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ORIGINAL ARTICLE

Construction of a web-based dynamic nomogram for predicting the prognosis in acute heart failure

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Abstract

Aims The early identification and appropriate management may provide clinically meaningful and substained benefits in patients with acute heart failure (AHF). This study aimed to develop an integrative nomogram with myocardial perfusion imaging (MPI) for predicting the risk of all-cause mortality in AHF patients.

Methods and results Prospective study of 147 patients with AHF who received gated MPI (59.0 [47.5, 68.0] years; 78.2% males) were enrolled and followed for the primary endpoint of all-cause mortality. We analysed the demographic information, laboratory tests, electrocardiogram, and transthoracic echocardiogram by the least absolute shrinkage and selection operator (LASSO) regression for selection of key features. A multivariate stepwise Cox analysis was performed to identify independent risk factors and construct a nomogram. The predictive values of the constructed model were compared by Kaplan–Meier curve, area under the curves (AUCs), calibration plots, continuous net reclassification improvement, integrated discrimination improvement, and decision curve analysis. The 1, 3, and 5 year cumulative rates of death were 10%, 22%, and 29%, respectively. Diastolic blood pressure [hazard ratio (HR) 0.96, 95% confidence interval (CI) 0.93–0.99; $P = 0.017$], valvular heart disease (HR 3.05, 95% CI 1.36–6.83; $P = 0.007$), cardiac resynchronization therapy (HR 0.37, 95% CI 0.17–0.82; $P = 0.014$), N-terminal pro-B-type natriuretic peptide (per 100 pg/mL; HR 1.02, 95% CI 1.01–1.03; $P < 0.001$), and rest scar burden (HR 1.03, 95% CI 1.01–1.06; $P = 0.008$) were independent risk factors for patients with AHF. The cross-validated AUCs (95% CI) of nomogram constructed by diastolic blood pressure, valvular heart disease, cardiac resynchronization therapy, N-terminal pro-B-type natriuretic peptide, and rest scar burden were 0.88 (0.73–1.00), 0.83 (0.70–0.97), and 0.79 (0.62–0.95) at 1, 3, and 5 years, respectively. Continuous net reclassification improvement and integrated discrimination improvement were also observed, and the decision curve analysis identified the greater net benefit of the nomogram across a wide range of threshold probabilities (0–100% at 1 and 3 years; 0–61% and 62–100% at 5 years) compared with dismissing the included factors or using either factor alone.

Conclusions A predictive nomogram for the risk of all-cause mortality in patients with AHF was developed and validated in this study. The nomogram incorporated the rest scar burden by MPI is highly predictive, and may help to better stratify clinical risk and guide treatment decisions in patients with AHF.

Keywords Acute heart failure; All-cause mortality; Prognosis; Rest scar burden; Dynamic nomogram

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Introduction

Acute heart failure (AHF), a clinical syndrome characterized by rapid new-onset or exacerbation of signs and symptoms of heart failure (HF), remains the leading cause of unplanned hospital admission in elderly patients aged ≥65 years.[1–3] Despite major advances in AHF treatment, mortality rates related to the disease at 1 and 12 months are 10% and 22–27%, respectively, posing a substantial economic and social burden.[4,5] Therefore, early identification and appropriate

management of AHF supported by evidence-based medicine are considered necessary.

Clinical practice guidelines recommend the use of clinical prediction models in patients with AHF, which allows clinicians to utilize a more individualized treatment strategy.[6,7] Several prediction models have been developed to explore patient characteristics associated with the prognosis of AHF.[8–10] However, a variety of inclusion criteria and measures are used to predict the odds of all-cause mortality in patients with AHF, leading to significant heterogeneity between different models and limiting their translation into clinical use.[11,12] Moreover, considering the low-to-moderate discrimination (defined as C-statistics of <0.8) and relatively poor calibration (as measured by the nomogram) in the majority of studies, the clinical benefits of prediction models in AHF are controversial and requires further investigation.[13,14]

Electrocardiogram (ECG)-gated single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) provides comprehensive information regarding left ventricular (LV) mechanical dyssynchrony and LV viability. It has been shown that LV mechanical dyssynchrony significantly increases the risk of all-cause mortality.[15,16] Our previous study further reveals that the combination of phase histogram bandwidth $>77.76°$ and QRS duration >120 ms may improve risk prediction of patients with AHF.[17] In addition, clinically meaningful improvements in cardiac resynchronization therapy (CRT) response, LV ejection fraction (LVEF), and the incidence of major adverse cardiovascular events are seen in patients with lower myocardial scar burden.[18–20] However, no studies have been conducted to establish a clinical prediction model using ECG-gated SPECT MPI to date.

This study aims to combine demographic information, laboratory tests, ECG, transthoracic echocardiogram (TTE), and ECG-gated resting SPECT MPI to develop and validate a simple and visualized nomogram, thus predicting the risk of all-cause mortality in patients with AHF at 1, 3, and 5 years.

Methods

Study population

This study was performed following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for reporting cohort studies checklist (*Table S1*).[21] We prospectively investigated 147 patients with AHF who received ^{99m}Tc-sestamibi ECG-gated resting SPECT MPI at the First Affiliated Hospital of Nanjing Medical University between 1 May 2012 and 31 December 2016 and met at least one of the inclusion criteria: (i) pulmonary congestion on chest X-ray and/or rale on physical examination; (ii) clinical manifestations of cardiac dysfunction (i.e. exertional dyspnoea, paroxysmal nocturnal dyspnoea, orthopnoea, and lower extremity oedema); and (iii) structural heart disease (i.e. hypertensive heart disease, ischaemic cardiomyopathy, myocardial infarction, dilated cardiomyopathy, and hypertrophic cardiomyopathy). Below were the exclusion criteria: (i) patients aged <20 years or ≥ 80 years; (ii) patients receiving previous pacemaker or implantable cardioverter defibrillator; and (iii) patients with concurrent malignancy or other major illness. The study has been approved by the Institutional Review Board of the First Affiliated Hospital of Nanjing Medical University, and written informed consent was obtained from all patients (Appendix S1). The study protocol was available at the Chinese Clinical Trial Registry (URL: http://www.chictr.org.cn; Public title: The registry study of acute heart failure in China: the diagnostic standard, risk stratification, and clinical outcome of acute heart failure; Registration number: ChiCTR-ONC-12001944).

