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## From Statistical Significance to Clinical Relevance: A Simple Algorithm to Integrate BNP and the Seattle Heart Failure Model for Risk Stratification in Heart Failure

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### Abstract

**Background**—Heart failure (HF) guidelines recommend brain natriuretic peptide (BNP) and multivariable risk-scores such as the Seattle HF Model (SHFM) to predict risk in HF with reduced ejection fraction (HFrEF). A practical way to integrate information from these two prognostic tools is lacking. We sought to establish a SHFM+BNP risk-stratification algorithm.

**Methods**—The retrospective derivation cohort included consecutive patients with HFrEF at Mayo. One-year outcome (death, transplantation or ventricular assist device) was assessed. The SHFM+BNP algorithm was derived by stratifying patients within SHFM-predicted risk categories ( 2.5%, 2.6– 10%, >10%) according to BNP above or below 700 pg/mL and comparing SHFM-predicted and observed event rates within each SHFM+BNP category. The algorithm was validated in a prospective, multicenter HFrEF registry (Penn HF Study).

**Results**—Derivation (n=441; one-year event rate 17%) and validation (n=1513; one-year event rate 12%) cohorts differed with the former being older and more likely ischemic with worse symptoms, lower EF, worse renal function, higher BNP and SHFM scores. In both cohorts, across the three SHFM-predicted risk strata, a BNP>700 pg/ml consistently identified patients with approximately three-fold the risk that the SHFM would have otherwise estimated regardless stage of HF, intensity and duration of HF-therapy, and comorbidities. Conversely, the SHFM was appropriately calibrated in patients with a BNP<700 pg/ml.

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#### Disclosures

Dr. Cappola reports receiving support for running biomarker assays from Abbott Diagnostics. Dr. Jaffe has or presently consults for most of the major diagnostic companies including those whose assays are used in this analysis. Drs. French, Fang, Sweitzer, AbouEzzedine and Redfield have no disclosures.

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**Conclusion**—The simple SHFM+BNP algorithm displays stable performance across diverse HFrEF cohorts and may enhance risk stratification to enable appropriate decisions regarding HF therapeutic or palliative strategies.

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## Introduction

Accurate risk stratification in heart failure (HF) patients is needed to facilitate informed decisions regarding medications, defibrillators, transplantation, ventricular assist devices (LVAD), experimental therapies and palliative or end-of-life care<sup>1</sup>. Clinical characteristics, biomarkers, exercise performance and imaging parameters have all been utilized to assess risk<sup>2</sup>. Recent HF guidelines recommend use of natriuretic peptides assays and multivariable clinical risk-scores to quantify risk<sup>1</sup>.

The Seattle HF Model (SHFM)<sup>3</sup> is a risk-score that integrates clinical, pharmacological, device and laboratory characteristics, offering a comprehensive profile of the HF patient. It has been reported to predict outcomes in clinical trial and registry cohorts<sup>4–14</sup>. However, it does not capture pertinent prognostic factors such as medication doses, delivered ICD therapies and HF hospitalizations. Elevated B-type natriuretic peptide (BNP) levels predict HF events and mortality in a wide variety of HF- cohorts<sup>15</sup> and may detect such facets of the HF clinical profile. However, despite decreasing costs of the BNP assay, its increased availability and widespread use<sup>16</sup>, for an individual patient, the predictive implications of the BNP level is difficult to ascertain<sup>15</sup>. BNP varies with age, sex, body size and renal function and declines with appropriate therapy. Hence, while elevated BNP values connote increased risk, interpretation of BNP levels must integrate information regarding patient characteristics, intensity of therapy and HF-stage. Notably, while guidelines recommend the use of BNP for risk stratification, they do not stipulate a specific BNP level above which its calibration is robust enough to identify high-risk patients that may benefit the most from particular management strategies.

Integrating BNP levels with the highly patient-specific characterization provided by the SHFM has great complementary potential. When added to the SHFM, BNP confers statistically significant improvement in discrimination (c-index) or reclassification as quantitated by net (NRI) or integrated (IDI) reclassification indices<sup>17–19</sup>. However, methods to translate these statistical indices to quantification of risk provided by the SHFM combined with BNP levels in clinical practice are lacking.

We sought to derive and validate a simple, clinically useful risk-assessment algorithm that incorporates both the SHFM and a specific BNP cutoff in patients with HF and reduced ejection fraction (HFrEF) seen across a spectrum of care environments and providers, at different stages in the natural history of HF, with variable intensity and duration of HF-therapy and with varying comorbidity burden.

