

A Survival Prediction for Acute Heart Failure Patients via Web-Based Dynamic Nomogram with Internal Validation: A Prospective Cohort Study

Ting Yin¹, Shi Shi¹, Xu Zhu¹, Iokfai Cheang¹, Xinyi Lu¹, Rongrong Gao¹, Haifeng Zhang^{1,2}, Wenming Yao¹, Yanli Zhou¹, Xinli Li¹

¹Department of Cardiology, The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital, Nanjing, 210029, People's Republic of China; ²Department of Cardiology, The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital, Gusu School, Nanjing Medical University, Suzhou, 215002, People's Republic of China

Correspondence: Xinli Li; Yanli Zhou, Tel +86 136 1157 3111; +86 137 7787 9077, Email xinli3267@njmu.edu.cn; zhyl88@qq.com

Purpose: The current study aimed to develop a convenient and accurate prognostic dynamic nomogram model for the risk of all-cause death in acute heart failure (AHF) patients that incorporates clinical characteristics including N-terminal pro-brain natriuretic peptide (NT-pro BNP) and growth stimulation expresses gene 2 protein (ST2).

Patients and Methods: We prospectively studied 537 consecutive AHF patients and derived a clinical prediction model. The least absolute shrinkage and selection operator regression model combined with clinical characteristics were used for dimensional reduction and feature selection. Multivariate Cox proportional hazard analysis and “Dynnom” package were used to build the dynamic nomogram for prediction of 1-, 2-, and 5-year overall survival for AHF. With bootstrap validation, the time-dependent concordance index (C-index) and calibration curves were used to assess predictive discrimination and accuracy. The contributions of NT-pro BNP and ST2 to the nomogram were evaluated using integrated discrimination improvement (IDI) and net reclassification improvement (NRI), while decision curve analysis (DCA) was used to assess clinical value.

Results: Patients were randomly divided into derivation (74.9%, n=402) and validation (25.1%, n=135) cohorts. Optimal independent prognostic factors for 1-, 2-, and 5-year all-cause mortality were BS-ACMR (B: NT-pro BNP; S: ST2; A: age; C: complete right bundle branch block; M: mean arterial pressure; and R: red cell distribution width >14.5%); these were incorporated into the dynamic nomogram (<https://bs-acmr-nom.shinyapps.io/dynnomapp/>) with bootstrap validation. The C-indexes in the derivation (0.793) and validation (0.782) cohorts were consistent with comparable performance parameters. The calibration curve showed good agreement between the nomogram-predicted and actual survival. Adding NT-pro BNP and ST2 provided a significant net benefit and improved performance over other less adequate schemes in terms of DCA of survival probability compared to those neglecting either of these two factors.

Conclusion: The study constructed a dynamic BS-ACMR nomogram, which is a convenient, practical and effective clinical decision-making tool for providing accurate prognosis in AHF patients.

Keywords: acute heart failure, all-cause mortality, dynamic nomogram, prediction model, internal validation

Introduction

Acute heart failure (AHF) results from any structural and/or functional cardiovascular disorder that causes hypoperfusion and the failure of systemic circulation. AHF is a worldwide primary increasingly frequent cause of disability and death.¹ Despite recent advances in treatment, the social and economic burden of AHF is expected to remain tremendously increased through 2030.^{2,3} The increasing recognition of clinical predictive models can contribute to exploration of patient-specific characteristics related to different outcome risks for a given disease.⁴ For better understand of individualized management, clinical practice guidelines and experts have committed to applying clinical prognostic models of AHF to support decision making.⁵

Regarding heart failure, there are established risk models of Seattle Heart Failure Model (SHFM) and the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) (database of 39,372 HF patients) having a relatively large cohort.^{6–8} However, these databases were mainly focused on Occidental and/or Caucasian generalized HF subjects, as well as with limited data on circulating biomarkers and medical history. Applying predictive models to heterogeneous subjects (such as Asian populations due to the different demographic characteristics) might reduce their accuracy.^{9–11}

Furthermore, there are studies using a variety of inclusion criteria and/or outcome measure^{12,13} to estimate the risk of death in Chinese HF patients, including specific population characteristics¹⁴ and etiologies,^{15,16} which result in heterogeneity of the models and limit the translation of the results to clinical applications. Furthermore, AHF as a heterogeneous syndrome with complicated pathogenesis and pathophysiological features¹⁷ distinct from chronic heart failure.^{18,19} Clinician should characterize acute and chronic settings of HF which can contribute to more precise management of the AHF population. Hence, a practical prognostic web-based nomogram of Asian demographics AHF would enable a more accurate risk assessment and optimal management for AHF patients.

Biomarkers are crucial for differentiating diagnosis and assessing prognosis in AHF. More recently, ACC/AHA guidelines recommend updated diagnostic criteria in the assessment of AHF, which includes the level of N-terminal pro-brain natriuretic peptide (NT-pro BNP) and growth stimulation expressed gene 2 protein (ST2).²⁰ Studies have shown that NT-pro BNP and ST2 levels in AHF patients at admission and follow-up provide better predictive value for all-cause mortality and rehospitalization.²¹ However, the etiology and population characteristics might affect the truncation values leading to inconsistency in clinical practice while using single marker. To further construct a nomogram of long-term prognostic model for AHF patients, our study incorporates these biomarkers into the prognostic nomogram with follow-up in AHF patients.²² Accordingly, to address the uncertainties mentioned above, our prospective study aimed to investigate and validate clinical variables that coexist with NT-pro BNP and ST2 to explore the all-cause mortality among Chinese patients with new-onset AHF and acute exacerbation of chronic HF.

Materials and Methods

Study Population

This single-center prospective cohort study was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University and registered at <http://www.chictr.org/cn> (Registration Number: ChiCTR-ONC- 12001944). The study methods have been previously published.^{23–25} Diagnosis of AHF was based on ESC acute heart failure guidelines at the time of presentation, and all patients received standard clinical evaluation and treatment.²⁶ Inclusion criteria: (1) age \geq 18 years old, gender was not limited; (2) new-onset AHF or worsening preexisting heart failure, usually with symptoms of pulmonary congestion, systemic congestion or cardiac output reduction, NT-pro BNP level $>$ 300 pg/mL, and echocardiography indicating abnormalities in cardiac structure or function; (3) subjects participated in the study voluntarily and signed the informed consent. Exclusion criteria: (1) Patients with malignant tumors, cognitive dysfunction or dementia, severe mental illness, or uncontrolled systemic disease; (2) Patients who were unwilling to sign the informed consent forms or were unable to complete all follow-up.

