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[Jeffrey Wang] **Date**

Incorporating Novel Biomarkers to Predict 6-Month Mortality in Patients Hospitalized for Acute Heart Failure

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Incorporating Novel Biomarkers to Predict 6-Month Mortality in Patients Hospitalized for Acute Heart Failure

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Louisisana State University – Health Science Center – New Orleans 2015

Advisor: Alanna A. Morris MD, MSc

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Abstract

Incorporating Novel Biomarkers to Predict 6-Month Mortality in Patients Hospitalized for Acute Heart Failure

By: Jeffrey Wang, MD

Background: Predicting heart failure is important as patients with a high short-term mortality may benefit from early referral for advanced therapies such as heart transplantation or durable mechanical circulatory support. While multiple models exist to predict mortality in patients admitted for acute heart failure, none incorporate novel biomarkers of urine sodium and urine microalbumin.

Methods: We used the Renal Optimization Strategies Evaluation Acute Heart Failure (ROSE-AHF) trial database which enrolled adults (≥18 years) hospitalized for acute heart failure with chronic kidney disease (estimated glomerula filtration rate of 15 – 30 ml/min/1.73m^2). Complete case analysis was performed for each biomarker. Biomarkers were Box-Cox transformed if skewed distribution. We evaluated the ability of each individual biomarker, N-terminus B-type natriuretic peptide (NT-proBNP), urine sodium, and urine albumin to predict 6-month mortality. Additional covariates were added using backward selection with a p-value threshold <0.05. Evaluation of multivariable logistic regression models was performed using K-fold (k=5) cross validation. Area under the receiver operating curves (AUC) with 95% confidence intervals was evaluated for model.

Results: The ROSE-AHF database has 360 patients enrolled, after removing missing values for each biomarker, 345 patients were included in the NT-proBNP cohort, 335 patients were included in the microalbumin cohort, 316 patients were included in the urine sodium cohort, and 297 patients were included in the all-biomarker cohort. Evaluation of the multivariable logistic regression models for NT-proBNP was 0.78 (95% Confidence Interval [CI]: 0.69 – 0.78), urine microalbumin (AUC: 0.77, 95% CI: 0.67 – 0.78), urine sodium (AUC 0.77, 95% CI: 0.68 – 0.78).

Conclusion: Urine microalbumin and urine sodium perform similarly well in fully adjusted logistic regression models when compared to serum NT-proBNP in predicting 6-month mortality in patients hospitalized for acute heart failure.

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Introduction:

Despite sustained progress in reducing heart failure related mortality over the last 30 years, this trend reversed in 2015, with heart failure related mortality rising annually.[1,2] An even more concerning finding is that this trend is seen even among young adults, in whom a premature diagnosis of HF will result in many lost years of productivity.[3] Predicting heart failure is important as patients with a high short-term mortality may benefit from early referral for advanced therapies such as heart transplantation or durable mechanical circulatory support.[4] Hospital admission for acute heart failure is a late, but often the first clear indicator that a patient's heart failure is worsening.[5] While validated mortality predictions models such as the MAGICC Score[6] and the Seattle Heart Failure Model[7] exist, these models have only been validated in the outpatient setting and have not been be applied to inpatients admitted for acute heart failure (AHF). There have been several published prediction models for predicting short term mortality in patients hospitalized for acute heart failure, however one limitation is that these models generally do not incorporate biomarkers and rely solely on clinical data obtained from the electronic medical record data.[8]

Biomarkers have been in use in to diagnose and risk stratify heart failure. B-type natriuretic peptide (BNP) is a 26 amino-acid chain molecule that was initially discovered in 1988. It is predominantly released by cardiomyocytes in the ventricle in response to myocyte stretch and dilation.[9] Its mechanisms of action are thought to counter the effects of heart failure by effecting arterial vasodilation, increased urine production – thereby improving stroke volume.[9] Since discovery, it is now an established criterion in the universal definition in the diagnosis of heart failure set forth by the American College of Cardiology guidelines.[10] BNP levels are also important in risk stratifying heart failure patients, with higher BNP levels being associated with worse health status, higher risk for hospital readmission and cardiovascular related mortality.[11] There has been a recent push to use BNP as a surrogate clinical endpoint given its strong associations with HF outcomes.[12] In addition to BNP, there has been interest in evaluating and validating two new biomarkers, urine sodium excretion (termed natriuresis) and urine microalbumin.[13,14]

Natriuretic response to loop diuretics is a complex process regulated by multiple inputs including renin-angiotensin-aldosterone-system (RAAS) activation[15], levels of circulating natriuretic peptides[16], and arterial blood pressure[17]. Traditionally, the volume of urine output has been the key measurement of patient response to diuretics. However, there is evidence that regardless of the volume of urine, the amount of sodium excreted, or natriuretic response, is a better predictor of adverse clinical outcomes including 6-month mortality.[18] Furthermore, natriuretic response can easily be assessed early after the administration of loop diuretics by checking a spot urine sodium.[18] The European Society of Cardiology now recommend both monitoring hourly urine output and checking a urine sodium concentration after administration of loop diuretics to ensure adequate diuretic response. have recommended checking a urine sodium concentration 2-hours after administration of loop diuretics.[19]

Urine microalbumin has been used traditionally as a marker of chronic kidney disease, with higher level of microalbuminuria being associated with more advanced kidney disease stage.[20] However, recent evidence suggests that microalbuminuria is both an important marker and potential mechanism in the development and worsening of heart failure.[14] In several large population studies, the presence of albuminuria, defined as a urine albumin to creatinine ratio of > 30 mg/g was associated with an approximately 2-fold higher risk of developing incident heart failure.[21] In retrospective analyses of several heart failure trials, the presence of albuminuria was associated with an approximately 2-fold higher risk of heart failure hospitalization.[22] Several proposed mechanisms have been proposed to explain the mechanism by which albuminuria contributes worsening heart failure, including impaired renal filtration, endothelial injury, and systemic inflammation all leading to neurohormonal activation.[14]

Several inpatient calculators exist to estimate short term mortality among patients hospitalized for acute heart failure, however none have widespread use. In a recent study comparing seven published calculators, the ten most commonly variables between the calculators were demographics, laboratory values, vital signs and comorbidities (**Supplemental Table 1**).[8] Only one of the seven calculators

included a biomarker, B-type natriuretic peptide, which was included in the Get With the Guidelines database model by Eapen at al..