## Methods

### Study Population

**Derivation Cohort**—We identified a retrospectively compiled cohort of consecutive HF patients seen at Mayo Outpatient Clinics and associated hospitals in Rochester, MN from July 1<sup>st</sup>, 2007 through December 31<sup>st</sup>, 2007, a time-frame intentionally chosen to pre-date the era of widespread LVAD referrals. Using a modification of a previously-described natural language processing program<sup>20</sup>, all electronic clinical notes were searched for non-negated terms (Supplemental Table 1) consistent with HF. Patients with ejection fraction (EF)  $\geq$  35% documented within two years were included in the study and underwent detailed medical record review. The date of the most recent echocardiogram was considered the fiducial point for assessment of risk-scores, comorbidities and outcomes. New York Heart Association functional class (NYHA) was verified by record review. Comorbidities, medications, electrocardiogram, echocardiogram and laboratory findings were extracted from the electronic medical record. Only patients with BNP levels on or within 30 days of the date of the echocardiogram were included in our cohort. The Triage® BNP assay, as previously reported<sup>21, 22</sup>, was utilized. The ascertainment of death (query date 3/1/2009) was determined from the Mayo registration database and included several procedures, as previously described<sup>23</sup>. Accurint®, an institutionally approved Web-based resource and location service that includes data from the Social Security Death Index was queried. Also, in addition to the deaths noted during clinical care, all death certificates for Olmsted County residents are obtained every year from the county office. Further, the Mayo Clinic registration office records the obituaries and notices of deaths in the local newspapers. Finally, data on all Minnesota deaths are obtained from the State of Minnesota every year. Heart transplantation or LVAD implantation was assessed by chart review and by cross-match with the surgical transplant and LVAD database of all heart transplantation or LVAD implantations at Mayo. One-year survival free from death, transplantation or LVAD implantation for all patients was ascertained. Only records of patients with consent for medical record use for research purposes were included. This study was approved by the Mayo institutional review board (IRB).

**Validation Cohort**—The Penn HF Study is a National Heart, Lung and Blood Institute sponsored, prospective, multicenter registry of outpatients with chronic HF recruited from the University of Pennsylvania (Philadelphia, PA), Case Western University (Cleveland, OH), and the University of Wisconsin (Madison, WI)<sup>18, 24, 25</sup>. The primary inclusion criterion was a clinical diagnosis of HF as determined by a HF-specialist. Participants were excluded if they have a non-cardiac condition resulting in an expected mortality of less than six months as judged by the treating physician, or if they were unable to provide consent. At time of study entry, clinical data were obtained using standardized questionnaires administered to the patient and physician, with verification through medical records. Blood samples were obtained at enrollment and BNP was measured using standard ARCHITECT immunoassays (Abbott Laboratories, Abbott Park, IL) as previously described<sup>26</sup>. Echocardiography was performed within 30 days of blood sampling. Follow-up events including all-cause mortality and cardiac transplantation or LVAD implantation were prospectively ascertained every six months through patient contact and verified through

death certificates, medical records, or contact with patients families by research personnel. All participants provided written informed consent, and the study protocol was approved by IRBs.

## SHFM

The SHFM is a multivariable risk-prediction score based on clinical, pharmacological, device and laboratory characteristics (Supplemental table 2). It has been validated in multiple HF populations as a predictor of mortality, cardiac transplantation or LVAD placement<sup>3</sup>. The version of the score used in this study was the SHFM-D, abbreviated as SHFM. The derivation and validation of the SHFM has been previously described<sup>4</sup>. Missing variables were quantified (Supplemental Table 2). For calculation of the SHFM, imputation of the mean value was performed.

## Derivation of the SHFM+BNP Algorithm

We derived a SHFM+BNP algorithm in the derivation cohort by stratifying patients within pre-specified categories of clinically relevant one-year risk [low (< 2.5%), intermediate (2.6–10%), and high (>10%)] per SHFM-predicted probabilities, calculated using the published SHFM score for one-year survival free of cardiac transplantation or LVAD placement. Next we stratified patients within each risk category according to BNP levels above or below the optimal partition-value based on ROC-analysis in the entire derivation cohort.

## Statistical Analysis

Baseline characteristics were summarized using standard descriptive statistics. Due to the skewed distribution of BNP, analyses were performed after log transformation. ROC curves were used to measure the ability of the SHFM and BNP (log-transformed, continuous variable) to discriminate those patients who died or required cardiac transplantation or LVAD implantation within one year. Using the derivation cohort ROC-analysis, we identified the optimal BNP value that maximized sensitivity and specificity and used it as the partition-value for the SHFM+BNP algorithm. We then estimated its corresponding sensitivity and specificity within the derivation and validation cohorts. Next, we compared the observed to the mean predicted risk within BNP subgroups of the SHFM-predicted risk categories within the derivation and validation cohorts.

We determined whether the prognostic potential associated with BNP varied across values of the SHFM by examining the statistical significance of the interaction term (SHFM by BNP partition value) in Cox-regression models. A statistically significant interaction term would suggest that the prognostic potential of BNP depended on the SHFM. For these analyses, we used a composite time-to-event outcome of time to death, cardiac transplantation or LVAD implantation. Patients who did not experience an outcome prior to one year were censored at one year. Sensitivity analyses examined the SHFM+BNP algorithm for the endpoint of one-year mortality alone, the use of optimal partition-value based on ROC analysis in the validation cohort, and use of N-terminal pro-B-type natriuretic peptide (NT-proBNP), which was available in a subset of the validation cohort.