For risk events with an incidence greater than twenty-five percent of AHF patients, assuming a true hazard ratio of 1.5 with the power of test of 0.8, using a two-sided alpha of 5% calculated sample size was 382 subjects used PASS software. In addition, 10% percentage rate of lost to follow-up or truncated frequency also taken into account and the minimum sample size was 420. The assumed HR of 1.5 is considered as clinically relevant and has taken into account the HF outcomes in the ADHERE trial.^{27,28} All participants have given written informed consent and the study was conducted in accordance with the Declaration of Helsinki. From March 2012 to June 2019, a total of 612 patients were assessed for eligibility. Among, 537 patients with the longest follow-up time of 80 months were enrolled for the further analysis ([Figure S1](#)).

Data Collection

Clinical characteristic, laboratory results, electrocardiography (ECG), transthoracic echocardiogram (TTE), Holter, medication (including the current medication and medication usage after admission), medical history, device therapy (including CRRT and ICD/CRT surgery) were collected.

Mean arterial pressure (MAP) was calculated by dividing the subtracting the (average) diastolic from the (average) systolic blood pressure value by 3 and adding this value to the diastolic blood pressure. Body mass index (BMI) calculated weight (kg) divided by height squared (meter). All venous blood for complete blood count, biochemistry, and biomarkers (NT-pro BNP and ST2) at baseline were analyzed in the central laboratory of the First Affiliated Hospital of Nanjing Medical University. TTE was obtained with Vivid E9 ultrasound system (GE Medical System, USA). The Simpson method was used to evaluate left ventricular function. Estimated glomerular filtration rate (GFR) was calculated by the chronic kidney disease epidemiology collaboration (CKD-EPI) equation.²⁹

Primary Endpoint and Follow-Up

The primary endpoint was defined as the all-cause mortality from the time of enrollment. According to the study protocol, outpatient and/or telephone follow-up every 3 months were performed during follow-up. All enrolled AHF patients received standard treatment and management. The endpoint events were confirmed by the patient's family members, hospital medical records and/or medical personnel. A detailed description of the study protocol, participants and data collection has been previously published.^{23–25}

Statistical Analysis

Continuous variables were expressed as mean \pm standard deviation, and categorical variables were expressed as n (%). Baseline characteristics were compared using the unpaired *t*-test (normal distribution) or Mann–Whitney *U*-test (non-normal distribution) for continuous variables, and the Pearson's chi-squared test for categorical variables. For missing values, multiple imputation based on five replications and a chained equation approach in the R Mice procedure were used.³⁰

All subjects (n=537) were assigned random numbers and randomly divided into derivation (74.9%, n=402) and validation (25.1%, n=135) cohorts on the basis of 3:1 ratio for development of a nomogram and internal validation. The Kaplan–Meier (KM) survival curve was used to describe death in patients with heart failure in the two cohorts. Given the number of events available, baseline variables that were considered clinically relevant or that showed a univariable relationship were carefully chosen, as were inclusion variables, to ensure parsimony of the final model.³¹

Depending on the randomization training set, the most prominent advantage of the LASSO regression was utilized for re-selection of the optimal prognostic variables in high dimensional data and for ameliorating the accuracy and interpretability of regression models through regularization.^{32–34} Variable selection criteria based on clinical knowledge, and other variables reported in previous studies with clinical significance were candidates for LASSO regression analysis to identify the independent risk factors for all-cause mortality. All 57 variable filters used in the LASSO regression analysis ([Table S1](#)). Vertical lines were drawn at the optimal values given by the minimum criteria and 1-SE criteria to identify the optimal prognostic variables.³² Multivariate models with substantiated 10-fold cross-validation and bootstrapping (500 re-sampling) were constructed to prevent over-fitting and increase model robustness.³¹ For all categorical variables, the proportionality of risk required by the Cox model was assessed using Schoenfeld residuals. Quantitative variables were fitted as a single continuous measurement unless there was nonlinearity. Linearity of risk was evaluated by restricted cubic spline (RCS) fitting for all continuous variables, which tested whether the nonlinear component was statistically significant (R rms package).³⁵ If nonlinearity was detected, we used segmented regression (R Segmented package) to fit a piecewise-linear relationship between continuous variables and AHF risk and to calculate the threshold inflection point using a recursive algorithm.³⁶ For variables involved in Cox regression, appropriate transformations were applied, modeling them on a continuous scale.³⁶ A nomogram was constructed based on statistically significant factors identified by multivariate survival analyses performed using Cox proportional hazard regression to predict 1-, 2-, and 5-year all-cause mortality; the R Regplot package was used to display the results. Discrimination and calibration analysis was used to verify the effectiveness of both the derivation and validation cohort models by time-dependent C-index analysis (R pec package). The C-index ranged from 0.5 to 1, with larger values indicating increased prediction accuracy.³⁷ Calibration of the nomogram was assessed by comparing the nomogram-predicted 1-, 2-, and 5-year all-cause mortality rates to the observed probability. In an ideal calibrated curve, the predictions should fall on a diagonal 45° line in the calibration plot.

Moreover, net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated in R survIDINRI to determine the overall improvement in the predictive accuracy of the nomogram provided by the addition of NT-pro BNP and ST2 at 60 months. NRI refers to the difference in proportions of patients with events correctly assigned a higher probability and patients without events correctly assigned a low probability by an updated model compared with the initial model.³⁸ IDI represents improvement in the average sensitivity (ie, true positive rate) without reducing the average specificity (ie, true negative rate) of a new model compared with that of a baseline model.³⁹ The clinical usefulness of the model was assessed by decision curve analysis (DCA).⁴⁰ Finally, “Dynnom” package (cran.r-project.org/web/packages/rms) to generate dynamic nomogram model with an interactive interface for clinical application.⁴¹ All tests were two-sided, and a P value < 0.05 was considered statistically significant. Statistical analyses were performed in R Studio (Version 3.3.4).

Results

Baseline Characteristics in the Derivation and Validation Cohorts

A total of 537 hospitalized patients with AHF were included in the present analysis. The baseline characteristics are shown in [Table 1](#). The mean follow-up time was 34.21±21.28 months (median 34 months), the longest follow-up period was 84 months. There were 174 (32.4%) patient deaths during follow-up. Males constituted 66.41% of the cohort, and left ventricle ejection fraction (LVEF) was 42.10±14.52% for all subjects.

The derivation and validation cohorts constituted 74.9% (n=402) and 24.1% (n=135) of the patient population, respectively. The mean follow-up time for the derivation and validation cohorts were 34.56±20.85 and 33.40±22.28 months, respectively. There were no significant differences in the majority of baseline characteristics between two groups (P>0.05), suggesting an equilibrium distribution for derivation and validation ([Table 1](#)).

After randomization grouping, KM survival curves showed no significant difference in all-cause mortality between the derivation and validation cohorts (P= 0.14) ([Figure 1](#)), indicating the even distribution between two cohorts and suitable for internal verification.

LASSO Method to Reselect Optimal Prognostic Variables

When lambda equaled 0.038 and log (λ) = -2.417, the residual sum of squares was shown to be 1-SE for all-cause mortality. Six optimal prognostic variables were identified, including NT-pro BNP, ST2, age, complete right bundle branch block (CRBBB), mean arterial pressure (MAP), and red blood cell distribution width (RDW) ([Figure 2](#)).