In this analysis, we will use the Renal Optimization Strategies Evaluation Acute Heart Failure (ROSE-AHF) trial database, which is publicly available through the National Heart, Lung, and Blood Institute (NHLBI) Biorepository. We will first investigate the relationship between these three biomarkers and 6-month mortality among patients hospitalized for acute heart failure. Secondly, we will create and validate a 6-month mortality risk calculator incorporating these three biomarkers. The ROSE-AHF database is well-positioned to investigate these biomarkers as it contains all three biomarkers.

Methods:

ROSE-AHF Database:

The ROSE-AHF was a randomized clinical trial designed to evaluate two strategies (in addition to one placebo controlled arm) to optimize management in patients admitted for acute heart failure with renal dysfunction. It compared either dopamine or low-dose nesiritide in conjunction with loop diuretics with placebo. The primary endpoints in this study were 72-hour urine output and change in serum cystatin C.

ROSE-AHF enrolled only adults, aged 18 years or older, who were hospitalized for acute heart failure and had evidence of renal dysfunction defined by an estimated glomerular filtration rate of 15 – 60 mL/min/1.73m^2. A total of 360 participants were enrolled, randomized essentially in a 1:1:1 fashion to either dopamine, low-dose nesiritide, or placebo. The findings of this study were that there was no difference in primary outcome between these three arms. Furthermore, there were no differences in secondary endpoints including decongestion, change in NT-proBNP, and 60-day combined mortality and hospital readmission. The clinical implications of this trial demonstrated that in patients with AHF and

renal dysfunction, adjunctive treatment with either nesiritide or dopamine along with diuretics did not improve decongestion or renal function.

Analytic Cohort:

Among the total patients enrolled, complete case analysis will be performed for each biomarker. When creating the analytic cohort for evaluate NT-proBNP as a biomarker, all patients with missing NT-proBNP at baseline will be excluded. The same approach will be applied to generate the analytic cohort for urine microalbumin and natriuresis. The primary outcome of interest is 6-month mortality.

Biomarkers:

The baseline (at time of enrollment into ROSE-AHF) values for NT-proBNP, urine microalbumin and the first 24-hour urine sodium collection were used. If biomarkers were significantly skewed then they were Box-Cox transformed. The relationship between biomarkers and the primary outcome of interest, 6-month mortality was first evaluated using boxplots stratified by 6-month mortality. Next. Univariate logistic regression was used to characterize the relationship between each biomarker of interest and 6-month mortality by calculating the probability of death for each given Box-Cox transformed biomarker value.

Univariate Model Development and Validation:

Four models were created (each individual biomarker along with a combined model including all three biomarkers) to predict 6-month mortality using logistic regression modeling. Model evaluation was performed using K-fold validation (with k=5). The approach of K-fold validation was selected which allows for full use of the dataset in validation. Traditional approaches of arbitrarily dividing the dataset

(i.e. 70% derivation to 30% validation) results in only partial use of the dataset whereas K-fold validation allows for complete use of the dataset, which was relevant in this case given the small sample size of the ROSE-AHF database. Furthermore, compared to other resampling methods such as bootstrapping, K-fold validation is considered to give a more accurate estimate of the model performance. The area under the receiver operating curve (AUC) was obtained from the analysis in each fold and was aggregated to provide an estimated AUC with 95% confidence interval.

Multivariate Model Development and Validation:

The complete database (n=360) was used to identify covariates that were significantly different between 6-month survivors and non-survivors. Differences were quantified using the Student's t-test and chi square analysis where appropriate. Covariates which had $p<0.1$ were selected for further testing. Using 6-month mortality as the outcome, all covariates selected were then placed into a logistic regression model then backward selection was used with a cutoff of $p=0.05$ to stop elimination. As a sensitivity analysis, the process was repeated with a cutoff of $p<0.2$ for selecting covariates to input into backward selection.

The final set of covariates selected using backward selection was then added to each of the four models (three models for individual biomarkers, one combined biomarker model), and validated using K-fold cross validation as described above. The outcome of interest was again AUC along with 95% Confidence Interval.

Results:

Analytic Cohort: Of the 360 patients enrolled, after excluding those with missing biomarkers for each analytic cohort, there were 345 patients available in the BNP analytic cohort, 335 patients in the urine

microalbumin cohort, 316 patients in the urine sodium cohort, and 297 patients in the combined biomarker cohort (**Figure 1**). Baseline characteristics of each cohort along with the total ROSE-AHF database cohort are shown in **Supplemental Table 2**.

Biomarker Distribution: The distribution of NT-proBNP, urine microalbumin concentration, and 24-hour urine sodium (Day 1) was found to be significantly skewed (**Supplemental Fig 2A-2C)**. After Box-Cox transformation, NT-proBNP and 24-hour urine sodium were not significantly skewed, however urine microalbumin concentration remained skewed (**Supplemental Fig 2D-2F**). Boxplots of biomarkers stratified by 6-month survival demonstrated that NT-proBNP was significantly lower in survivors compared to non-survivors (**Figure 2A**). While 24-hour urine sodium was numerically lower in non-survivors compared to survivors, this did not reach statistical significance (**Figure 2B**). There were no clinically meaningful differences in urine albumin to creatinine ratio between survivors and non-survivors (**Figure 2C**). Univariate logistic regression was used to investigate the relationship between each biomarker and predicted odds for 6-month mortality. The probability of death (a continuous value) was plotted against the Box-Cox transformed value of each biomarker. Overall, there is a direct relationship regarding Box-Cox transformed NT-proBNP and 6-month mortality (**Figure 2D**). While there appears to be an indirect relationship between Box-Cox transformed urine microalbumin/creatinine ratio, there were no clinically meaningful differences between survivors and non-survivors in Figure 2B therefore this relationship is not considered statistically significant (**Figure 2E**). Finally, there is an indirect relationship between Box Cox transformed 24-hour urine sodium and 6-month mortality with higher levels associated with lower odds of mortality (**Figure 2F**).