In secondary analyses, we assessed whether BNP (as a log-transformed, continuous variable) provided incremental predictive information to the SHFM by comparing the c-index for scores without and with BNP. To assess discrimination, we derived Harrell's concordance index [c-index (95% confidence interval), ROC curve equivalent for right-censored data<sup>27</sup>] and compared as previously described<sup>28</sup>. Risk reclassification (net reclassification improvement; NRI) and discrimination (integrated discrimination improvement; IDI) analyses<sup>29, 30</sup> were performed as per recent recommendations<sup>31</sup>.

A p-value < 0.05 was considered statistically significant. Statistical analyses were performed using JMP version-7.0.1 (SAS Institute), MedCalc version-12.3.0 and R 3.0.1 (R Development Core Team, Vienna, Austria).

## Results

### Baseline Characteristics and outcomes

In the derivation cohort, of the 441 consecutive patients identified; 268 (61%) were community patients (residing within 100 miles of center) and 308 (70%), 101 (23%), and 32 (7%) were seen in cardiovascular, non-cardiovascular subspecialty and primary care settings, respectively. In the validation cohort, 1513 patients were included. Baseline characteristics from each cohort are shown (Table 1). Missing data was rare with one patient having no creatinine level, 12 having no NYHA classification and four having no sodium level available. The derivation cohort was older, more often male, had a higher prevalence of ischemic cardiomyopathy, lower BMI, lower EF, higher NYHA and more severe renal dysfunction. The derivation cohort patients were less likely to be on ACE-inhibitors, angiotensin-receptor blockers, aldosterone antagonists and beta-blockers. On average, the derivation cohort had higher BNP levels and SHFM scores, consistent with higher risk.

Follow-up was available for all patients in the derivation cohort at one year, at which time 61 (14%) had died, 8 (2%) had received cardiac transplantation and 6 (1%) had received a LVAD. The validation cohort was followed for at least one year, at which time 89 (12%) patients had died, 70 (5%) had received cardiac transplantation and 18 (1%) had received a LVAD.

### Predictive Characteristics of SHFM and BNP

**Derivation Cohort**—C-indices of the SHFM [0.75 (0.71,0.79)] and BNP [0.74 (0.70,0.78)] were significantly greater than 0.50 (Figure 1a). SHFM and BNP were each associated with one-year survival free of cardiac transplantation, or LVAD and offered similar (p=0.75) risk discrimination. There was only a moderate correlation between SHFM and BNP (R=0.43; p<0.001), suggesting that these variables assess different prognostic factors. BNP as a log-transformed, continuous variable enhanced the performance of the SHFM in predicting the composite one-year endpoint with a significant improvement in discrimination and reclassification criteria ( c-index of 0.03, NRI 10%, IDI 2%, p 0.04 for each).

**Validation Cohort**—C-indices of the SHFM [0.76 (0.72, 0.80)] and BNP [0.78 (0.75, 0.81)] were significantly greater than 0.50. SHFM and BNP were each associated with one-

year survival free of cardiac transplantation, or LVAD and offered similar ( $p=0.32$ ) risk discrimination. There was only a moderate correlation between SHFM and BNP ( $R=0.54$ ;  $p<0.001$ ).

### SHFM+BNP Algorithm

In the derivation cohort, a BNP value of 700 pg/mL maximized sensitivity (0.71) and specificity (0.70) for predicting one-year events (Figure 1). In the validation cohort, this value corresponded to a sensitivity of 0.55 and specificity of 0.82 and hence was used as the partition-value for the SHFM+BNP algorithm.

The ratio of observed-to-predicted risk was similar across the three categories of SHFM-predicted risk, indicating similar calibration of the SHFM within each cohort (Figure 2). The SHFM consistently underestimated risk in both cohorts. Across each SHFM-risk category, those with elevated BNP ( $\geq 700$  pg/mL) had higher observed events than predicted by the SHFM. Differences in observed versus predicted risk within the BNP subgroups were similar in the derivation and validation cohort across the three SHFM-risk categories (Figure 3).

Figure 4 displays hazard ratios (HR) comparing the hazard of the composite outcome of death, cardiac transplantation or LVAD implantation between BNP  $\geq 700$  pg/mL and BNP  $<700$  pg/mL, stratified by categories of clinically relevant one-year risk ( $\leq 2.5\%$ , 2.5–10%, and  $>10\%$ ) per the SHFM. Although the estimated HR decreased with increasing SHFM, there was no evidence to suggest that the HR differed by SHFM category in the derivation ( $P=0.29$ ) or validation ( $P=0.33$ ) cohorts. Confidence intervals (CI) were broad for the derivation cohort due to limited sample size, particularly among those with SHFM risk  $\leq 2.5\%$  ( $n=45$ ).