Demographic information

Demographic information (age and sex), health behaviours (smoking status and alcohol consumption), clinical manifestations [New York Heart Association (NYHA) functional class, heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP)], pre-existing conditions [hypertension, diabetes mellitus, ischaemic heart disease, atrial fibrillation (AF), valvular heart disease (VHD), and dilated cardiomyopathy], device therapy (CRT), and medications (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, beta-blocker, diuretic, antisterone, and aspirin) were collected from medical records. Following the European Society of Cardiology treatment guideline for AHF, evidence based guideline-directed medical therapy was initiated or up-titrated by cardiologists in AHF patients during the period of hospitalization.[22,23] To ensure medication adherence, inpatient medications were all administered by nurses, and discharged patients were required to see their doctors and adjust prescription medications monthly. After a 5 min rest in a sitting position, blood pressure was measured by a cardiologist with a mercury sphygmomanometer according to the recommendations from the American Heart Association.[24] Three groups of SBP and DBP were obtained and averaged for each patient. MAP was calculated as DBP plus one-third of pulse pressure.

Laboratory tests, electrocardiogram, and transthoracic echocardiogram

Data concerning laboratory tests [NT-proBNP, haemoglobin, red blood cell distribution width, sodium, potassium, calcium, alanine aminotransferase, aspartate transaminase, albumin, creatinine, blood urea nitrogen, uric acid, estimated glomeru-

lar filtration rate (eGFR), and D-dimer], 12-lead resting ECG [QRS duration, QTc interval, PR interval, left bundle branch block (LBBB), and right bundle branch block (RBBB)], and TTE (LVEF, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, and pulmonary artery systolic pressure) were acquired from examination reports. Blood samples were analysed by a central laboratory of the First Affiliated Hospital of Nanjing Medical University. The eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation.[25] The 12-lead resting ECG was recorded after hospital admission with Fukuda Denshi FX-8322 (Fukuda Denshi, Tokyo, Japan), with QRS duration, QTc interval, and PR interval automatically measured. TTE was performed with Vivid E9 ultrasound system (GE HealthCare, Wauwatosa, USA), with LVEF measured by modified biplane Simpson's method.

Myocardial ^{99m}Tc-sestamibi scintigraphy

Detailed procedure of ^{99m}Tc-sestamibi ECG-gated resting SPECT MPI has been described previously.[17,26] All patients were required to lie down for more than 4 hours prior to SPECT MPI to ensure completing the scans successfully. Eligible patients received SPECT MPI thereafter. SPECT MPI acquisition was performed by a dual-head detector gamma camera (Philips Medical Systems, Milpitas, USA). SPECT planar images were gathered in a semicircular orbiter (25 s per step) by a 64 × 64 matrix and 8 frames per cardiac cycle. The 20% energy window was centred around 140 keV gamma peak for scatter correction. SPECT images were reconstructed using ordered subset expectation maximization with 3 iterations, 10 subsets, and a 0.4 Butterworth filter. After the reorientation of transaxial slices by an experienced technologist, the short-axis images were entered into Emory Cardiac Toolbox (ECToolbox, Atlanta, USA) for standardized quantification of LV dyssynchrony (as measured by phase histogram bandwidth and phase standard deviation) and LV viability (as measured by rest scar burden) based on the 1-harmonic Fourier approximation. Myocardial segments with a tracer uptake less than half of the maximum uptake were regarded as myocardial scar.

Primary outcome and follow-up

The primary outcome of this study was death from any cause. Follow-up time was defined as the interval from the first discharge to the date of death, the last contact date, or the end of the study period (31 December 2020), whichever occurred first. Patient outcomes and the date of death were ascertained by phone contact with their family numbers, the review of medical records, and government death records if necessary. Follow-up was conducted every 6 months after discharge for each patient.

Statistical analysis

We performed statistical analyses following the recommendations from the American Heart Association Scientific Publication Committee.[27] To maintain statistical power and decrease selection bias due to missing data, we performed multiple imputation based on five replications (*Table S2*).[28,29] Continuous variables were presented as mean with standard deviation (normal distribution) or median with interquartile range (skewed distribution), and categorical variables were presented as frequency with percentage. Shapiro–Wilk test was performed to check for normal distribution. Baseline characteristics were compared between survivors and non-survivors using unpaired *t*-test (normally distributed continuous variables), Mann–Whitney *U* test (skewed distributed continuous variables), or Pearson's χ^2 test (categorical variables).

In order to ensure the model simplicity and decrease the likelihood of overfitting, the least absolute shrinkage and selection operator (LASSO) regression was performed for the selection of key features related to all-cause mortality in patients with AHF.[8,9] An optimal value of the tuning parameter λ was calculated by 10-fold cross-validation; the model simplicity increased with the value of λ. Notably, the potential predictors should be selected in combination with clinical significance, sample size, and statistical power.[30] We used univariate Cox regression analysis to identify key candidate predictors of all-cause mortality and incorporated significant variables with a *P* level of <0.05 level into multivariate analysis. The variables with a *P* level of <0.05 in stepwise Cox analysis were retained for the development and validation of the nomogram to predict the risk of all-cause mortality in patients with AHF at 1, 3, and 5 years.

Mortality risk score was calculated by the 'linear.predictors' component of the 'coxph' object (equivalent to the nomogram) using the 'predict.coxph' function of the 'survival' package in R software version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria), with the 'type' parameter set as 'risk'.[31] We compared the differences in cumulative mortality across quartiles of risk scores using Kaplan–Meier analysis with log-rank test; between-group comparisons were adjusted by the Benjamini–Hochberg method. Discrimination of the model was quantified using the area under the curves (AUCs) before and after 100 iterations of three-fold cross-validation, respectively.[32] Distribution of cross-validated AUCs were illustrated with raincloud plots. By calculating continuous net reclassification improvement (cNRI) and integrated discrimination improvement (IDI), we assessed the improvement from baseline model in the discriminating ability when additionally considering key

indicators of SPECT MPI.[33] Calibration of the model was examined by comparing the actual frequencies with the nomogram-predicted 1, 3, and 5 year all-cause mortality rates based on a bootstrapped resample with 1000 iterations.[32] In an ideal calibration plot, the predictions fall on the 45° diagonal line. Decision curve analysis (DCA) was used to evaluate the clinical applicability of the model by quantifying net benefits at different threshold probabilities.[34] Finally, we developed an easy-to-use nomogram website based on the proposed model. All analyses were performed by R software version 4.1.1. A two-sided *P* of <0.05 was considered statistically significant.

Results

Patient characteristics

A total of 147 patients with AHF were enrolled after a median follow-up of 49 months (interquartile range, 31–72 months). *Table 1* provides a summary of baseline characteristics stratified by survival status. In the overall cohort, the median age was 59 years and most patients (78%) were men. About two-thirds of patients were of NYHA functional class III, 56% were diagnosed with DCM, and 19% were diagnosed with ischaemic heart disease. Comparisons between survivors and non-survivors did not reach statistical significance, except for DBP, MAP, VHD, CRT, NT-proBNP, uric acid, D-dimer, RBBB, and rest scar burden. Notably, rest scar burden was significantly higher ($P = 0.009$) in survivors than in non-survivors (27.6 vs. 19.1%). The 1, 3, and 5 year cumulative rates of death were 10%, 22%, and 29%, respectively.