Covariate Selection: When stratified by 6-month mortality, non-survivors were older, more likely to be self-identified White race, and had significantly lower body mass index (BMI) and systolic blood

pressure. When identifying covariates with a $p<0.1$, non survivors had lower eGFR and were more likely to have ischemic etiology. Covariates significantly different at the $p<0.05$ level were inputted into a model and after backward selection (R package: stats, version 3.6.2), resulted in selection of ischemic etiology, estimated GFR, systolic blood pressure and body mass index. As a sensitivity analysis, covariates with a difference of $p<0.1$ were used, with the same covariates selected after applying backwards selection.

Model Evaluation and Calibration: Using 6-month mortality as the outcome, univariate models for the three biomarkers individually along with a combined 3-biomarker model were created. Using K-fold validation, the area under the receiver operating curve (AUC) with 95% confidence interval was found to most predictive using NT-proBNP alone (AUC: 0.67, 95% CI: 0.57 – 0.76) and the three-biomarker model (AUC: 0.67, 95% CI: 0.61 – 0.74, Fig 3). After adding in the covariates using backwards selection, all four models performed similarly with the all-biomarker model having an AUC: 0.75 (95% CI: 0.68 – 0.82, Fig 4). When the covariates selected by backward selection (ischemic etiology, estimated GFR, systolic blood pressure and body mass index) were used to create a model to predict 6-month mortality alone, they also had generally strong performance with an AUC: 0.74 (95% CI: 0.69 – 0.78). When split into six equal groups, calibration plot demonstrated that the all-biomarker model was well calibrated to the outcome (Fig 5).

Discussion:

In our analysis of the ROSE-AHF, we found that in univariate modeling, NT-proBNP remains the best biomarker to predict of 6-month mortality. Furthermore, incorporating four clinically relevant covariates that are readily available from the electronic medical record (ischemic etiology, estimated GFR, systolic blood pressure and body mass index) resulted in a parsimonious model with an AUC of

0.75 in predicting 6-month mortality. This model was well calibrated and with agreement between the predictions and observations across the predicted values.

In our final multivariate model incorporating NT-proBNP resulted in an AUC of 0.75, which is comparable to other published models predicting survival among patients admitted for acute heart failure, with AUCs from 0.69 to 0.81. Furthermore, with only five total variables, this would make this the most parsimonious model published to date in predicting mortality. As these five variables can be readily obtained upon admission, this model could potentially help with early identification of patients who may need evaluation by heart failure specialists for advanced therapies such as left ventricular assist device (LVAD) implantation or orthotopic heart transplantation (OHT). Early identification of these patients is important as the most common reason for not offering advanced therapies to patients with advanced heart failure are that they are too sick.[23]

Another important aspect of our model is its derivation and validation in the inpatient setting. Multiple mortality prediction models such as the Seattle Heart Failure Model and the MAGICC Score exist, however these scores were derived and validated on chronic outpatient heart failure populations. Worsening heart failure has traditionally been defined as an inpatient admission for acute heart failure and this is often the first "hard endpoint" triggers clinicians to assess whether a patient's heart failure is worsening.[24] However, this is considered a late sign and literature now suggests using other outpatient metrics such as outpatient intravenous diuretic therapy, escalation of diuretic therapy, and emergency room visit without admission as more modern definitions of heart failure worsening.[24] Our final model including NT-proBNP along with the four covariates, could be applied as a point of care tool to rapidly assist frontline clinicians to decide whether heart failure consultation should be obtained early during hospitalization.

While NT-proBNP performed well on univariate analysis, it was unexpected that both microalbumin/creatinine ratio did not perform well on univariate analysis. Microalbumin/creatinine ratio is a relatively new biomarker in heart failure that has been of significant interest given its ease in

collection and seemingly strong ability to predict incident heart failure along with rehospitalization for acute heart failure. The 95% confidence interval of the aggregate AUC from the microalbumin/creatinine ratio failed to clear the null line making it non-superior to a mere coin-flip. This discrepancy can be partially explained by the ROSE-AHF database inclusion criteria, which enrolled acute heart failure patients with comorbid chronic kidney disease, defined as an estimated glomerular filtration rate between 15 – 60 ml/min/1.73 m2. The KDIGO 2012 guidelines utilize albuminuria as a criteria for diagnosing chronic kidney disease. Furthermore, it is established that in heart failure patients, comorbid chronic kidney disease portends a worse prognosis compared to those with heart failure alone.[25] One hypothesis that could explain the lack of impact of albuminuria in our analytic cohort is that the presence of CKD, which was an enrollment criterion, is more influential factor on 6-month mortality. The presence of albuminuria in a CKD population has minimal ability to further risk stratify mortality risk among heart failure patients with comorbid CKD.

It was also unexpected that addition of 24-hour urine sodium did not noticeably improve the AUC in predicting 6-month mortality when added to NT-proBNP. There were significant differences in 24-hour urine sodium between 6-month survivors and non-survivors as evidenced by the boxplot, however the AUC with 95% confidence intervals were visually similar to NT-proBNP alone. One possible explanation for this finding is that NT-proBNP is one of the determinants of natriuresis. Natriuretic response is a complex final pathway that receives input from natriuretic peptides, systolic blood pressure (i.e. pressure natriuresis), renin-angiotensin, aldosterone system, and sympathetic tone. In heart failure, natriuretic peptides are released in response to congestion to induce natriuresis and diuresis to relieve congestion as a compensatory mechanism. This inverse relationship could thereby provide an explanation why addition of 24-hour urine sodium did not improve AUC. In examining the ROSE-AHF, while there is a weak correlation between Box Cox transformed NT-proBNP and Box Cox transformed 24-hour urine sodium, this correlation was not statistically significant ($r = -0.09$, $p=0.10$, supplemental figure 3).

There are several limitations to our analysis, first is that our population is limited to those with chronic kidney disease due to the inclusion criteria in the ROSE-AHF database, potentially limiting the generalizability of these findings. Secondly, our sample size and the number of events (mortality) were small. Thirdly, there was missingness in our data, therefore complete case analysis was performed.

In summary, our findings support that NT-proBNP remains the strongest biomarker in predicting 6-month mortality. Using multivariate logistic regression, we developed a parsimonious model to predict 6-month mortality in patients admitted for acute heart failure, that requires only baseline NT-proBNP along with four easily obtained EMR clinical variables (ischemic etiology, estimated GFR, systolic blood pressure and body mass index). This easily applied model can be used by the bedside clinician to assist in risk stratifying and identify patients at high short term mortality risk and would therefore benefit from early referral to advanced therapies (i.e. LVAD and OHT).