RCS Analysis of Nonlinear Associations Determined the Cutoff Values of Optimal Variables

The shape of the relationship between optimal prognostic variables and all-cause mortality of AHF was explored using the restricted cubic spline regression model and ANOVA to test for nonlinearity. Age (P nonlinearity = 0.823), MAP (P nonlinearity = 0.421), and RDW (P nonlinearity = 0.132) were linearly associated with all-cause mortality for AHF, whereas NT-pro BNP (P nonlinearity = 0.010) and ST2 (P nonlinearity < 0.001) exhibited a nonlinear association ([Figure S2](#)). Regarding the strong U-shaped relationship between predicted NT-pro BNP and ST2 and all-cause mortality, the plot showed a substantial reduction in risk within the lower range of the predicted NT-pro BNP and ST2, which indicated a clearly increased risk around 5582 pg/mL and 86 ng/mL, respectively.

Multivariable Cox Hazard Regression for All-Cause Mortality

Multi-variable Cox analysis was carried out to further verify the hazard ratio and coefficient for each variable reselected by the LASSO method. As a result, NT-pro BNP (>5582 pg/mL vs <5582 pg/mL; HR: 1.616; 95% CI: 1.092–2.393; P=0.016), ST2 (>86 ng/mL vs <86 ng/mL; HR: 4.040; 95% CI: 2.734–5.968; P<0.001), age (per 10 year increase; HR: 1.338; 95% CI: 1.179–1.520; P<0.001), CRBBB (HR: 3.227; 95% CI: 2.077–5.014; P<0.001), MAP (per 10 mm Hg increase; HR: 0.765; 95% CI: 0.667–0.877; P<0.001), and RDW (per 5 unit increase; HR: 2.366; 95% CI: 1.522–3.677; P<0.001) remained independent risk factors for 1-, 2-, and 5-year all-cause mortality ([Figure 3](#)).

Table I Demographic Characteristics of the Enrolled Patients with AHF

	Number (%) / Median \pm Standard Deviation			P-value
	All Patients (n = 537)	Derivation Cohort (n = 402)	Validation Cohort (n = 135)	
Age, years (mean \pm SD)	61.07 \pm 15.98	61.19 \pm 16.35	60.71 \pm 14.89	0.761
Gender: male, n (%)	357 (66.48%)	270 (67.16%)	87 (64.44%)	0.564
BMI (kg/m ²), mean \pm SD	23.77 \pm 5.87	23.77 \pm 5.87	23.77 \pm 5.87	0.437
Smoke, n (%)	208 (38.73%)	148 (36.81%)	60 (44.44%)	0.159
Heart rate (bpm), mean \pm SD	81.23 (18.46)	85.71 (21.00)	84.44 (20.64)	0.542
NYHA class, n (%)				
2	91 (16.95%)	74 (18.40%)	17 (12.59%)	0.226
3	289 (53.81%)	215 (53.48%)	74 (54.81%)	
4	158 (29.42%)	113 (28.11%)	45 (33.33%)	
Sim LVEF (%), mean \pm SD	42.10 \pm 14.52	42.46 \pm 14.55	41.02 \pm 14.44	0.320
\geq 50%, n (%)	157 (29.23%)	111 (27.61%)	46 (34.07%)	
40–49%, n (%)	96 (17.87%)	67 (16.67%)	29 (21.48%)	0.107
\leq 40%, n (%)	268 (49.90%)	184 (45.77%)	84 (62.22%)	
SBP (mmHg), mean \pm SD	126.49 \pm 22.06	127.17 \pm 22.46	124.49 \pm 20.79	0.221
DBP (mmHg), mean \pm SD	78.46 \pm 14.99	78.57 \pm 15.67	78.11 \pm 12.84	0.756
MAP (mmHg), mean \pm SD	94.47 \pm 15.56	94.77 \pm 16.13	93.57 \pm 13.74	0.437
ST2 (ng/mL), Q4	39.42(22.67, 79.05)	38.49 (22.62, 74.83)	42.04 (23.35, 93.37)	0.138
NT pro-BNP (pg/mL), Q4	2410.00 (1270.75, 6124.25)	2387.50 (1262.75, 5834.50)	2670.50 (1452.75, 6563.00)	0.122
D-dimer (ng/mL), mean \pm SD	1.66 \pm 3.56	1.65 \pm 3.92	1.68 \pm 2.18	0.939
Potassium (mmol/L), mean \pm SD	4.00 \pm 0.51	4.00 \pm 0.49	3.98 \pm 0.55	0.643
Sodium(mmol/L), mean \pm SD	139.56 \pm 3.95	139.79 \pm 3.76	138.85 \pm 4.38	0.016
Calcium (mmol/L), mean \pm SD	2.25 \pm 0.15	2.25 \pm 0.15	2.24 \pm 0.14	0.589
ALB (g/L), mean \pm SD	36.74 \pm 4.89	36.91 \pm 4.81	36.22 \pm 5.10	0.152
Hemoglobin (g/L), mean \pm SD	132.14 \pm 21.73	132.65 \pm 21.31	130.65 \pm 22.93	0.354
RDW (%), mean \pm SD	14.67 \pm 1.78	14.68 \pm 1.79	14.64 \pm 1.74	0.783
Uric Acid (umol/L), Q4	472.50 (383.70, 584.02)	470.50 (386.95, 579.75)	482.40 (382.00, 613.25)	0.090
BUN (mmol/L), Q4	7.37 (5.88, 9.84)	7.20 (5.91, 9.71)	7.76 (5.83, 10.24)	0.179
Cys C (umol/L), mean \pm SD	1.52 \pm 0.74	1.53 \pm 0.75	1.49 \pm 0.70	0.601
eGFR _{crs} (mL/min 1.73m ²), Q4	73.61 (55.13, 92.10)	73.01 (55.12, 91.78)	73.80 (55.15, 93.38)	0.906
FT3 (pmol/L), mean \pm SD	3.89 \pm 1.15	3.97 \pm 1.17	3.66 \pm 1.04	0.007
FT4 (nmol/L), mean \pm SD	18.69 \pm 6.86	18.81 \pm 7.04	18.32 \pm 6.31	0.473
FSH (mIU/L), mean \pm SD	3.61 \pm 4.41	3.30 \pm 2.88	4.52 \pm 7.19	0.006
ALT (u/L), Q4	26.0 (16.50,45.10)	26.0 (17.30, 47.20)	25.80 (15.0,41.70)	0.076
AST(u/L), Q4	27.90 (21.70,42.30)	28.8 (22.15, 44.30)	26.50 (21.40,39.10)	0.142
LVDD (mm), mean \pm SD	61.66 \pm 12.22	61.15 \pm 11.75	63.15 \pm 13.44	0.099
LVDDs (mm), mean \pm SD	49.06 \pm 13.84	48.48 \pm 13.38	50.78 \pm 15.05	0.094
PASP (mmHg), mean \pm SD	43.62 \pm 16.38	43.74 \pm 16.61	43.29 \pm 15.74	0.786
CRBBB, n (%), mean \pm SD	57 (10.61%)	43 (10.70%)	14 (10.37%)	0.113
CLBBB, n (%), mean \pm SD	125(23.27%)	86(26.62%)	39(18.22%)	0.354
QRS (s), mean \pm SD	129.79 \pm 39.51	129.67 \pm 39.83	130.16 \pm 38.68	0.900
QTc (s), mean \pm SD	444.86 \pm 88.85	440.35 \pm 95.61	458.22 \pm 63.32	0.042
Longest PR (s), mean \pm SD	193.56 \pm 97.07	195.24 \pm 100.24	188.60 \pm 87.18	0.491
Medical history				
Hypertension, n (%)	274 (50.02%)	202 (50.25%)	72 (52.33%)	0.657
AF, n (%)	182 (33.89%)	142 (35.32%)	40 (29.63%)	0.201
ACS, n (%)	57 (10.61%)	41 (10.20%)	16 (11.85%)	0.725
DM, n (%)	205 (38.18%)	155 (38.56%)	50 (37.04%)	0.782
IHD, n (%)	137 (25.51%)	96 (23.88%)	41 (30.37%)	0.182