We then fit Cox-regression models for the composite outcome that included SHFM as a continuous variable, BNP cut-point ( $\geq 700$  versus  $<700$  pg/mL) and their interaction to determine whether the prognostic potential of BNP was consistent across all levels of the SHFM. There was no evidence to suggest that the prognostic potential of BNP depended on the SHFM in either the derivation ( $P=0.11$ ) or validation ( $P=0.11$ ) cohorts.

In the absence of a statistically significant interaction, we estimated the prognostic potential of BNP in addition to the SHFM from Cox-regression models for the combined outcome that included SHFM as a continuous variable and BNP cut-point ( $\geq 700$  versus  $<700$  pg/mL). In the derivation cohort, the HR associated with a BNP  $\geq 700$  versus  $<700$  pg/mL was 2.6, 95% CI: (1.5, 4.4). In the validation cohort, the HR was 3.4, 95% CI: (2.5, 4.7).

We obtained similar results in a sensitivity analysis in which the outcome was limited to mortality alone (Supplemental Figure 1). In the derivation cohort, the HR associated with a BNP  $\geq 700$  versus  $<700$  pg/mL was 2.0, 95% CI: (1.1, 3.5). In the validation cohort, the HR was 4.2, 95% CI: (2.7, 6.6).

Sensitivity analysis of a SHFM+NT-proBNP algorithm was performed in the validation cohort (NT-proBNP levels were not available in derivation cohort). Consistently, across each SHFM risk category, using an optimal NT-proBNP cut-point of 1110 pg/mL, those patients



with elevated NT-proBNP had higher observed events than those with lower NT-proBNP (Figure 5). The HR associated with a NT-proBNP  $\geq 1110$  versus  $<1110$  pg/ml was 3.2, 95% CI: (2.1, 4.6).

## Discussion

In a single-center, retrospectively defined, derivation cohort of patients with HF<sub>rEF</sub> seen across a spectrum of care environments and providers, application of a simple SHFM+BNP risk-stratification algorithm revealed that regardless of patients SHFM predicted category of risk, a BNP  $\geq 700$  pg/mL identifies patients with two-fold risk of mortality than the SHFM would suggest while a BNP  $<700$  pg/ml identifies patients in whom the SHFM risk is well calibrated. In an external, prospective, validation cohort that was younger, less symptomatic, more commonly with non-ischemic etiology, higher EF, better renal function and lower BNP and SHFM scores, the SHFM+BNP algorithm performed similarly. This algorithm provides a method to integrate information from two well validated risk-prediction tools and provides a partition-value (BNP  $\geq 700$  pg/mL) that has reliable performance when interpreted in the context of the SHFM-predicted risk.

As compared to the average annual SHFM estimated mortality risk of approximately 20% in the high-risk category of our cohort, patients presented to the advanced HF therapeutics committee at a large HF center and listed as UNOS status II had an average annual SHFM estimated mortality risk of 16%<sup>5</sup>. This highlights the external validity and clinical relevance of the findings in our cohort that indeed is representative of patients being considered for advanced HF therapies and for whom better risk categorization is of benefit.

Consistent with previous reports<sup>17–19</sup>, our data shows that the combination of SHFM and BNP provides incremental, statistically significant risk prediction information. In a cohort of nonclinical trial, hospital-based patients with HF, BNP was found to add predictive information to the SHFM for predicting one-year survival free from death, transplantation or LVAD implantation (c-index of 0.05)<sup>17</sup>. Likewise, Ky et al. showed that adding NT-proBNP to the SHFM improved prediction of transplant-free survival at one year in a population of ambulatory patients with chronic HF (c-index of 0.02)<sup>18</sup>.

While this and other studies demonstrate that BNP assays provide statistically significant increments in the prognostic information provided by the SHFM, a practical way to integrate the information from these risk-assessment tools has been lacking. Ideally, the most rigorous method of complementing prognostic information from the SHFM with BNP would be an incorporation of BNP into the SHFM model whereby beta-estimates are used to generate an enhanced model. This would require a large population of patients with values for each of the 16 SHFM variables and simultaneous BNP levels. This is not feasible; hence, our proposal. To our knowledge, this is the first risk-assessment algorithm incorporating both the SHFM and BNP for clinical use in HF.

The information provided by the SHFM allows one to interpret the BNP level in the context of HF-stage and extent of HF-therapy. A limitation of BNP assays is that any given value of BNP may have different connotations depending on the duration or HF-stage and the

intensity of medical therapy. A high level in a decompensated patient with new-onset HF on little or no medical therapy does not necessarily carry the same risk as an identical level in a patient on maximal medical therapy and high-dose diuretics.

While the SHFM offers adequate risk discrimination in advanced HF, Kalogeropoulos et al.<sup>6</sup> showed that it systematically overestimated survival and underestimated risk, especially in blacks and in patients with devices. This finding was more prominent when including transplantation and LVAD implantation as an end point. Here, in a cohort that included up to 42% of patients with devices and 22% blacks, we show that the information provided by the BNP level overcomes this tendency of the SHFM to underestimate risk. This is likely explained by the ability of BNP to provide additional information regarding the heart structure and function, wall stress<sup>32</sup> and level of humoral activation and inflammatory/oxidative stress<sup>33</sup>.