The LASSO and Cox regression for model development

As shown in *Figure 1*, 51 features were screened by the LASSO algorithm with an optimal value of the tuning parameter λ. When ln(λ) was set at -2.366 ($\lambda = 0.094$), the residual sum of squares was under the 1-SE criteria and 6 potential predictors were identified, including DBP, VHD, CRT, NT-proBNP, RBBB, and rest scar burden (*Table S3*). After univariate Cox regression analysis, all six variables remained survival-related and were further included in multivariate analysis (*Table 2*). Multivariable Cox regression analysis revealed that DBP [hazard ratio (HR) 0.96, 95% confidence interval (CI) 0.93–0.99; $P = 0.017$], VHD (HR 3.05, 95% CI 1.36–6.83; $P = 0.007$), CRT (HR 0.37, 95% CI 0.17–0.82; $P = 0.014$), NT-proBNP (per 100 pg/mL; HR 1.02, 95% CI 1.01–1.03; $P < 0.001$), and rest scar burden (HR 1.03, 95% CI 1.01–1.06; $P = 0.008$) were independent prognostic factors for all-cause mortality in patients with AHF.

Construction of the nomogram model

Fifty-one variables decreased to 5 variables after the LASSO and Cox regression analyses, including DBP, VHD, CRT, NT-proBNP, and rest scar burden. Given their clinical significance and statistical power, we included the 5 factors in a nomogram model to predict 1, 3, and 5 year all-cause mortality rates in patients with AHF (*Figure 2*). Higher total score (calculated as the sum of the scores of all variables) indicated a worse clinical outcome and a higher risk of all-cause mortality. To help understand the usage of the nomogram, an example was given. Specifically, an individual with AHF, together with DBP = 84 mmHg, VHD = No, CRT = No, NT-proBNP = 1775 pg/mL, and rest scar burden = 53%, had a total score of 133. The estimated probabilities of 1, 3, and 5 year death were 12%, 31%, and 44%, respectively; corresponding probabilities of survival at 1, 3, and 5 years were 88%, 69%, and 56%, respectively.

Validation of the nomogram model

To evaluate the discrimination of the model, the overall survival (OS) rates were displayed as Kaplan–Meier curves stratified by quartiles of risk scores (Q1: <0.27; Q2: 0.27–0.59; Q3: 0.60–1.87; Q4: ≥ 1.88) calculated from the nomogram (*Figure 3*). Patients with the highest quartile of risk score had the worst outcome (5 year OS rates of 51%) compared with those in the lower quartiles (5 year OS rates of 97%, 81% and 57%, respectively; log-rank $P < 0.001$). Furthermore, multiple comparisons adjusted by the Benjamini-Hochberg method indicated that a higher risk score corresponded to a higher risk of all-cause mortality (Q2 vs. Q1, $P = 0.046$; Q3 vs. Q1, $P < 0.001$; Q4 vs. Q1, $P < 0.001$; Q3 vs. Q2, $P = 0.015$; Q4 vs. Q2, $P < 0.001$). No significant difference was observed between Q3 and Q4 ($P = 0.197$).

Time-dependent discrimination analysis was also performed to assess the prognostic performance of the nomogram model. The AUCs (95% CI) based on the entire cohort were 0.89 (0.81–0.98), 0.85 (0.78–0.92), and 0.81 (0.72–0.90) for 1, 3, and 5 year all-cause mortality, respectively (*Figure 4A*). After 100 iterations of three-fold cross-validation, the model showed a stable predictive capability for all-cause mortality, with mean AUC values (95% CI) of 0.88 (0.73–1.00), 0.83 (0.70–0.97), and 0.79 (0.62–0.95) at 1, 3, and 5 years, respectively. Distribution of cross-validated AUCs is shown in *Figure 4B*. Moreover, the inclusion of rest scar burden improved cNRI and IDI to a greater extent than baseline model (comprising DBP, VHD, CRT, and NT-proBNP; *Table 3*); this result was generally seen regardless of the follow-up time. Additionally, calibration plots showed satisfactory coherence between the estimated and actual probabilities of all-cause death at 1, 3, and

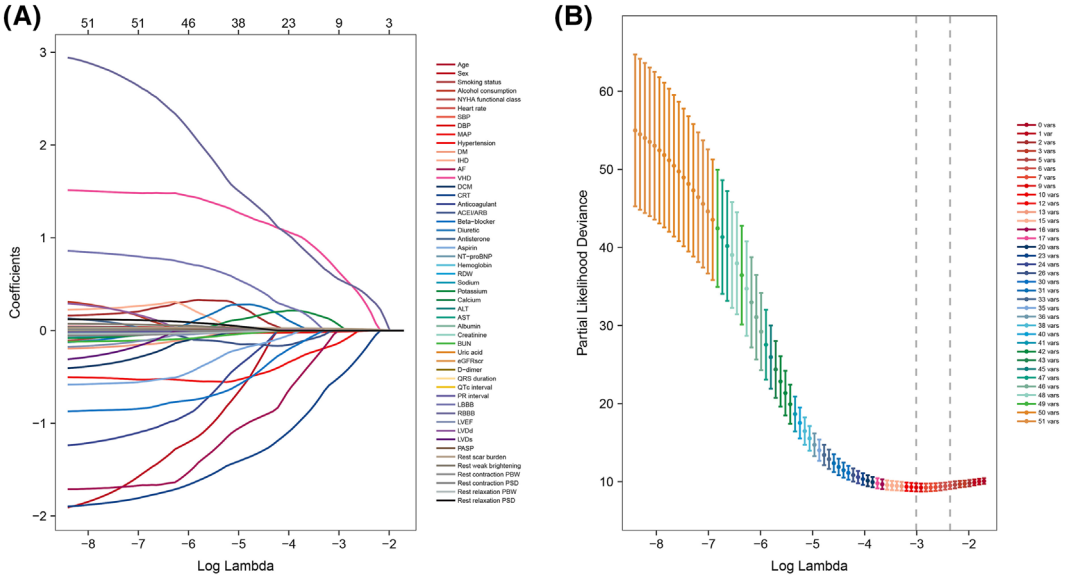
Table 1 Baseline characteristics of the included patients with acute heart failure