(Continued)

Table I (Continued).

	Number (%) / Median ± Standard Deviation			P-value
	All Patients (n = 537)	Derivation Cohort (n = 402)	Validation Cohort (n = 135)	
Device therapy				
CRRT, n (%)	53 (9.86%)	31 (9.59%)	22 (10.28%)	0.059
ICD/CRT Surgery, n (%)	26 (4.84%)	18 (4.48%)	8 (5.92%)	0.668
Medication at admission				
Anticoagulants, n (%)	212 (39.48%)	161 (40.05%)	51 (37.78%)	0.671
ACEIs/ARBs, n (%)	417 (77.65%)	308 (76.62%)	109 (80.74%)	0.463
Beta-blockers, n (%)	428 (79.70%)	315 (78.36%)	113 (83.70%)	0.289
Antisterone, n (%)	479 (89.20%)	382 (95.02%)	132 (97.77%)	0.451
Diuretic, n (%)	510 (94.97%)	379 (94.28%)	131 (97.04%)	0.481
Aspirin, n (%)	225 (41.90%)	163 (40.55%)	62 (45.93%)	0.353

Abbreviations: BMI, body mass index; NYHA, New York Heart Association Functional Class; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; ST2, growth stimulation expresses gene 2 protein; NT pro-BNP, N-terminal pro-B-type natriuretic peptide; RDW, red cell distribution; TSH, thyroid stimulating hormone; BUN, blood urea nitrogen; Cys C, cystatin c; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillators; CRT, cardiac resynchronization therapy; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; AF, atrial fibrillation; ACS, acute coronary syndromes; LVDD, left ventricular diastolic diameter; LVDs, left ventricular internal diameter at end-systole; PASP, pulmonary artery systolic pressure; CRBBB, complete right bundle branch block; CLBBB, complete left bundle branch block; IHD, ischemic heart disease; ALT, alanine aminotransferase; AST, aspartate transaminase; AF, atrial fibrillation; DM, diabetes mellitus; ACS, acute coronary syndrome; CRRT, continuous renal replacement therapy.

Construction of the Nomogram for 1-, 2-, and 5-Year All-Cause Mortality

Based on multivariate analysis, six variables were included in a nomogram for predicting 1-, 2-, and 5-year overall survival (Figure 4). Positions in the nomogram are in order of importance as defined by standard deviation, top to bottom. Each clinicopathological factor corresponds to a specific point by drawing a line straight up to the Points axis. The sum of the points located on the total points axis represents the probability of 1-, 2-, and 5-year survival by drawing a line straight down to the survival axis. The calculated ratio is used to determine the relative predictive value of these

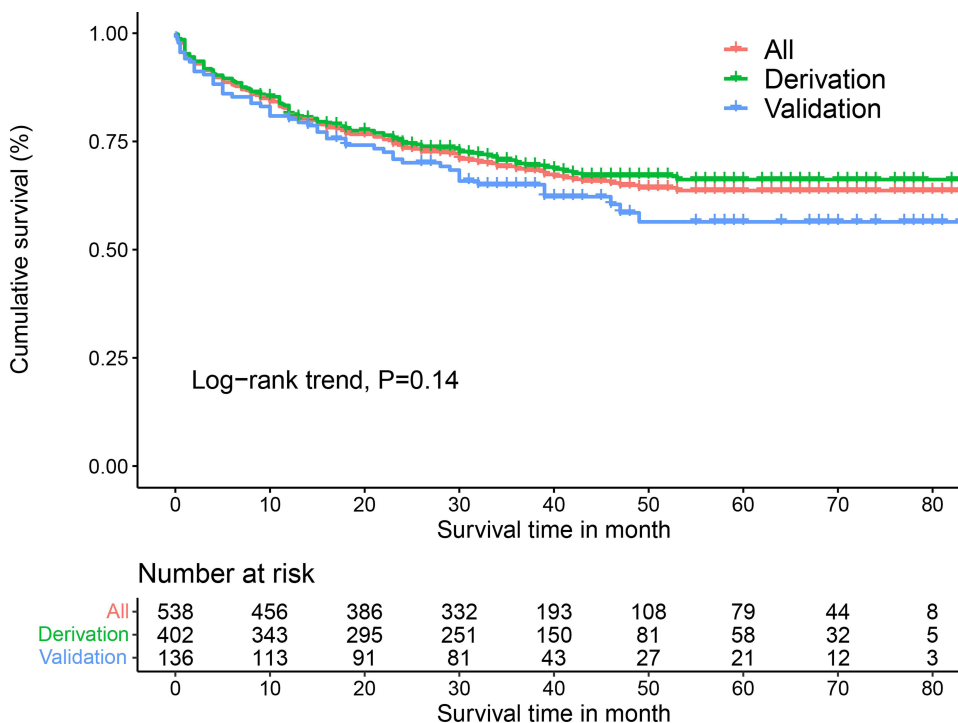


Figure 1 Kaplan–Meier survival curve of enrolled AHF patients, derivation cohort and validation cohort.

