0.76, 0.86)
100	0.147, (0.112, 0.188)	0.975, (0.969, 0.981)	0.905, (0.894, 0.915)	0.416, (0.329, 0.508)	5.92, (4.22, 8.30)	0.87, (0.84, 0.91)	4000	0.131, (0.098, 0.170)	0.965, (0.958, 0.972)	0.902, (0.891, 0.912)	0.314, (0.241, 0.394)	3.77, (2.73, 5.21)	0.90, (0.86, 0.94)
250	0.062, (0.039, 0.093)	0.995, (0.991, 0.997)	0.898, (0.887, 0.908)	0.579, (0.408, 0.737)	11.43, (6.06, 21.55)	0.94, (0.92, 0.97)	10000	0.049, (0.029, 0.076)	0.988, (0.984, 0.992)	0.895, (0.885, 0.906)	0.333, (0.211, 0.475)	4.12, (2.37, 7.18)	0.96, (0.94, 0.99)

*NPV = Negative predictive values,

†PPV= Positive predictive values,

‡LR+=Positive likelihood ratios,

§LR-=Negative likelihood ratios

‖95% CIs=95 % Confidence Intervals

Table 4.

Multivariate Model of 30-Day Outcomes, Complete Data

Variable	Estimate	Std. Error	z value	Pr(>|z|)
Age (10yrs)	−0.236	0.074	−3.180	0.001
Male Gender	−0.033	0.132	−0.253	0.800
Black	−0.231	0.200	−1.154	0.248
Other Race	−0.094	0.406	−0.231	0.817
Congestive Heart Failure	−0.270	0.178	−1.514	0.130
Coronary Artery Disease	−0.298	0.146	−2.042	0.041
Arrhythmia	0.775	0.135	5.744	0.000
Dyspnea	0.436	0.139	3.134	0.002
Hypotension	0.294	0.176	1.668	0.095
Abnormal Electrocardiogram	0.414	0.149	2.782	0.005
Physician Risk Assessment	0.015	0.004	4.089	0.000
Log(hscTnT)	*0.415*	*0.069*	*6.005*	*0.000*
Log(NT-proBNP)	*0.245*	*0.054*	*4.545*	*0.000*

*AIC: 1801, AUC: 0.7751

†n=3043 complete cases

Table 5.

Unadjusted and Predicted Adjusted Absolute Risk Association between Biomarkers and Outcomes

hscTnT (ng/L)*	**Patients**	**Event**	**Event Proportion**	**Adjusted Absolute Risk**	**Risk (95% CIs)**
<=5	672 (20.4)	27	0.04	0.04	(.03, .05)
6–19	1572 (47.7)	131	0.08	0.08	(.07, .09)
20–25	299 (9.1)	38	0.13	0.14	(.12, .15)
26–50	442 (13.4)	70	0.16	0.17	(.15, .18)
>50	311 (9.4)	88	0.28	0.29	(.26, .33)
Total	*2942*	*354*	*0.11*		
NT-proBNP (ng/L)†	**Patients**	**Event**	**Event Proportion**	**Adjusted Absolute Risk**	**Risk (95% CIs)**
<=125	1148 (33.8)	43	0.04	0.04	(.04, .05)
126–450	1074 (31.7)	87	0.05	0.08	(.08, .10)
451–850	398 (11.7)	64	0.16	0.13	(.12, .14)
851–2000	413 (12.2)	76	0.18	0.18	(.16, .20)
>2000	359 (10.6)	97	0.27	0.29	(.25, .32)
Total	*3025*	*367*	*0.11*		

*Limit of detection of HscTnT is 5 ng/L; 99th% (US) reference limit 19 ng/L

†Recommended clinical threshold of NT-proBNP 125 ng/L for age <75 years and 450 ng/L for age ≥ 75

‡CIs=Confidence intervals

§ng/L=nanograms per liter

Table 6.

Adjusted Odds Ratios for Primary Outcome of all 30-Day Serious Events

hscTnT Value (ng/L)	OR	OR (95% CIs)	NT-proBNP Value (ng/L)	OR	OR (95% CIs)
5	reference	NA	125	reference	NA
19	1.52	(1.21, 1.92)	450	1.49	(1.24, 1.78)
25	1.66	(1.25, 2.20)	850	1.82	(1.39, 2.38)
50	2.07	(1.38, 3.09)	2000	2.38	(1.61, 3.50)
100	2.57	(1.52, 4.34)	4000	3.16	(1.88, 5.30)
250	3.43	(1.73, 6.80)	10000	3.92	(2.12, 7.25)

*OR= Odds ratios

†CIs=Confidence intervals

‡ng/L=Nanograms per liter

Table 7.