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Figure 1: CONSORT diagram describing the criteria used to create the analytic cohorts for N-Terminal Pro B-Type Natriuretic Peptide, Microalbumin, Urine Sodium and the Combined biomarker analyses groups.

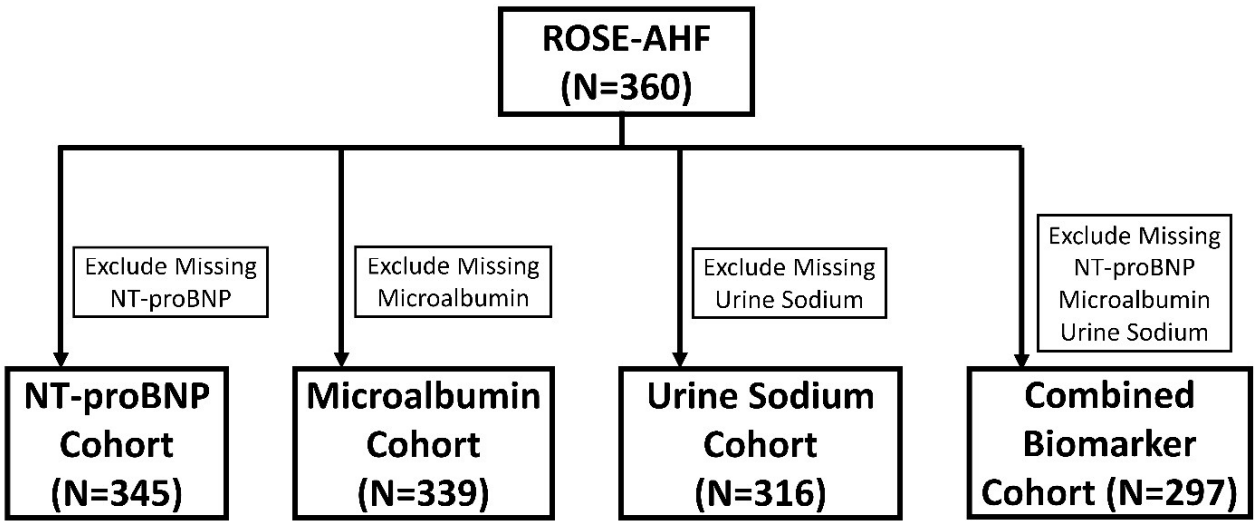
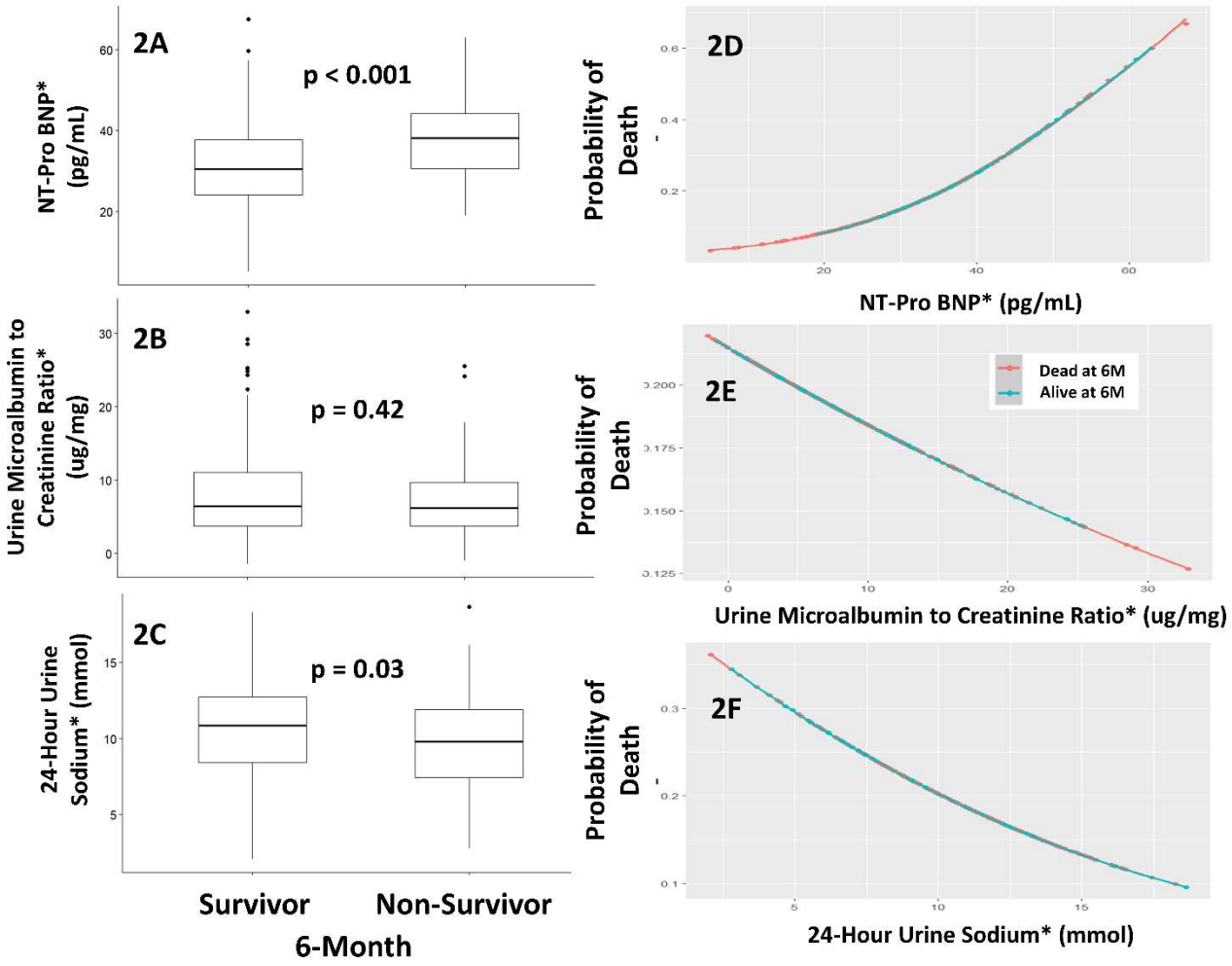