Characteristics	All (n = 147)	Nonevent (n = 107)	Event (n = 40)	P value
Age, year	59.0 [47.5, 68.0]	58.0 [48.0, 67.0]	61.5 [44.8, 69.2]	0.447
Male, %	115 (78.2)	85 (79.4)	30 (75.0)	0.562
Smoking status, %	71 (48.3)	53 (49.5)	18 (45.0)	0.625
Alcohol consumption, %	56 (38.1)	42 (39.3)	14 (35.0)	0.637
NYHA functional class, %				0.514
II	23 (15.6)	19 (17.8)	4 (10.0)	
III	96 (65.3)	68 (63.6)	28 (70.0)	
IV	28 (19.0)	20 (18.7)	8 (20.0)	
Heart rate, b.p.m.	80.0 [70.0, 90.0]	80.0 [70.0, 90.0]	81.0 [72.0, 90.5]	0.913
SBP, mmHg	120.0 [106.0, 131.0]	122.0 [107.0, 135.0]	112.5 [104.8, 124.0]	0.056
DBP, mmHg	76.0 [70.0, 88.0]	77.0 [70.0, 88.0]	72.0 [65.8, 80.2]	0.044
MAP, mmHg	91.3 [83.0, 101.2]	92.3 [85.0, 101.7]	87.7 [80.0, 95.9]	0.028
Hypertension, %	68 (46.3)	54 (50.5)	14 (35.0)	0.094
DM, %	27 (18.4)	19 (17.8)	8 (20.0)	0.755
IHD, %	28 (19.0)	21 (19.6)	7 (17.5)	0.770
AF, %	17 (11.6)	14 (13.1)	3 (7.5)	0.514
VHD, %	20 (13.6)	10 (9.3)	10 (25.0)	0.014
DCM, %	83 (56.5)	61 (57.0)	22 (55.0)	0.827
CRT, %	56 (38.1)	48 (44.9)	8 (20.0)	0.006
Anticoagulant, %	45 (30.6)	32 (29.9)	13 (32.5)	0.761
ACEI/ARB, %	125 (85.0)	94 (87.9)	31 (77.5)	0.117
Beta-blocker, %	120 (81.6)	89 (83.2)	31 (77.5)	0.429
Diuretic, %	58 (39.5)	41 (38.3)	17 (42.5)	0.644
Antisterone, %	140 (95.2)	101 (94.4)	39 (97.5)	0.725
Aspirin, %	68 (46.3)	50 (46.7)	18 (45.0)	0.852
NT-proBNP, pg/mL	2146.0 [1236.5, 4455.3]	1777.0 [1086.0, 3003.0]	3116.0 [2143.8, 7275.5]	<0.001
Haemoglobin, g/L	136.0 [123.5, 149.0]	136.0 [124.5, 149.0]	138.0 [121.0, 149.5]	0.967
RDW, %	14.2 [13.2, 15.2]	14.1 [13.2, 15.1]	14.3 [13.3, 15.8]	0.254
Sodium, mmol/L	139.3 [136.6, 141.7]	139.6 [136.6, 141.9]	138.4 [136.6, 140.9]	0.115
Potassium, mmol/L	4.0 [3.6, 4.3]	3.9 [3.6, 4.3]	4.0 [3.6, 4.4]	0.296
Calcium, mmol/L	2.3 [2.2, 2.4]	2.3 [2.2, 2.4]	2.3 [2.2, 2.3]	0.736
ALT, μ/L	31.3 [18.6, 58.0]	30.5 [18.4, 55.6]	33.9 [20.2, 65.4]	0.418
AST, μ/L	28.3 [20.6, 48.2]	28.3 [20.4, 42.3]	30.2 [21.5, 61.0]	0.327
Albumin, g/L	38.3 [35.2, 41.8]	38.2 [34.5, 41.9]	38.3 [35.8, 41.8]	0.829
Creatinine, μmol/L	83.8 [72.0, 109.7]	82.4 [70.7, 109.2]	89.3 [79.0, 111.1]	0.104
BUN, mmol/L	7.2 [5.9, 8.9]	7.1 [5.8, 8.7]	7.7 [6.2, 9.2]	0.253
Uric acid, μmol/L	484.0 [400.6, 587.9]	479.0 [393.5, 548.6]	538.6 [443.3, 651.2]	0.015
$eGFR_{scr}$, mL/min/1.73 m^2	66.0 (23.5)	68.0 (23.9)	60.7 (21.6)	0.095
D-dimer, ng/mL	0.7 [0.3, 1.7]	0.6 [0.2, 1.5]	0.9 [0.5, 2.2]	0.018
QRS duration, ms	126.0 [104.0, 154.9]	125.0 [102.0, 159.5]	130.0 [115.5, 148.0]	0.470
QTc interval, ms	473.0 [448.0, 501.0]	479.0 [448.0, 507.0]	465.0 [448.0, 480.0]	0.059
PR interval, ms	177.0 [159.5, 197.0]	177.0 [158.0, 194.0]	175.5 [163.5, 200.2]	0.641
LBBB, %	74 (50.3)	56 (52.3)	18 (45.0)	0.429
RBBB, %	15 (10.2)	6 (5.6)	9 (22.5)	0.007
LVEF, %	30.5 [25.8, 37.3]	30.5 [26.1, 37.3]	30.7 [24.8, 37.5]	0.828
LVDd, mm	68.7 (10.9)	68.0 (10.8)	70.5 (11.1)	0.219
LVDs, mm	57.9 (11.9)	57.3 (11.9)	59.5 (11.8)	0.316
PASP, mmHg	40.0 [30.0, 50.0]	40.0 [30.0, 48.0]	45.5 [28.0, 55.0]	0.180
Rest scar burden, %	22.0 [13.6, 31.6]	19.1 [12.9, 28.3]	27.6 [15.7, 42.9]	0.009
Rest weak brightening, %	20.3 [7.8, 32.6]	19.5 [7.5, 30.3]	22.7 [9.9, 39.5]	0.135
Rest contraction PBW, °	130.0 [72.0, 243.5]	130.0 [66.0, 242.5]	125.0 [92.8, 285.5]	0.318
Rest contraction PSD, °	33.6 [20.0, 55.0]	33.9 [17.1, 53.9]	33.1 [23.3, 60.8]	0.372
Rest relaxation PBW, °	182.0 [111.5, 286.5]	187.0 [100.5, 285.0]	176.5 [126.0, 297.0]	0.440
Rest relaxation PSD, °	53.1 [32.1, 71.3]	50.6 [31.2, 69.9]	53.5 [40.9, 73.4]	0.271

Data are presented as mean (SD), median [interquartile range], or n (%).