Predicted Risk Associated with Cardiac Biomarker Levels for 30-Day Serious Events Identified After Index Emergency Department Visit

hscTnT (ng/L)	Absolute Risk	Risk (95% CIs)	NT-proBNP (ng/L)	Absolute Risk	Risk (95% CIs)
<=5	0.02	(.01, .02)	<=125	0.02	(.01, .02)
6–19	0.04	(.03, .04)	126–450	0.04	(.03, .04)
20–25	0.06	(.05, .07)	451–850	0.05	(.05, .06)
26–50	0.07	(.06, .09)	851–2000	0.08	(.06, .09)
>50	0.14	(.11, .17)	>2000	0.15	(.12, .18)

* CIs=Confidence intervals

† ng/L=Nanograms per liter

Table 8

Diagnostic Yield for 30-day Serious Events Identified After Index ED Visit by hscTnT and NT-proBNP cutoffs

hscTnT							**NT-proBNP**						
Cut Point	Sensitivity (95% CIs)	Specificity (95% CIs)	NPV (95% CIs)	PPV (95% CIs)	LR+ (95% CIs)	LR-(95% CIs)	Cut Point	Sensitivity (95% CIs)	Specificity (95% CIs)	NPV (95% CIs)	PPV (95% CIs)	LR+ (95% CIs)	LR-(95% CIs)
5	0.934, (0.882, 0.968)	0.211, (0.196, 0.225)	0.985, (0.973, 0.993)	0.054, (0.046, 0.063)	1.18, (1.13, 1.24)	0.31, (0.17, 0.57)	125	0.893, (0.834, 0.936)	0.350, (0.333, 0.367)	0.985, (0.976, 0.991)	0.063, (0.054, 0.074)	1.37, (1.29, 1.46)	0.31, (0.19, 0.48)
19	0.592, (0.510, 0.671)	0.694, (0.678, 0.710)	0.972, (0.965, 0.979)	0.086, (0.069, 0.104)	1.94, (1.68, 2.23)	0.59, (0.48, 0.71)	450	0.686, (0.607, 0.757)	0.672, (0.655, 0.688)	0.977, (0.970, 0.983)	0.093, (0.077, 0.111)	2.09, (1.86, 2.35)	0.47, (0.37, 0.59)
25	0.467, (0.386, 0.550)	0.783, (0.768, 0.797)	0.968, (0.961, 0.975)	0.094, (0.074, 0.117)	2.15, (1.79, 2.58)	0.68, (0.59, 0.79)	850	0.547, (0.466, 0.626)	0.788, (0.774, 0.802)	0.973, (0.966, 0.978)	0.113, (0.091, 0.137)	2.58, (2.21, 3.02)	0.57, (0.48, 0.68)
50	0.257, (0.189, 0.334)	0.912, (0.901, 0.921)	0.962, (0.955, 0.969)	0.123, (0.089, 0.164)	2.90, (2.16, 3.89)	0.82, (0.74, 0.90)	2000	0.308, (0.237, 0.386)	0.904, (0.893, 0.914)	0.964, (0.956, 0.970)	0.136, (0.103, 0.176)	3.21, (2.49, 4.15)	0.77, (0.69, 0.85)
100	0.138, (0.088, 0.203)	0.967, (0.960, 0.973)	0.959, (0.951, 0.965)	0.168, (0.107, 0.245)	4.18, (2.69, 6.48)	0.89, (0.84, 0.95)	4000	0.151, (0.099, 0.216)	0.960, (0.953, 0.967)	0.958, (0.951, 0.965)	0.157, (0.103, 0.224)	3.78, (2.52, 5.68)	0.88, (0.83, 0.94)
250	0.046, (0.019, 0.093)	0.990, (0.986, 0.993)	0.955, (0.948, 0.962)	0.184, (0.077, 0.343)	4.67, (2.09, 10.44)	0.96, (0.93, 1.00)	10000	0.057, (0.026, 0.105)	0.986, (0.981, 0.990)	0.955, (0.947, 0.962)	0.167, (0.079, 0.293)	4.07, (2.02, 8.17)	0.96, (0.92, 0.99)

*NPV = Negative predictive values,

†PPV= Positive predictive values,

‡LR+=Positive likelihood ratios,

§LR-=Negative likelihood ratios

‖95% CIs=95% Confidence Intervals