The implications of our approach are three-fold: First, it identifies that patients with a BNP>700 have approximately three-fold the risk that the SHFM would estimate regardless of what HF-stage a patient is evaluated in, and irrespective of the intensity and duration of HF-therapy and comorbidity burden. Second, it allows a simple approach for risk-assessment relative to decisions for aggressive optimization of medical therapy, appropriate transition to advanced HF therapies and palliative or end-of-life care. Third, the stable performance of our algorithm across varied HF-cohorts suggests that this approach affords a means of indexing HF-populations for risk, something that may prove useful in clinical trials and daily practice.

## Limitations

Our study should be interpreted in the context of inherent methodological limitations of retrospective studies. NYHA, comorbidities and medications were obtained by individualized chart review and were limited by care providers documentation. Missing values were imputed for calculation of composite scores. Other studies validating composite risk-scores have been retrospective and had similar rates of missing data that had to be imputed<sup>5</sup>. The similar performance in a prospectively enrolled registry of patients suggests that the retrospectively derived data were valid. NT-proBNP levels were not available in the derivation cohort. Many facilities now use NT-proBNP rather than BNP. The sensitivity analysis in the validation cohort provides a level for NT-proBNP to use in a SHFM+NT-proBNP algorithm, but this requires replication. Cause of death was not determined and we are unable to determine whether the tool specifically identifies death to progressive pump failure, arrhythmia or non-HF related causes. Finally, we determined whether the prognostic potential of BNP was consistent across levels of the SHFM based on a statistical test for the interaction between the SHFM and BNP cut-point. It is possible that we were simply underpowered to detect an interaction.

## Conclusions

Establishing a specific BNP cutoff that identifies a higher-risk subset of patients, our proposed algorithm offers a simple approach to integrate prognostic information provided by