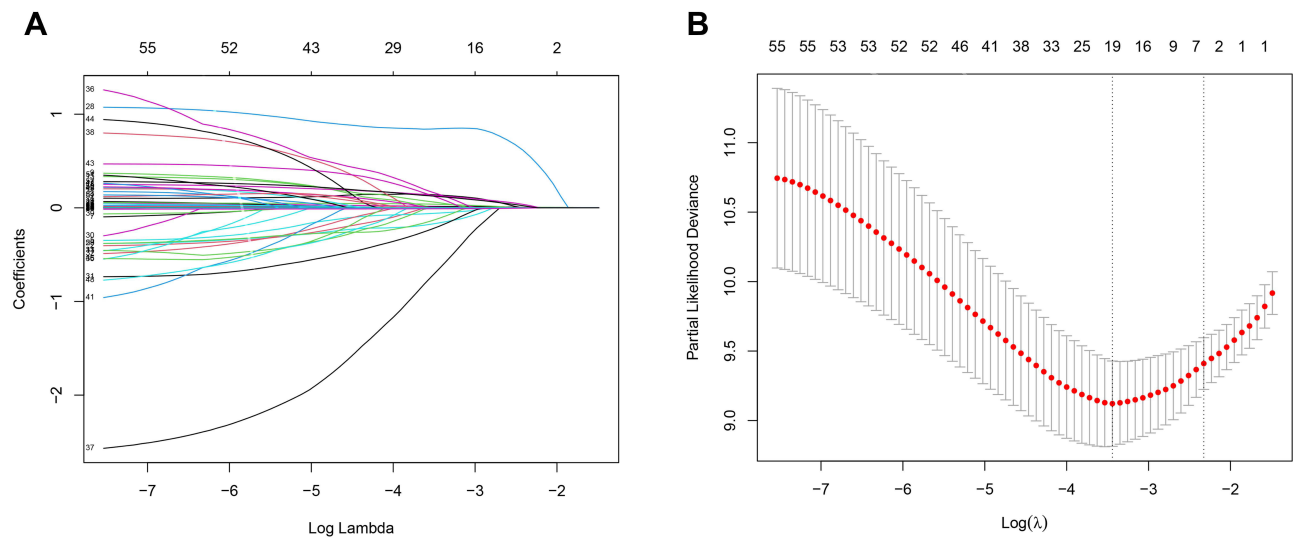


Figure 2 Selection of variables for all-cause mortality was performed using the LASSO regression plot with COX regression model. **(A)** LASSO model coefficient trendlines of the 57 variables (shown in [Table S1](#)) for all-cause mortality. **(B)** Tuning parameter (Lambda, λ) selection cross-validation error curve. Vertical lines were drawn at the optimal values given by the minimum criteria and I-SE criteria. The right line was identified by I-SE criteria ($\lambda = 0.038$). The parameter $\lambda = 0.038$ was selected under the I-SE criteria. The vertical line was drawn at the value selected by 10-fold cross-validation, including optimized six non-zero coefficients proceed with further COX regression analysis.

Abbreviations: LASSO, least absolute shrinkage and selection operator; SE, standard error.

variables. The projection to the total points scale at the bottom of the nomogram indicates the estimated probability of all-cause mortality and estimate the risk of death.

Internal Validation of the Nomogram and Risk Reclassification

Time-dependent discrimination analysis was used to evaluate the predictive performance of our model for AHF patient outcomes. In the derivation cohort, the time-independent C-indices of the nomogram for all-cause mortality were 0.838 (95% CI: 0.804–0.871) and 0.793 (95% CI: 0.752–0.833) in all models and the nomogram model, respectively ([Figure 5A](#)). Meanwhile, the time-independent C-indices in the validation cohort were 0.716 (95% CI: 0.651–0.781) and 0.782 (95% CI: 0.720–0.844) in all models and the nomogram model, respectively ([Figure 5B](#)). These results indicate that the predictive power of the nomogram model was relatively stable over time, meaning that it could be used to predict death over all time periods.

The results of the NRI and IDI calculations are given in both the derivation and validation models, use of multiple variables to construct a comprehensive nomogram significantly improved risk reclassification for prediction of 5-year overall mortality by adding NT-pro BNP and ST2 to the model ([Table 2](#)). The calibration plots showed consistency between the observed AHF mortality risks and those predicted by the nomogram at 1-, 2-, and 5- years ([Figure 6](#)).

Decision Curve Analysis of the Nomogram

Decision curve analysis (DCA) was performed to assess the net benefit of the clinical prediction model. Based on the nomogram constructed in this study, the decision curve showed that the threshold probability of AHF patients was 23–67%, 25–85%, and 35–80% at 1, 2, and 5 years, respectively. These results demonstrate that use of this nomogram to predict all-cause mortality could increase accuracy compared with either neglecting these factors or using an inadequate scheme ([Figure 7](#)).

Web-Based Dynamic Nomogram

A web-based calculator was built (<https://bs-acmr-nom.shinyapps.io/dynnomapp/>) to facilitate the use of the nomogram for clinicians ([Figure S3](#)). The dynamic BS-ACMR nomogram can be easily obtained predicted probability of all-cause

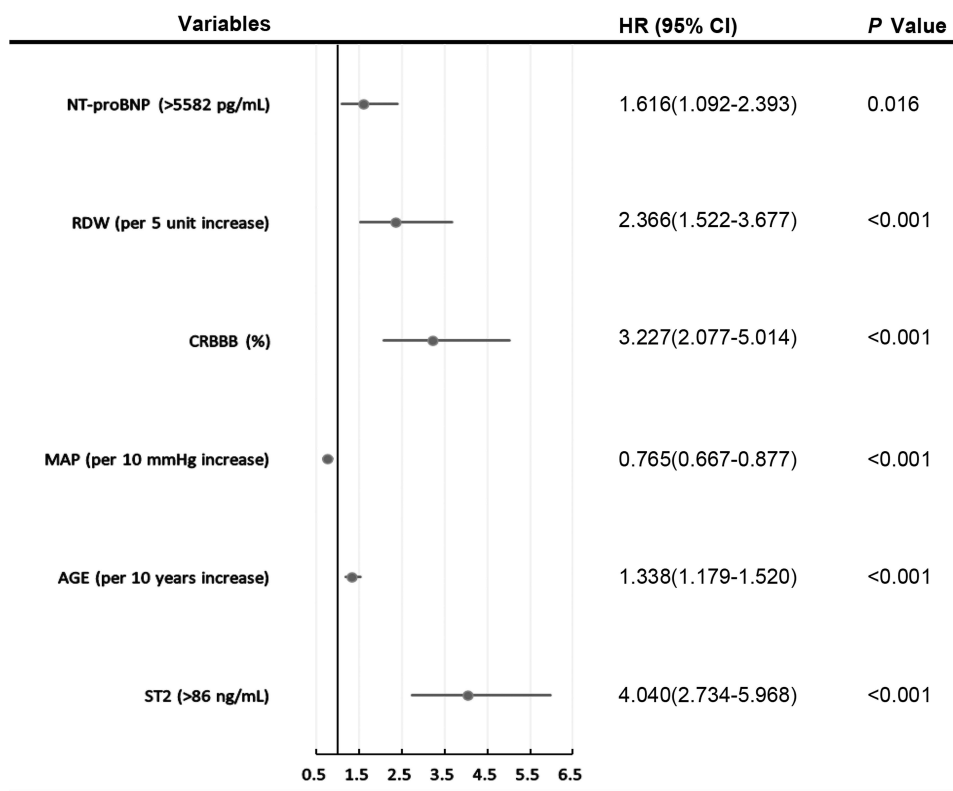


Figure 3 Forest plot with hazard ratio (HR) for the optimal prognostic variables of the final multivariable model in the derivation cohort. HRs above one indicates that a variable is positively associated with the event probability and thus negatively with survival time. A horizontal line parallel to the X-axis has a logarithmic scale represents a more precise confidence interval (95% CI).

mortality of AHF patients after inputting the six independent variables and survival time (months) and reading output results generated by the website.