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate transaminase; BUN, blood urea nitrogen; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; DCM, dilated cardiomyopathy; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; IHD, ischaemic heart disease; LBBB, left bundle branch block; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; PBW, phase histogram bandwidth; PSD, phase standard deviation; RBBB, right bundle branch block; RDW, red blood cell distribution width; SBP, systolic blood pressure; VHD, valvular heart disease.

Figure 1 Selection of key features related to survival by the least absolute shrinkage and selection operator (LASSO) regression. *(A)* The LASSO regression coefficient trendlines of the 51 candidate features. *(B)* Determination of the tuning parameter λ by 10-fold cross-validation. Two vertical lines were drawn, representing a more concise model within one standard error. The tuning parameter λ = 0.094 was selected under the 1-SE criteria with 6 non-zero coefficients included. ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate transaminase; BUN, blood urea nitrogen; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; DCM, dilated cardiomyopathy; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; IHD, ischaemic heart disease; LBBB, left bundle branch block; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; PBW, phase histogram bandwidth; PSD, phase standard deviation; RBBB, right bundle branch block; RDW, red blood cell distribution width; SBP, systolic blood pressure; VHD, valvular heart disease.



5 years (*Figure 5*). These results demonstrated the accuracy of the nomogram for predicting the prognosis of AHF over the longer term.

Clinical applicability of the nomogram model

The DCA plots of the nomogram model are displayed in *Figure 6*. Clinical benefits were seen across a wide range of threshold probabilities (0–100% at 1 and 3 years; 0–61% and 62–100% at 5 years). This result indicated superior net benefit of the nomogram in OS prediction compared with dismissing the included factors or using either factor alone.

Construction of the web-based dynamic nomogram

To make the use of the nomogram simpler and easier for clinicians, we further created a decision support tool [DVCNS (D: DBP; V: VHD; C: CRT; N: NT-proBNP; S: rest scar burden) heart prognostic nomogram; https://decision-support-tool.shinyapps.io/dvcns/] using the proposed statistical model. The estimated probabilities of survival could be easily obtained from the website after inputting the five independent prognostic factors and follow-up time (months).

Discussion

Although recent research on AHF has focused on clinical manifestations, laboratory tests, instrumental examinations, and medical history, there was no study conducted to establish a clinical prediction model using ECG-gated SPECT MPI.[8,9,35,36] This study revealed that DBP, VHD, CRT, NT-proBNP, and rest scar burden as measured by SPECT MPI were independent predictors of all-cause mortality in patients with AHF. A web-based dynamic nomogram was thus developed, which might improve the estimation of the prognosis of AHF, thereby allowing for a more individualized treatment strategy.

The strength of this study is that it considers a wide spectrum of prognostic factors previously shown to exert effects on the prognosis of patients with AHF. Factors reported to be associated with patient outcomes markedly differ between different studies. To date, there is a relative lack of consensus on which factors are key for the determination of patients with AHF. Some studies reported that demographic information (age), clinical manifestations (NYHA functional class, SBP, DBP, and MAP), pre-existing conditions (diabetes mellitus and AF), medications (vasopressors), laboratory tests (NT-proBNP, haemoglobin, sodium, albumin, creatinine, blood urea nitrogen, and eGFR), and 12-lead rest-

Table 2 Univariate and multivariate Cox regression analyses of significant predictors of all-cause mortality in patients with acute heart failure

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
DBP	0.97 (0.94–0.99)	0.014	0.96 (0.93–0.99)	0.017
VHD	2.57 (1.26–5.27)	0.010	3.05 (1.36–6.83)	0.007
CRT	0.34 (0.16–0.74)	0.006	0.37 (0.17–0.82)	0.014
NT-proBNP (per 100 pg/mL)	1.02 (1.01–1.03)	<0.001	1.02 (1.01–1.03)	<0.001
RBBB	4.23 (2.00–8.97)	<0.001	1.91 (0.78–4.69)	0.159
Rest scar burden	1.04 (1.02–1.06)	<0.001	1.03 (1.01–1.06)	0.008

Key variables screened by the least absolute shrinkage and selection operator (LASSO) regression were included in univariate analysis; significant variables with a *P* value of <0.05 were further included in multivariate analysis.
Abbreviations: CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RBBB, right bundle branch block; VHD, valvular heart disease.

Figure 2 The DVCNS [D: DBP; V: VHD; C: CRT; N: NT-proBNP; S: rest scar burden] heart prognostic nomogram for predicting the risks of 1, 3, and 5 year all-cause mortality in patients with acute heart failure. The level or category of each variable corresponded to a score on the points scale. After summing the scores of all variables and locating the total score on the total points scale, a line was drawn straight down to 1, 3, and 5 year survival scales and the estimated probabilities of death were obtained. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$. CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; VHD, valvular heart disease.