SHFM and BNP. Its stable characteristics and performance across these two diverse cohorts support its utility today in diverse clinical settings as physicians counsel HF patients regarding medications, defibrillators, advanced HF therapies, experimental therapies and palliative or end-of-life care.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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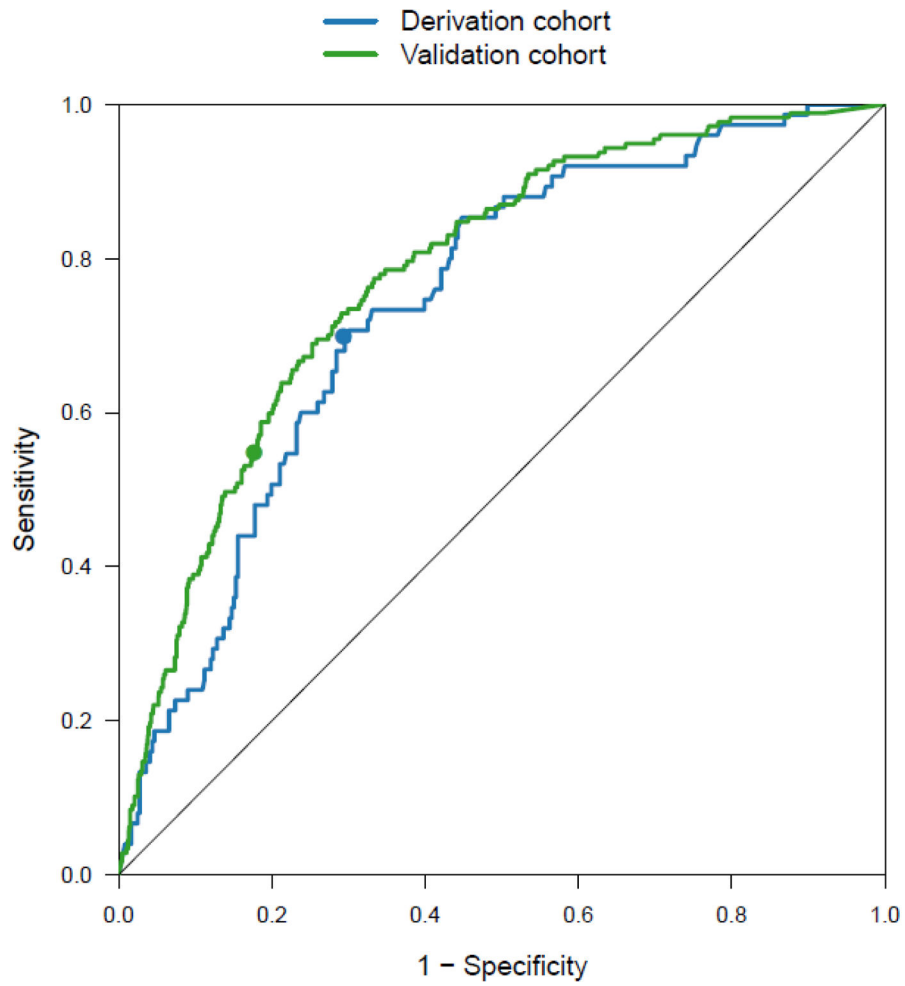
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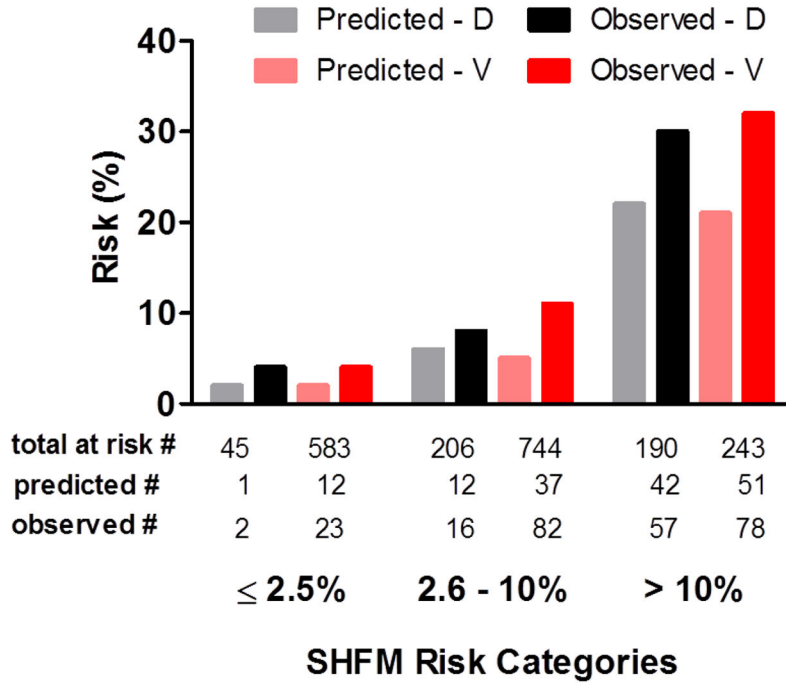
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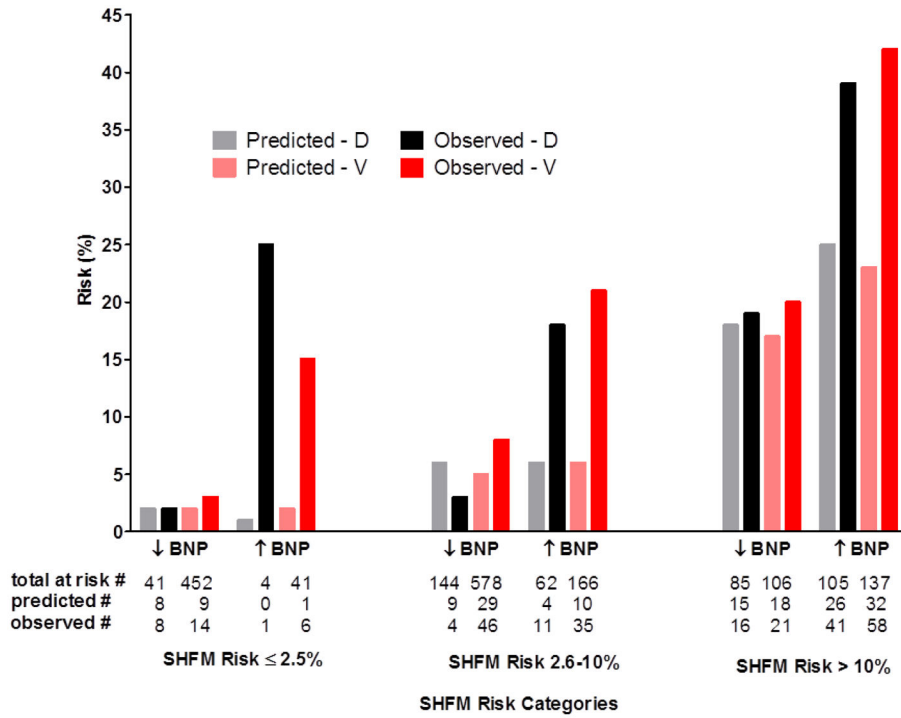
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**Figure 1.** Receiver operating characteristic (ROC) curves demonstrating the prediction accuracy of BNP for the composite outcome of death, cardiac transplantation or ventricular assist device implantation at one year in the derivation and validation cohorts. Circles indicate (1-specificity, sensitivity) for the BNP cut-point of 700 pg/mL.