Discussion

In the present study, a predictive tool incorporating selected biomarkers and clinical indicators was constructed. This BS-ACMR (B: NT-pro BNP; S: ST2; A: Age; C: CRBBB; M: MAP; and R: RDW >14.5%) nomogram score system is a prognostic model of all-cause mortality that provided accurate predictions of survival in AHF patients. For a median follow-up of 34 months and maximum follow-up of 80 months, cross-validation was helpful for effective use of our limited data. The accuracy (C-index) of the nomogram tool in predicting all-cause mortality risk for AHF patients at 1-, 2-, and 5-years was 0.793 in the derivation cohort and 0.782 in the validation cohort. By exact truncation of variables and comprehensive model evaluation, the nomogram tool constructed here combined NT-pro BNP, ST2, and routine clinical features (age, MAP, RDW, CRBBB) to establish an effective and accurate clinical prognostic model, and to enhance its clinical applications. The range of values also suggested that further exploration of specific thresholds of these prognostic significance variables could provide incremental value for assessing the prognosis of AHF patients.

Myocardial remodeling represents the key pathway of development from cardiac dysfunction to advanced heart failure. Biomarkers reflects these pathological changes of hemodynamic overload, progressive myocardial fibrosis and increased cardiomyocyte stiffness in AHF have been shown to have important applications to the management of patients. ST2 reflects tissue fibrosis and may promote cardiac hypertrophy, fibrosis, and ventricular dysfunction.⁴² Also indicate cardiac remodeling and therefore represent valuable additive risk stratification of patients with acute and chronic HF.⁴³ Although ST2 predicts mortality in HFpEF individuals with acute dyspnea,²¹ the threshold of ST2 for poor prognosis of HF are inconsistent. For instance, a value ≥ 35 ng/mL (median, 42.7 ng/mL) in HF patients,⁴⁴ 67.4 ng/mL in non-survivors, and 35.8 ng/mL in survivors of acute decompensated heart failure at 1 year,⁴⁵ and a median of 148 ng/mL

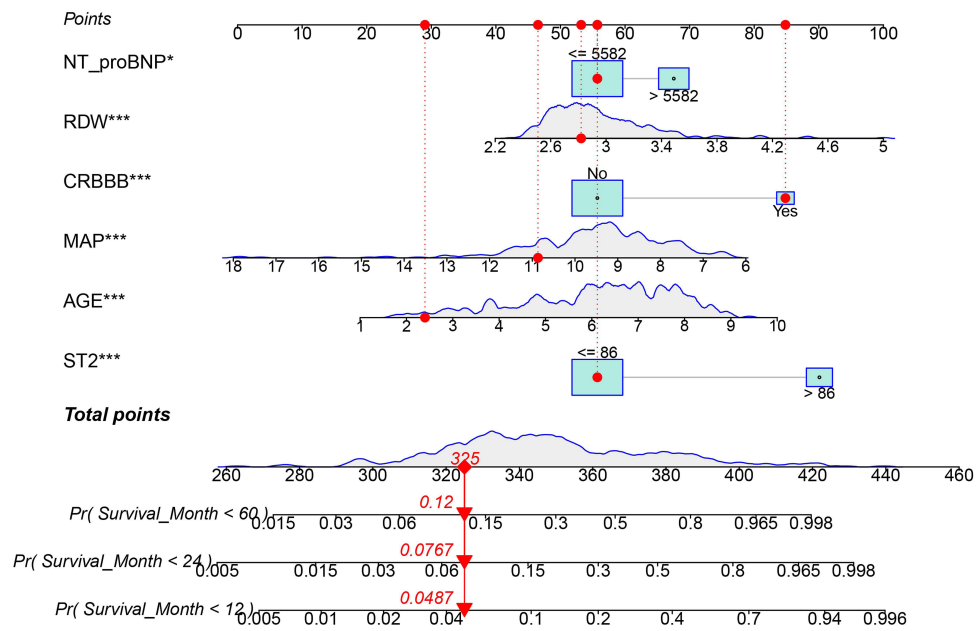


Figure 4 The BS-ACMR heart prognostic nomogram obtained from the optimal Cox model to predict 1-, 2- and 5- year overall survival for acute heart failure in derivation cohort. Each clinicopathological factor corresponds to a specific point by drawing a vertical line from that variable to the points axis. After sum of the scores for each variable located on the Total Points axis. Finally, the sum represents the probability of 1-, 2- and 5- year survival by drawing straight down to the survival axis. For example, a 24-year-old AHF patient with NT-pro BNP \leq 5582 pg/mL, ST2 \leq 86 ng/mL, MAP \leq 109 mm Hg, RDW \leq 2.82% and CRBBB, the total score will be given by 29+56+56+46+53+85 = 325, corresponding to 1-, 2-, and 5-year risks of dying of 0.049, 0.077, and 0.12, respectively. The AHF patient will accordingly have approximately 96.1%, 92.3%, and 88% survival probabilities at 1, 2, and 5 years, respectively. * $P < 0.05$; *** $P < 0.001$.