Figure 2. Biomarker distribution stratified by 6-month mortality and estimated probability of Death. N-Terminal Pro B-Type Natriuretic Peptide for Each Biomarker. **2A – 2F Box plot distribution stratified by 6-month mortality and relationship**



(See PowerPoint)

Table 1: Baseline characteristics that vary according to 6-month mortality

	Alive at 6-Months (n=289)	**Died by 6-Months** (n=71)	**Overall** (n=360)	**P-Value**
Age, y	68.9 ± 12.5	72.2 ± 10.6	69.5 ± 12.2	0.04
Male	209 (72.3%)	55 (77.5%)	264 (73.3%)	0.47
Race **White** **Black** **Other**	 210 (72.7%) 68 (23.5%) 11 (3.8%)	 62 (87.3%) 6 (8.5%) 3 (4.2%)	 272 (75.6%) 74 (20.6%) 14 (3.9%)	 0.02
BMI, kg/m^2	33.3 ± 8.2	28.0 ± 5.5	32.3 ± 8.0	<0.001
Heart Rate, BPM	76.4 (13.9)	75.2 (14.8)	76.2 (14.0)	0.51
Systolic BP, mmHg	120 (19.2)	108 (12.2)	118 (18.6)	<0.001
eGFR, mL/min/1.73 m^2	43.7 [33.2, 53.7]	40.8 [29.0 ,50.6]	42.9 [32.2,53.3]	0.05
Diabetes	166 (57.4%)	34 (47.9%)	200 (55.6%)	0.19
Ischemic Etiology	160 (55.4%)	49 (69.0%)	209 (58.1%)	0.05
ICD in Place	121 (41.9%)	36 (50.7%)	157 (43.6%)	0.23
24-houe Urine Output	2740 [1890, 3800]	2430 [1850, 3510]	2650 [1860, 3710]	0.45
NT-pro BNP, pg/mL	4290 [1990, 8850]	9270 [4380, 15500]	4970 [2330, 10300]	<0.001
Microalbumin/Creatinine Ratio, mcg/mg	42.7 [13.0, 175]	38.1 [12.5, 109]	41.4 [12.7, 172]	0.40
24-hour Urine Sodium, mmol	170 [85.3, 269]	128 [62.2, 221]	158 [80. 8, 261]	0.10

Data are presented as mean ± SD, median [Interquartile range], n (%)

Abbreviation: BMI: Body Mass Index, BPM: Beats Per Minute, BP: Blood Pressure, eGFR: Estimated Glomerular Filtration Rate, ICD: Implantable Cardiac Defibrillator, NTproBNP: N-Terminal Pro B-Type Natriuretic Peptide

Figure 3: Evaluation of Univariate Biomarker Models to Predict 6-month Mortality. The area under the receiver operating curve along with 95% confidence intervals are plotted for the univariate models for NTproBNP: N-Terminal Pro B-Type Natriuretic Peptide, urine microalbumin/creatinine ratio, 24-hour urine sodium and all three biomarkers.

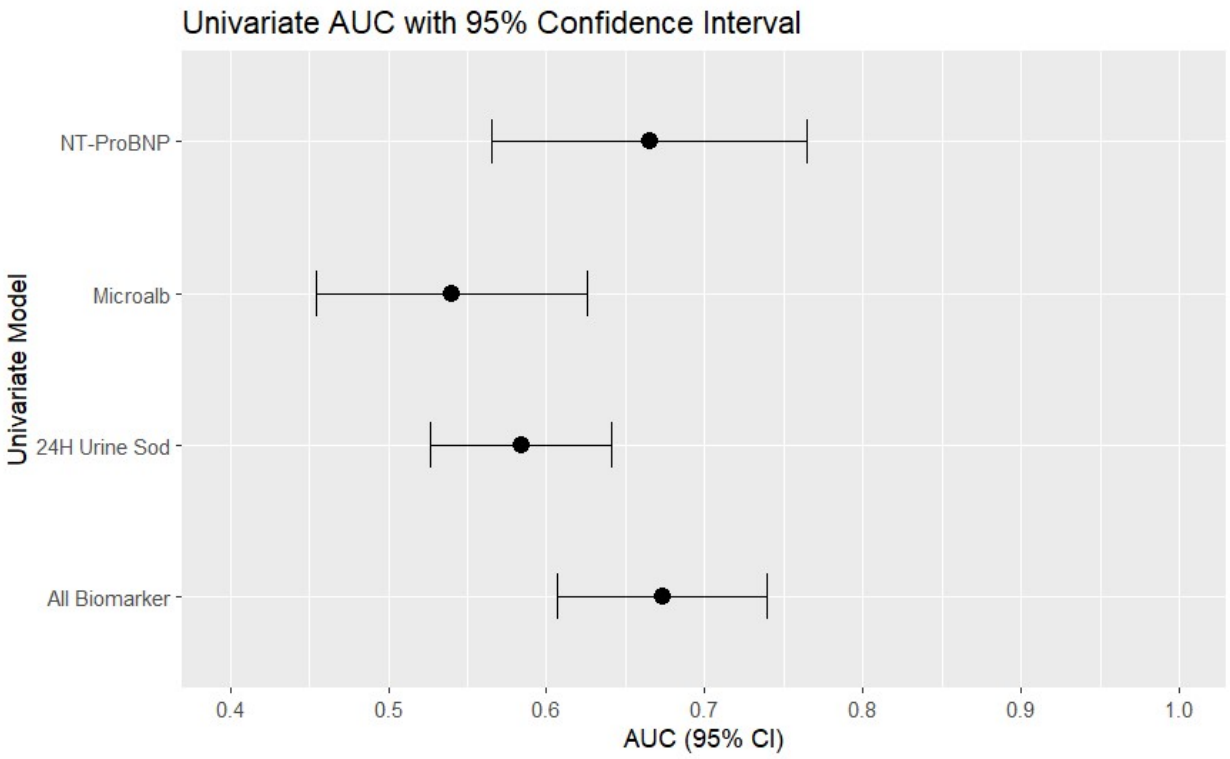


Figure 4: Evaluation of Multivariate Biomarker Models to Predict 6-month Mortality. The area under the receiver operating curve along with 95% confidence intervals are plotted for the adjusted multivariate models for NTproBNP: N-Terminal Pro B-Type Natriuretic Peptide, urine microalbumin/creatinine ratio, 24-hour urine sodium, covariates alone, and all three biomarkers.

