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From statistical significance to clinical relevance: A simple algorithm to integrate brain natriuretic peptide and the Seattle Heart Failure Model for risk stratification in heart failure

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BACKGROUND: Heart failure (HF) guidelines recommend brain natriuretic peptide (BNP) and multivariable risk scores, such as the Seattle Heart Failure Model (SHFM), to predict risk in HF with reduced ejection fraction (HFrEF). A practical way to integrate information from these 2 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 the Mayo Clinic. 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 ($\leq$2.5%, 2.6% to $\leq$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; 1-year event rate 17%) and validation (n = 1,513; 1-year event rate 12%) cohorts differed with the former being older and more likely ischemic with worse symptoms, lower EF, worse renal function and higher BNP and SHFM scores. In both cohorts, across the 3 SHFM-predicted risk strata, a BNP >700 pg/ml consistently identified patients with approximately 3-fold the risk that the SHFM would have otherwise estimated, regardless of 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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CONCLUSION: The simple SHFM+BNP algorithm displays stable performance across diverse HFrEF cohorts and may enhance risk stratification to enable appropriate decision-making regarding HF therapeutic or palliative strategies.
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Accurate risk stratification in heart failure (HF) patients is needed to facilitate informed decisions regarding medications, defibrillators, transplantation, left ventricular assist devices (LVADs), experimental therapies and palliative or end-of-life care.[1] Clinical characteristics, biomarkers, exercise performance and imaging parameters have all been utilized to assess risk.[2] Recent HF guidelines recommend use of natriuretic peptide assays and multivariable clinical risk scores to quantify risk.[1]

The Seattle Heart Failure Model (SHFM)[3] is a risk score that integrates clinical, pharmacologic, 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.[4–14] However, it does not capture pertinent prognostic factors such as medication doses, delivered implantable cardioverter-defibrillator (ICD) therapies and HF hospitalizations. Elevated brain-type natriuretic peptide (BNP) levels predict HF events and mortality in a wide variety of HF cohorts,[15] and may detect such facets of the HF clinical profile. However, despite decreasing costs of the BNP assay, its increased availability and widespread use,[16] the predictive implications of the BNP level is difficult to ascertain for an individual patient.[15] BNP varies with age, gender, body size and renal function and declines with appropriate therapy. Hence, although elevated BNP values connote increased risk, interpretation of BNP levels must integrate information regarding patient characteristics, intensity of therapy and HF stage. Notably, although 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 who may benefit 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.[17–19] However, methods to translate these statistical indices to quantification of risk provided by the SHFM combined with BNP levels in clinical practice are lacking.

In this study we sought to derive and validate a simple, clinically useful risk-assessment algorithm that incorporates both the SHFM and a specific BNP cut-off 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, Minnesota, from July 1, 2007 through December 31, 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,[20] all electronic clinical notes were searched for non-negated terms (refer to Table S1 in Supplementary material available online at www.jhltonline.org/) consistent with HF. Patients with an ejection fraction (EF) $\leq$35% documented within 2 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. The New York Heart Association (NYHA) functional class 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,[21,22] was utilized. The ascertainment of death (query date March 1, 2009) was determined from the Mayo registration database and included several procedures, as described elsewhere.[23] Accurint, an institu tionally 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 the Mayo Clinic. 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 institutional review board (IRB) of the Mayo Clinic.

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).[18,24,25] The primary inclusion criterion was a clinical diagnosis of HF as