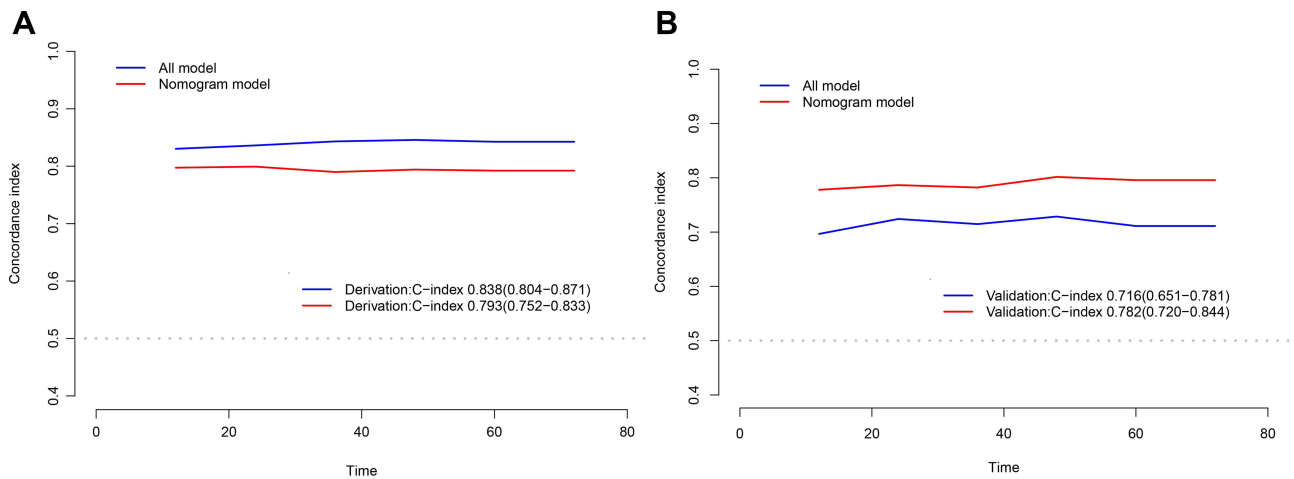


Figure 5 Discrimination analyses between derivation cohort (A) and the validation cohort (B).

(interquartile range of 88 to 226 ng/mL) in more advanced HF patients.⁴⁶ In the current study, ST2 was one of the most significant predictive indicator shown nonlinear relationship for ST2 > 86 ng/mL, and all-cause mortality risk increased 4.04-fold over the range. While the ST2 threshold of our result could not generalize as the preliminary precaution signal of myocardial fibrosis, the increase level of ST2 provides healthcare providers to recognize higher-risk AHF patients.

Concentrations of NT-pro BNP are related to left ventricle (LV) filling pressures and wall stress,^{44,48} especially in the context of ventricular fibrosis. Accordingly, the utility of ST2 is additive with that of NT-pro BNP as a predictor of mortality.⁴⁷ The increased NT-pro BNP levels during left ventricular dysfunction and acute myocardial infarction, and serve to counteract mechanisms of heart failure through diuresis, natriuresis, and antihypertensive effects.^{50,52} Threshold levels of NT-pro BNP associated with diagnosis of heart failure ranged variate from 30 to 400 pg/mL in different studies,

Table 2 Integrated Discrimination Improvement and Net Reclassification Improvement for All-Cause Mortality at 60 Months by Adding NT-Pro BNP and ST2 to Model

Model	Biomarker	IDI (95% CI)	P-value	NRI (95% CI)	P-value
Derivation MAP, Age, CRBBB, RDW	+NT-proBNP	0.043(0.004–0.101)	0.020	0.219(0.047–0.348)	0.028
	+ST2	0.128(0.064–0.195)	<0.001	0.349(0.207–0.454)	<0.001
	+ NT-proBNP and ST2	0.141(0.077–0.211)	<0.001	0.354(0.180–0.482)	<0.001
Validation MAP, Age, CRBBB, RDW	+NT-proBNP	0.009(–0.010–0.065)	0.479	0.136(–0.297–0.381)	0.443
	+ST2	0.191(0.060–0.336)	0.004	0.327(0.036–0.621)	0.040
	+ NT-proBNP and ST2	0.194(0.067–0.338)	0.004	0.346(0.049–0.653)	0.016

Abbreviations: NT-pro BNP, N-terminal pro-brain natriuretic peptide; ST2, growth stimulation expresses gene 2 protein; MAP, mean arterial pressure; CRBBB, complete right bundle branch block; RDW, red cell distribution; CI, confidence interval.

with a large range of sensitivities (6–97%) and specificities (35–100%).^{49,50} Whereas, paucity of un-uniformity clinical prognosis thresholds makes it difficult to translate the results to clinical application.^{51,52} Our NT-pro BNP level of >5582 pg/mL was strongly associated with increased all-cause mortality of AHF, which accounts certain efficiency to identify critically ill patients and guide clinical decisions. To our knowledge, our study is the first clinical nomogram model which incorporates NT-pro BNP, ST2, and clinicopathology to assess the long-term risk of all-cause mortality in AHF patients. Additionally, BS-ACMR nomogram incorporating clinical features provides greater clinical utility than solely ST2 or NT-pro BNP evaluation.

Beside the two biomarkers in the model, age was a proven independent prognostic indicator all-cause mortality,^{36,43,44,49,50} which weighted second in our model superior to MAP, CRBBB, RDW, and NT-pro BNP. Secondly, our study also found that CRBBB increases the risk for all-cause mortality about 3.227-fold (95% CI: 2.077–5.014). Previous epidemiological studies, CRBBB was found related to myocardial ischemia, an independent predictor of decreased right ventricular ejection fraction.⁵⁵ One possible pathophysiological mechanism that may contribute to cardiovascular mortality, may be right ventricular dyssynchrony.^{53,54} CRBBB could consider a sign of other underlying cardiovascular conditions, including but not limited to ischemic, inflammatory, infiltrative heart disease, and pulmonary embolism, which associated to complete heart block, ventricular arrhythmias, HF, and death.⁵³ Although inconsistent results regarding the association between CRBBB and clinical outcomes such as all-cause and cardiovascular mortality have been reported,⁵⁵ there were large prospective cohort - Copenhagen City Heart Study with 18,441 participants⁵⁶ and a recent Mayo Clinic study with 31,979 subjects⁵³ both reported that CRBBB was predictive of all-cause (Copenhagen and Mayo) and cardiovascular-related (Mayo) mortality, even in patients without CVD. Our findings are consistent with those studies. Despite our study only enrolled limited patients with CRBBB, our result and these previous studies support by incorporating CRBBB into the model can provide certain guidance for prognostic assessment.

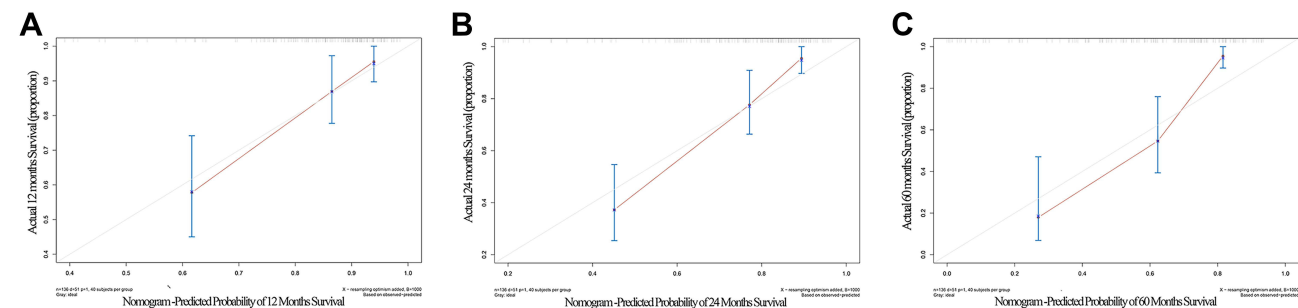


Figure 6 Calibration plot of nomogram predicted probability of 1- (A), 2- (B) and 5- (C) year all-cause mortality. Shown that the prediction model was no statistical departure with observed values.