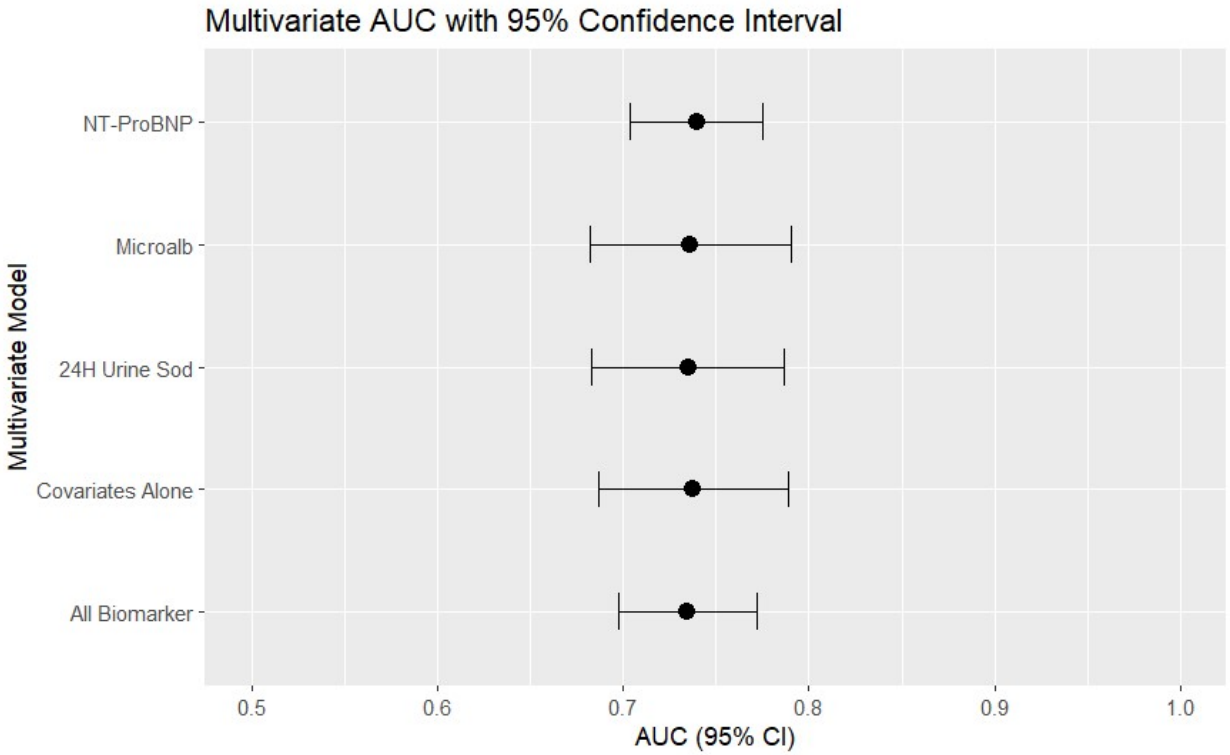
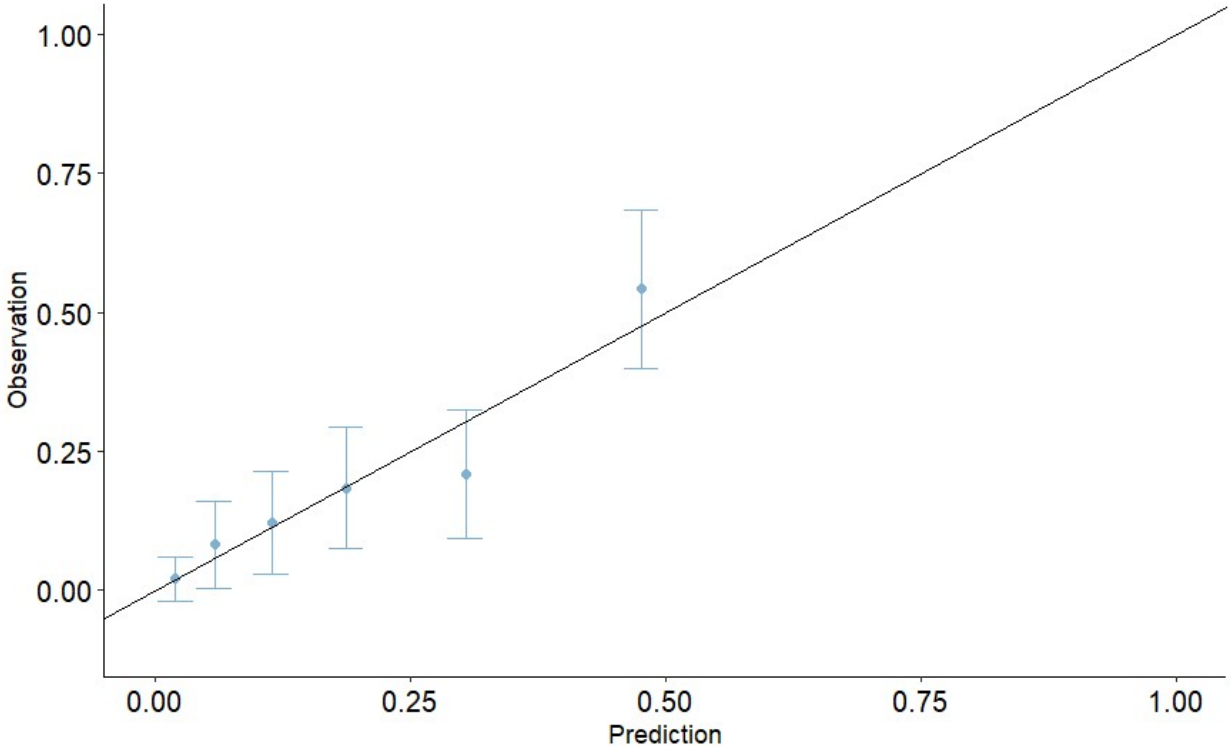


Figure 5: Calibration Plot of the Multivariate Model using N-Terminal Pro B-Type Natriuretic Peptide alone.