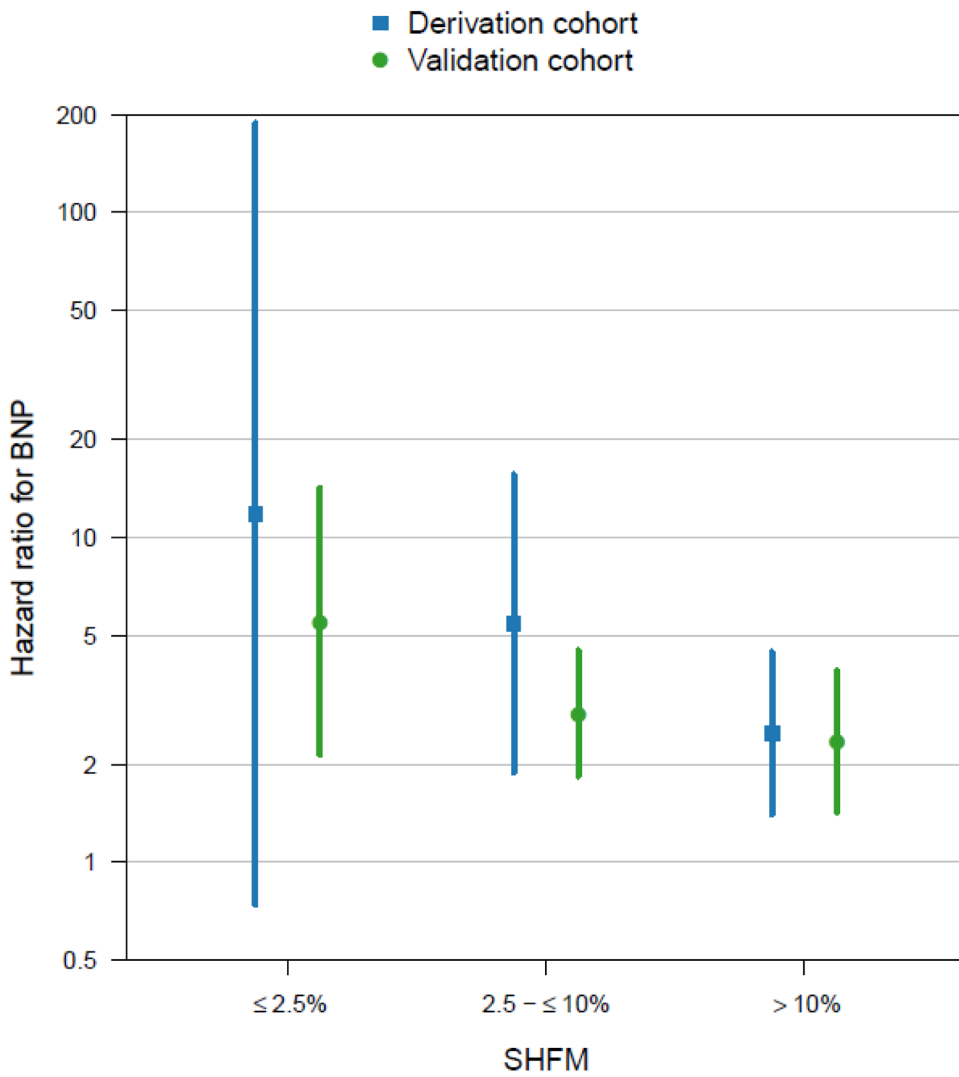


**Figure 2.** Calibration histograms in each of derivation (D) and validation (V) cohorts. Patients are stratified within the pre-specified categories of clinically relevant one-year risk [low (< 2.5%), intermediate (2.6– 10%), and high risk (>10%)] according to SHFM -predicted probabilities. One-year predicted SHFM mortality risk in each of the derivation cohort (grey bar) and validation cohort (pink bar). Observed composite one-year outcome of mortality, cardiac transplantation or ventricular assist device implantation in each of the derivation cohort (black bar) and validation cohort (red bar).