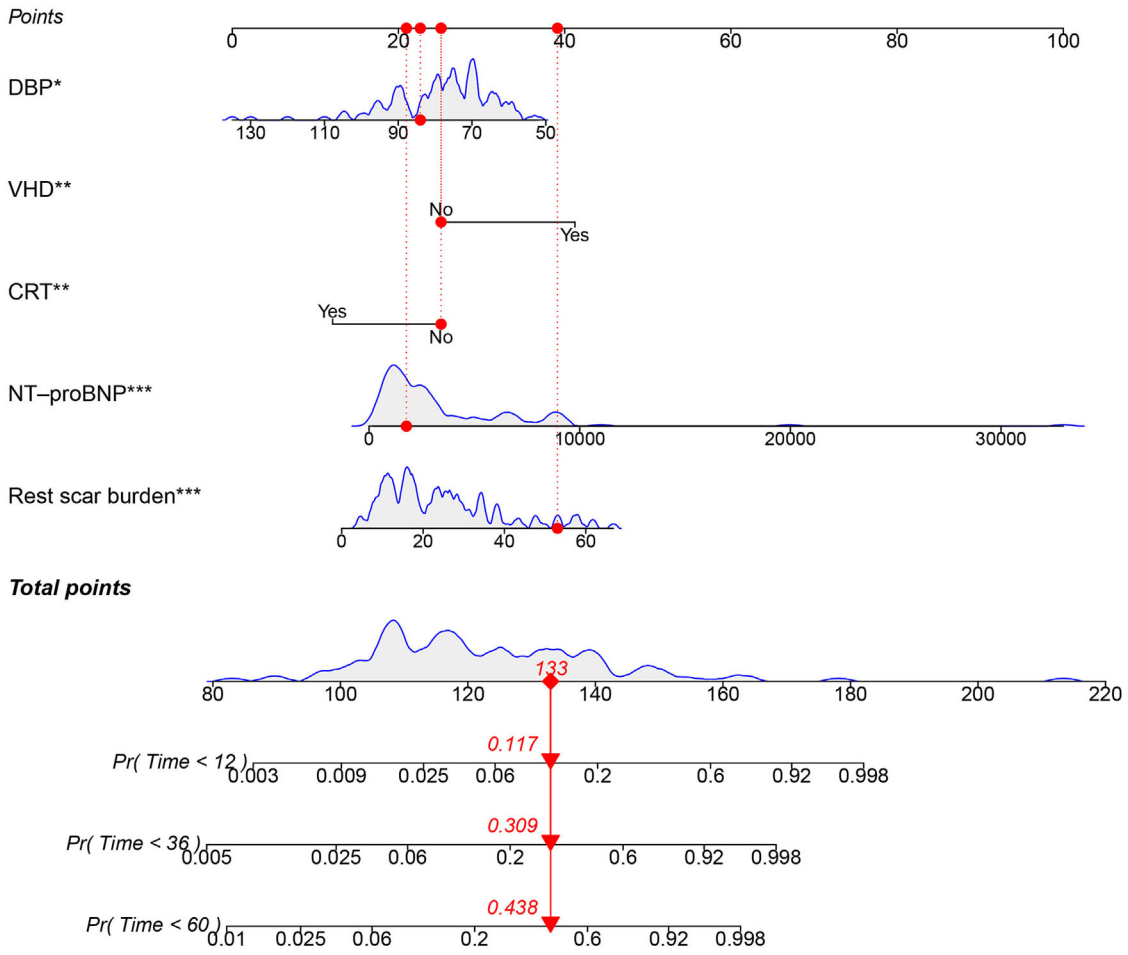
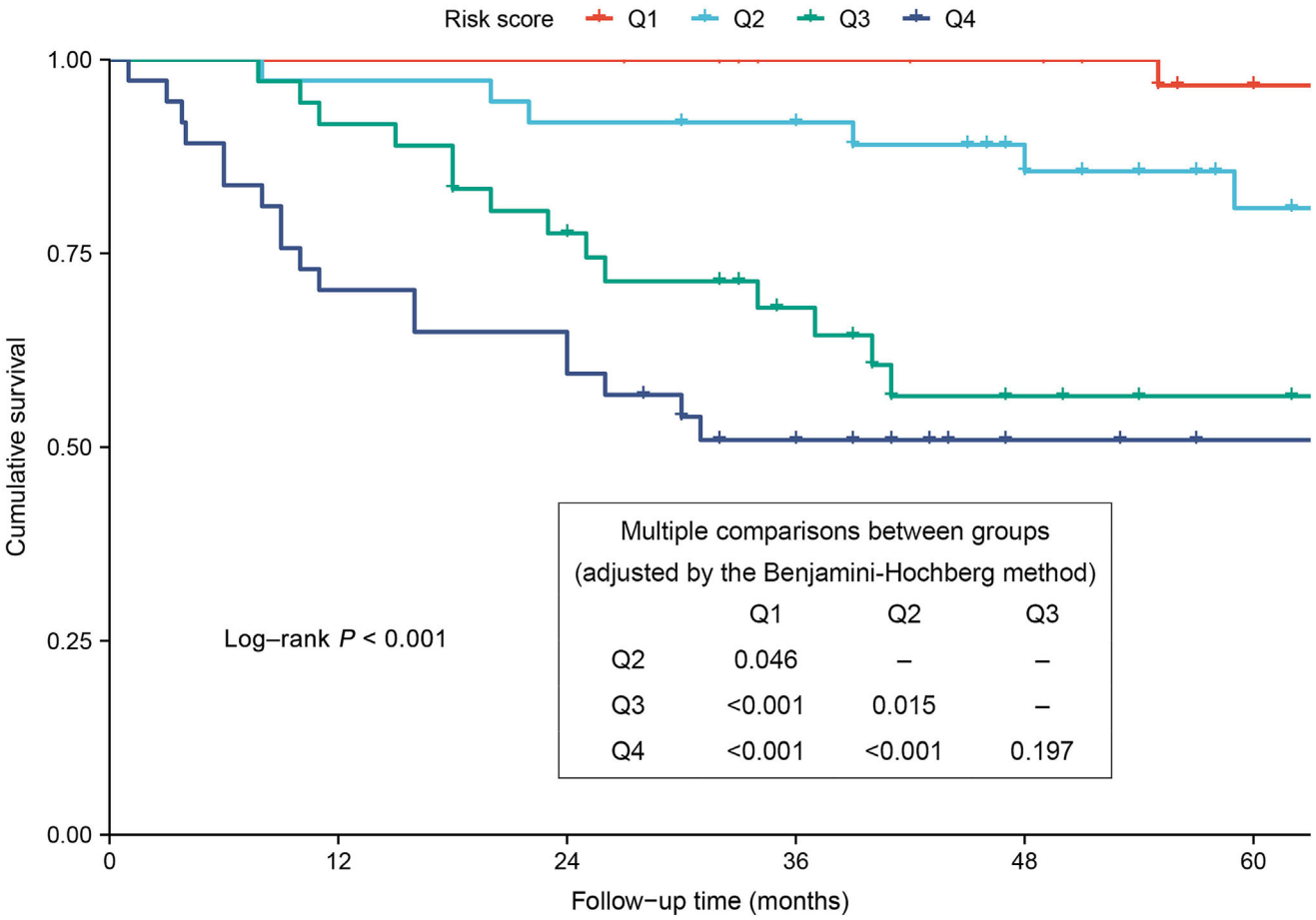


Figure 3 Kaplan–Meier curves of overall survival (OS) stratified by quartiles of risk scores (Q1: <0.27; Q2: 0.27–0.59; Q3: 0.60–1.87; Q4: ≥1.88) in patients with acute heart failure. Multiple comparisons between groups were adjusted by the Benjamini–Hochberg method.



Number at risk

Q1	37	37	37	33	32	24
Q2	37	36	34	33	26	17
Q3	36	33	27	19	9	7
Q4	37	26	24	16	9	7

ing ECG (RBBB) were significantly associated with OS.[8,9,37–40] However, in the other studies, there was no apparent association of demographic information (age), clinical manifestations (SBP and DBP), pre-existing conditions (AF), medications, and laboratory tests (NT-proBNP, haemoglobin, sodium, and creatinine) with long-term survival.[41–43] To our knowledge, this study is the first risk stratification model to consider including VHD, CRT, and indicators of SPECT MPI (i.e. rest scar burden) to predict the prognosis of AHF.