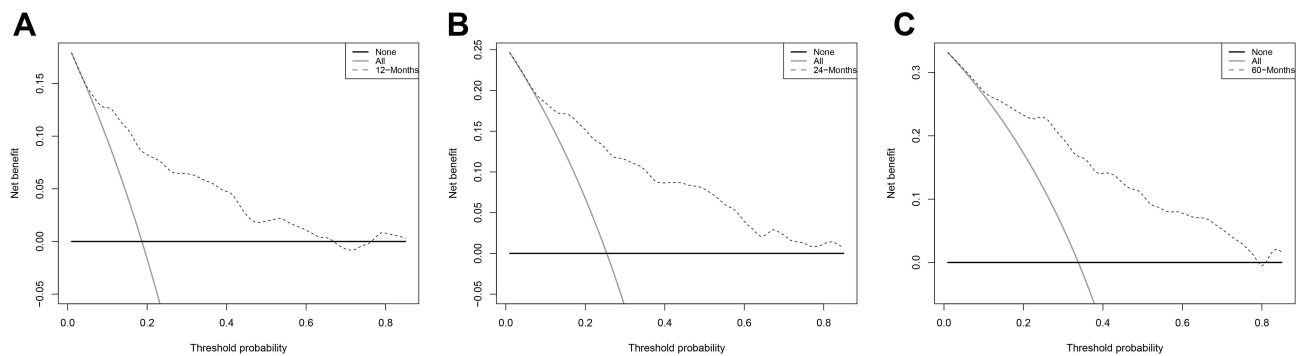


Figure 7 Decision curve of the nomogram. The black dotted line represents the nomogram. The grey solid line represents net benefit without intervention. The decision curve indicates that when the threshold probability of AHF patients of this nomogram strategies would add significant net benefit of the all-cause mortality of 1- (A), 2- (B) and 5- (C) year.

Additionally, every 5-unit increase of RDW was associated with a 2.366-fold (95% CI: 1.522–3.677) increase in adverse outcomes of AHF. As a measure of variability in the size of circulating red blood cells, RDW was used as an independent predictor of adverse outcomes in chronic⁵⁷ and acute decompensated HF.⁵⁸ Previous studies have demonstrated that elevated RDW was associated with high left ventricular end-diastolic pressure,⁵⁹ which is a strong predictor of poor prognosis and sudden death regardless of LVEF.⁶⁰ Both RDW and NT-pro BNP are included in our BS-ACMR nomogram, which is supported by their well-established correlation with LV filling pressure and hemodynamics. Similarly, MAP is a valuable factor as it reflects cardiac capacity, myocardial function, and peripheral artery resistance. Prognosis of AHF patients needs to consider preservation of organ perfusion and capacity management. Atypical factors reflecting hemodynamic states included in the BS-ACMP nomogram are sensitive prognostic factors of pathological manifestations of heart failure, which provide clues to cardiac insufficiency.

Reviewing the previous prognostic AHF models, study showed model based on three easy parameters (age, serum creatinine and lactate) was associated with regarding 28-day mortality in the acute decompensated HF complicated by cardiogenic shock.⁶¹ Another study enrolled 1033 AHF patients in emergency setting exhibited elevated troponin and renal function were significant predictors of adverse events.⁶² In addition, results via the AHEAD scoring system (A: atrial fibrillation; H: hemoglobin; E: elderly; A: abnormal renal parameters; D: diabetes mellitus) also could be factor in assessing prognosis.⁶³ Furthermore, our study showed a similar result to the Massachusetts study⁶⁴ which explored 1-year mortality for acute decompensated HF based on ejection fraction with higher proportion of reduced EF (49.9% VS 35%) and lower proportion of preserved EF (29.23% VS 52%). Compare with model in the study, different predictors risk factors included chronic obstructive pulmonary disease history, SBP <150 mm Hg on admission, and hyponatremia. Distinct to the previous study, our findings that integrate the clinical features and significant biomarkers (NT-pro BNP and ST2) emphasized the changes in clinicopathological status, and the long-term follow-up may provide a reference risk evaluation of AHF over different time periods.

Strengths and Limitations

In the present study, distinct to the previous nomogram that roughly calculate an approximation, our research by conducting a dynamic network calculator and a visual BS-ACMR nomogram could provide a convenient method with each significant explanatory variable. Also, result from our prospective study could provide additive clinical values for recognizing the high risk AHF patients, which could guide an optimal medical management in selected condition. Moreover, incorporating NT-pro BNP and ST2 which reflect hemodynamic states in to the models, redefined truncation value of these markers helps early identification these particular patients closely related to all-cause death.

Our study has certain limitations. Only 537 AHF patients from a single center was prospectively collected. However, the prognostic analysis with systematic data collection and long-term follow-up could minimize potential bias. Second, although the models have not been externally validated, we developed a 10-fold cross-validation and bootstrap re-sampling technique to maximize power and calibration of the predicted probabilities against mortality rates, which

indicated a good outcome given the limitations of the study. Third, unlike previous studies,^{12–14} medication and ICD/CRT device therapy was not incorporated with our nomogram which are potentially affected mortality rate of AHF. Expanding the study population and kinetic measurement of indicators should be considered to improved popularization meanings of the model in the future. Despite these limitations, our study provided a robustness and accurate prediction model to assess the all-cause mortality risk of AHF. Additionally, the main advantages of our study were that all the included prognosticators were feasible and accessible in routine clinical practice.

In the future, on the premise of sufficient sample size, further stratification analysis considering of various comorbidities of AHF patients (like obesity, T2DM, hypertension and anemia etc.) will help to increase model precision. Investigators are invited to share their data implement external validation regarding AHF clinical settings in order to further improve the absolute risk estimates of the current model.

Conclusions

We developed and validated a web-based BS-ACMR nomogram risk calculator, which can address the relative long-term time-dependent death risk of AHF patients via clinical data includes redefined truncation value of biomarkers (NT-pro BNP and ST2) that help to identification patients closely related to all-cause death. The multivariable dynamic practical nomogram demonstrated good calibration, discrimination, and clinical utility. These findings could help clinicians in stratifying the risk of AHF patients, clinical decision-making, and early prevention.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author (xinli3267@njmu.edu.cn) upon reasonable request. The request will be reviewed by the Twelve-Fifth National Key Technology R&D Program for approval.

Ethical Standards

The study was approved by the ethics committee of the First Affiliated Hospital of Nanjing Medical University, and all patients provided written informed consent. All procedures conformed to the standards of the Declaration of Helsinki.

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Author Contributions

Xinli Li and Yanli Zhou contributed as co-corresponding authors. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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