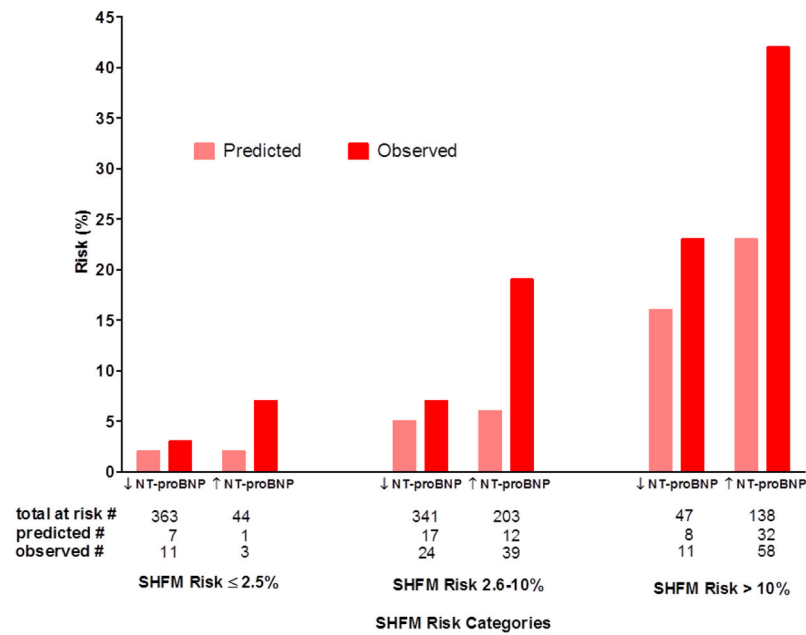


**Figure 3.** Calibration histograms in each of derivation (D) and validation (V) cohorts are shown with one-year predicted SHFM mortality risk in each of the derivation cohort (grey bar) and validation cohort (pink bar). Observed composite one-year outcome of mortality, cardiac transplantation or ventricular assist device implantation in each of the derivation cohort (black bar) and validation cohort (red bar). Patients are stratified within the pre-specified categories of clinically relevant one-year risk [low (< 2.5%), intermediate (2.5– 10%), and high risk (>10%)] according to SHFM-predicted probabilities and subsequently according to BNP levels above (↑) or below (↓) the optimal partition-value (700 pg/ml) based on ROC-analysis in the derivation cohort.





**Figure 4.** Hazard ratios for the composite outcome of death, cardiac transplantation or ventricular assist device implantation between BNP  $\geq 700$  pg/mL and BNP  $< 700$  pg/mL, stratified by categories of clinically relevant one-year risk ( $\leq 2.5\%$ ,  $2.5-10\%$ , and  $>10\%$ ) according to the SHFM. Sample sizes in each group are provided in Figure 3.



**Figure 5.** NT-proBNP sensitivity analysis within validation cohort. Calibration histograms shown: one-year observed mortality, cardiac transplantation or ventricular assist device implantation (red bar) and SHFM-predicted mortality risk (pink bar). Patients are stratified within the pre-specified categories of clinically relevant one-year risk [low ( ≤ 2.5%), intermediate (2.5– 10%), and high risk (>10%)] according to SHFM -predicted probabilities and subsequently according to NT-proBNP levels above (↑) or below (↓) the optimal partition-value (NT-proBNP > 1100) based on ROC-analysis in the validation cohort.

**Table 1**

## Baseline Characteristics of Derivation and Validation Cohorts

| <b>PATIENT CHARACTERISTICS</b>                      | <b>Derivation Cohort<br/>n=441</b> | <b>Validation Cohort<br/>n=1513</b> |
|---|------------------------------------|-------------------------------------|
| Age (years), mean $\pm$ SD                          | 69 $\pm$ 14                        | 56 $\pm$ 15                         |
| Male Sex, n (%)                                     | 317 (72)                           | 1000 (66)                           |
| Race, n (%)   |                                    |                                     |
| White   | 410 (93)                           | 1114 (74)                           |
| African American                                    | 9 (2)                              | 330 (22)                            |
| Other   | 22 (5)                             | 69 (4)                              |
| Body Mass Index (Kg/m <sup>2</sup> ), mean $\pm$ SD | 29 $\pm$ 6                         | 30 $\pm$ 7                          |
| Systolic BP (mmHg), Mean $\pm$ SD                   | 115 $\pm$ 20                       | 114 $\pm$ 20                        |
| Ejection Fraction (%), mean $\pm$ SD                | 26 $\pm$ 6                         | 34 $\pm$ 17                         |
| Ischemic Cardiomyopathy, n (%)                      | 250 (57)                           | 455 (30)                            |
| NYHA Functional Class III/IV, n (%)                 | 294 (67)                           | 558 (37)                            |
| Implantable Defibrillator, n (%)                    | 181 (44)                           | 636 (42)                            |
| Estimated GFR, mL/min/1.73m <sup>2</sup>            | 58 $\pm$ 25                        | 84 $\pm$ 32                         |
| SHFM Score, mean $\pm$ SD                           | 0.80 $\pm$ 0.9                     | -0.07 $\pm$ 1.0                     |
| <b>LABORATORIES</b>                                 |                                    |                                     |
| BNP (pg/mL), median (IQR)                           | 547 (276,1146)                     | 171 (47,576)                        |
| Creatinine (mg/dL), median (IQR)                    | 1.3 (1.0, 1.6)                     | 0.9 (0.8,1.3)                       |
| Sodium (mEq/L), mean $\pm$ SD                       | 139 $\pm$ 3.7                      | 139 $\pm$ 3.4                       |
| Uric Acid (mg/dL), median (IQR)                     | 7.8 (5.9,9.8)                      | 7.0 (5.7,8.8)                       |
| <b>MEDICATIONS (%)</b>                              |                                    |                                     |
| ACE inhibitors or ARBs                              | 71                                 | 87                                  |
| Aldosterone Antagonists                             | 25                                 | 34                                  |
| Beta-Blockers                                       | 81                                 | 88                                  |
| Digoxin   | 41                                 | 39                                  |
| Diuretics   | 76                                 | 78                                  |
| Statin  | 53                                 | 50                                  |

**Abbreviations;** BNP, brain natriuretic peptide; BP, blood pressure; GFR, glomerular filtration rate; NYHA, New York Heart Association, SHFM, Seattle Heart Failure Model.