Results of DBP in patients with AHF and in the real-world setting were generally consistent with those seen in several studies.[44,45] Elevated SBP has been shown to prolong survival time in patients with AHF[46]; however, we found that DBP was more relevant to the risk of all-cause mortality than SBP, suggesting that we should consider DBP in addition to SBP in further studies regarding the prognosis or clinical prediction models in patients with AHF. While the exact mechanism by which higher DBP improves survival outcomes is yet to be established, it is presumed that the haemodynamic ability to elevate blood pressure (BP) and tolerate an increased afterload represents preserved cardiac function, and thus may correlate with the extent and severity of HF.[47] Moreover, routine management of AHF usually includes preload- and afterload-reducing drugs with appreciable BP-lowering effects.[48] It is straightforward to treat patients with AHF induced by high BP using them, and a more favourable prognosis in AHF with higher DBP may be partly explained by this fact. Further investigation is warranted to determine the role of DBP as a biomarker for the prediction of disease progression in AHF.

VHD and HF are major adverse cardiovascular events with an increasingly widespread prevalence in the Western world.

Figure 4 Prognostic performance of the nomogram model to predict the risk of all-cause mortality in patients with acute heart failure. (A) The mean time-dependent area under the curves before and after 100 iterations of three-fold cross-validation. (B) Distribution of time-dependent area under the curves after 100 iterations of three-fold cross-validation at 1, 3, and 5 years.

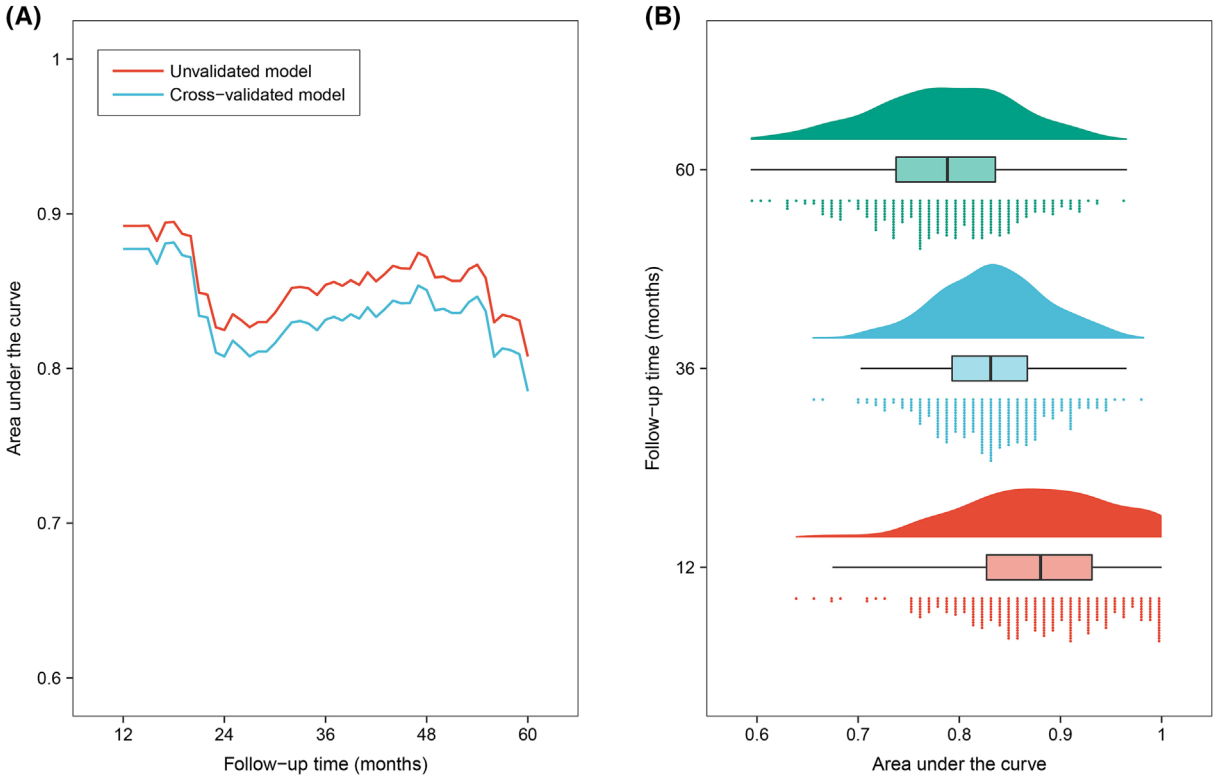


Table 3 Incremental prognostic value of considering rest scar burden in patients with acute heart failure at 1, 3, and 5 years

Model	IDI (95% CI)	*P* value	NRI (95% CI)	*P* value
1 year follow-up				
Baseline model[a]	Reference		Reference	
Baseline model + Rest scar burden	0.11 (0.03–0.22)	<0.001	0.45 (0.10–0.69)	0.010
3 year follow-up				
Baseline model[a]	Reference		Reference	
Baseline model + Rest scar burden	0.08 (0.01–0.17)	0.012	0.28 (0.02–0.50)	0.032
5 year follow-up				
Baseline model[a]	Reference		Reference	
Baseline model + Rest scar burden	0.06 (0.01–0.14)	0.006	0.33 (0.02–0.50)	0.026

Abbreviations: cNRI, continuous net reclassification improvement; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; IDI, integrated discrimination improvement; NT-proBNP, N-terminal pro-B-type natriuretic peptide; VHD, valvular heart disease.
[a]Estimates were adjusted for DBP, VHD, CRT, and NT-proBNP.

These two diseases are commonly co-present, which may interfere with the estimation of the severity of valve stenosis or regurgitation and influence therapeutic decision making.[49] Lancellotti *et al.*[50] reported that primary VHD resulting in HF or secondary VHD resulting from myocardial remodelling and dysfunction in HF was likely to increase cardiac load, complicate HF, and worsen both clinical manifestations and prognosis. Indeed, severe valve lesion can cause progressive LV dysfunction and chronic HF with an annual mortality rate of 5% in symptomatic patients who received no intervention.[51,52] Medical care can help to alleviate symptoms but cannot reverse disease progression.[52] Furthermore, a number of symptomatic patients do not receive valve surgery due to the high risk from older age or multiple comorbidities, and a deficiency of clinical data supporting valve surgery for secondary VHD with LV dysfunction.[53–55] Hence, VHD usually carries a poor prognosis in patients with HF. However, the clinical relevance of the two diseases remains unclear. A

Figure 5 The 49-sample bootstrapped calibration plots of the nomogram model to predict the risk of all-cause mortality in patients with acute heart failure at (A) 1, (B) 3, and (C) 5 years. Blue line represents the ideal fit; circle represents nomogram-predicted probability of death; cross represents the bootstrap-corrected estimate; and error bar represents the corresponding 95% confidence interval.