Supplemental Table 1: Table listing the 10 most commonly incorporated electronic medical record variables in seven published mortality prediction models in patients hospitalized for acute heart failure[8].

	LAPS2	ADHERE	EFFECT	GWTW-Pet	GWTG-Eap	Premier	Premier +
AUC	**0.80**	**0.68**	**0.70**	**0.69**	**0.70**	**0.76**	**0.81**
Age	✓	✓	✓	✓	✓	✓	✓
Race	✓			✓	✓	✓	✓
BUN	✓	✓	✓	✓	✓		
Systolic BP	✓	✓	✓	✓	✓		
Sodium	✓		✓	✓	✓		
HR	✓	✓		✓	✓		
COPD			✓	✓		✓	✓
Sex	✓					✓	✓
Resp Rate	✓		✓		✓		
Dementia			✓			✓	✓

Abbreviations: ADHERE: Acute Decompensated Heart Failure National Registry Algorithm, EFFECT: Enhanced Feedback for Effective Cardiac Treatment – Heart Failure, Eap: Eapen, GWTW: Get With The Guidelines, LAPS2: Laboratory Acute Physiology Score, Pet: Peterson,

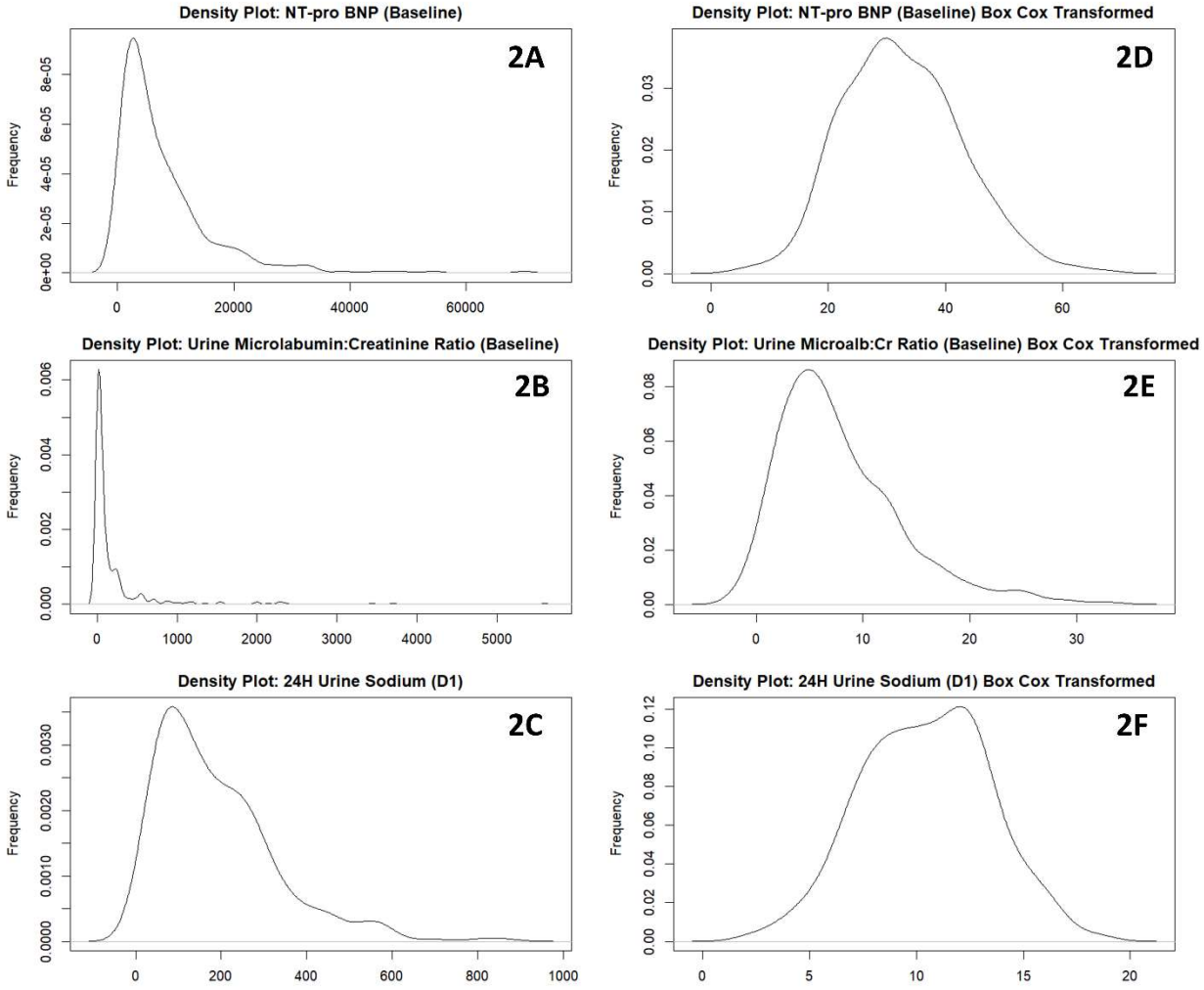
Supplemental Table 2: Baseline Characteristics of Analytic Cohorts: Baseline characteristics after exclusion of those missing baseline biomarkers for the NT-proBNP cohort, Microalbumin Cohort, Urine Sodium Cohort and the Combined Biomarker Cohort.

	Total Cohort (n=360)	**NT-pro BNP Cohort** (n=345)	**Microalbumin Cohort** (n=335)	**Urine Sodium Cohort** (n=316)	**Combined Biomarker Cohort** (n=297)
Age, y	69.5 ± 12.2	69.7 ± 12.1	69.7 ± 12.0	70.2 ± 12.0	70.2 ± 11.9
Male	264 (73.3%)	257 (74.5%)	245 (73.1%)	233 (73.7%)	219 (73.7%)
Race					
White	272 (75.6%)	261 (75.7%)	252 (75.2%)	241 (76.3%)	228 (76.8%)
Black	74 (20.6%)	72 (20.9%)	69 (20.6%)	62 (19.6%)	57 (19.2%)
Other	13 (3.9%)	12 (3.5%)	14 (4.2%)	13 (4.1%)	12 (4.0%)
BMI, kg/m^2	32.3 ± 8.0	32.3 ± 7.9	32.5 ± 8.0	32.3 ± 7.9	32.4 ± 7.9
Heart Rate, BPM	76.2 ± 14	76.0 ± 13.9	76.1 ± 14.0	75.7 ± 13.8	75.8 ± 13.9
Systolic BP, mmHg	118 ±18.6	118 ± 18.5	118 ± 18.6	118 ± 17.9	118 ± 18.1
eGFR, mL/min/1.73 m^2	42.9 [32.2, 53.3]	42.9 [32.2, 53.3]	42.8 [31.8, 53.1]	42.8 [31.8, 53.1]	42.5 [31.7, 53.1]
Diabetes	200 (55.6%)	190 (55.1%)	187 (55.8%)	178 (56.3%)	168 (56.6%)
Ischemic Etiology	209 (58.1%)	200 (58%)	195 (57.9%)	184 (58.2%)	174 (58.6%)
ICD in Place	157 (41.9%)	148 (42.9%)	146 (43.6%)	133 (42.1%)	122 (41.1%)
24-H Urine Output, mL	2650 [1860, 3710]	2700 [1870, 3740]	2700 [1890, 3780]	2650 [1870, 3750]	2700 [1900, 3800]
NT-pro BNP, pg/ml	4970 [2330, 10300]	4970 [2330, 10300]	4970 [2330, 9880]	5120 [2360, 10300]	5250 [2360, 10100]
Microalbumin/Creatinine Ratio, mg/g	41.4 [12.7, 172]	40.7 [12.5, 175]	42.0 [13.8, 175]	41.9 [13.7, 178]	41.8 [13.6, 180]
24-H Urine Sodium, mmol	158 [80.8, 261]	160 [82.4, 264]	159 [81.2, 263]	158 [80.8, 261]	163 [81.6, 266]
6-Month Mortality	71 (19.7%)	66 (19.1%)	64 (19.1%)	63 (19.9%)	58 (19.5%)

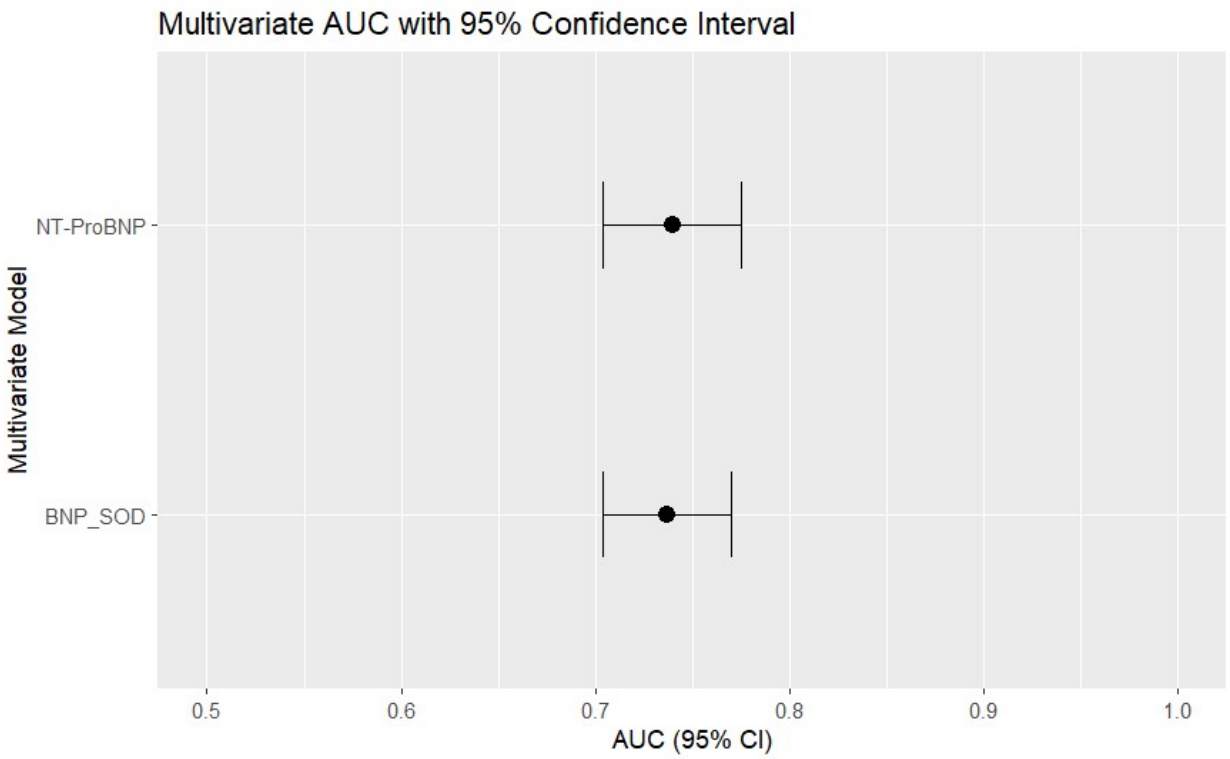
Data are presented as mean ± SD, median [Interquartile range], n (%)

Abbreviation: BMI: Body Mass Index, BPM: Beats Per Minute, BP: Blood Pressure, eGFR: Estimated Glomerular Filtration Rate, ICD: Implantable Cardiac Defibrillator, NTproBNP: N-Terminal Pro B-Type Natriuretic Peptide

Supplemental Figures 1. Baseline distribution of N-Terminal Pro B-Type Natriuretic Peptide, Urine microalbumin/creatinine ratio, and 24-hour urine sodium before (2A-2C) and after Box-Cox transformation (2D-2F).



Supplemental Figure 2: Evaluation of Addition of 24-hour urine sodium to N-Terminal Pro B-Type Natriuretic Peptide in predicting 6-month mortality.



Supplemental Figure 3. Scatterplot of Box-cox transformed 24-hour urine sodium vs. Box-Cox transformed N-Terminal Pro B-Type Natriuretic Peptide with regression line overlaid.