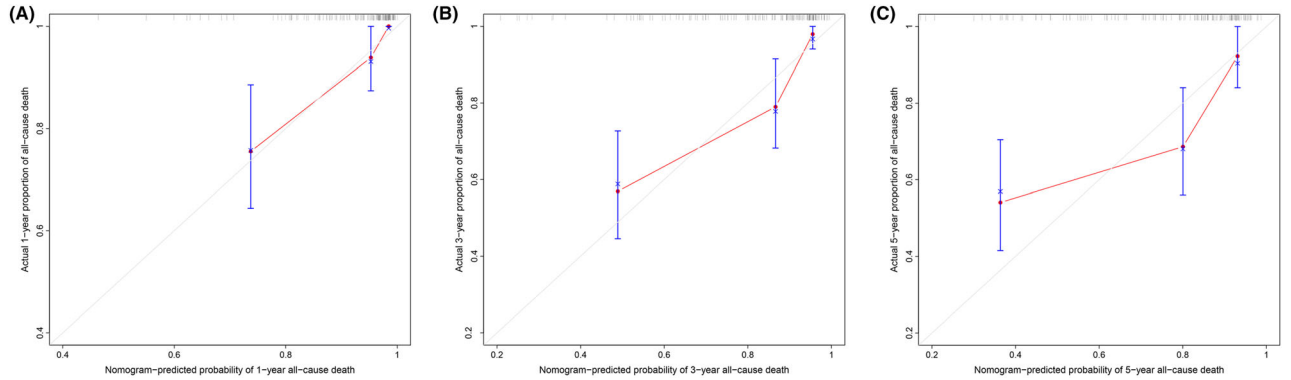
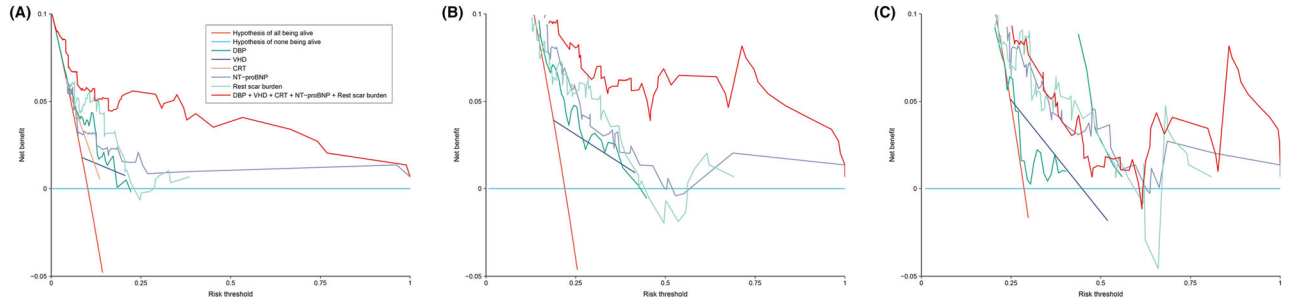


Figure 6 Decision curves of the nomogram model to predict the risks of (A) 1, (B) 3, and (C) 5 year all-cause mortality in patients with acute heart failure. Dark red line represents net benefit of the nomogram model; light red line represents net benefit of the hypothesis that all patients were alive; blue line represents net benefit of the hypothesis that all patients were dead; the remaining line represents the respective net benefit of each variable included in the nomogram model. Clinical applicability of the model increases with increasing net benefit. CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; VHD, valvular heart disease.



retrospective study demonstrated that the risk of all-cause mortality was increased by up to 7.56-fold in patients with concomitant HF and VHD.[56] Similar results were seen in our cohort (HR 3.05, 95% CI 1.36–6.83) after adjusting for DBP, CRT, NT-proBNP, and rest scar burden. These results indicated that the risk of all-cause mortality was increased when HF patients had VHD. Nevertheless, caution is advised because of the relatively limited sample size.

The third independent prognostic factor for OS in this study was CRT, a first-line treatment option for HF patients with systolic dysfunction, QRS duration of >130 ms, and NYHA functional class III or IV symptoms.[1] Among patients with standard indication, CRT is likely to decrease morbidity and mortality, and may also result in improved cardiac function and quality of life.[57–59] In this study, the median age was 59 (48–68) years, most patients (79%) were male, 45% had QRS duration of >130 ms, and 50% had LBBP. The observed results may be primarily generalized to patients with AHF who meet CRT indication. Given that LBBB usually co-exists with wider QRS duration, considerable debate has existed on whether QRS duration or morphology is the main predictor of beneficial CRT response. Experience from randomized clinical trials confirmed the role of QRS duration of >130 ms in predicting CRT response and reducing potential damage.[58,60,61] It has been shown that HF patients with LBBB are more likely to benefit from CRT, but there is less certainty in those without LBBB.[62] Furthermore, evidence from several meta-analyses indicated that after adjusting for QRS duration, its morphology had no clinically meaningful impact on morbidity and mortality in patients receiving CRT.[58,63] Robust head-to-head trials would be beneficial.

Plasma concentrations of NT-proBNP are dependent on LV filling pressure and wall size, and are not significantly affected by the use of angiotensin receptor-neprilysin inhibitors, recombinant brain natriuretic peptide (BNP), or other drugs. Plasma levels of NT-proBNP are generally consistent with

those of BNP in patients with AHF, which exert cardioprotective effects via urinary excretion, sodium excretion, and antihypertension.[64,65] This study indicated that reduced NT-proBNP level was associated with OS improvements and comparable to that seen in other studies[8,36,65]; however, most of these studies analysed NT-proBNP as a categorical variable without considering the dynamic and non-linear interaction between NT-proBNP and other clinical indicators. In a meta-analysis of 12 638 HF patients with reduced ejection fraction, the association of NT-proBNP with long-term prognosis was independent of the specific thresholds used.[66] In this study, we analysed NT-proBNP as a continuous variable and patient outcome was predicted more accurately when compared with using a threshold alone. Identifying patients with high NT-proBNP levels is an important consideration in AHF management.

Myocardial remodelling represents the inflammatory pathways that mediate the development from cardiac dysfunction to decompensated HF. The remodelling response varies across individuals when the time of myocardial ischaemia or the damaged area is extensive, from adequate wound healing to adverse remodelling leading to HF.[67] Patients with myocardial scar who are receiving CRT have fewer improvements in LV function and appear less likely to experience favourable remodelling.[68] Adelstein *et al*.[20] demonstrated a significant negative association between myocardial scar burden and CRT response regardless of baseline dyssynchrony. In a multivariable analysis of 178 patients with HF who received standard drug therapy, after adjusting for left anterior descending artery, total scar score was found to be a significant predictor of LVEF change.[19] Moreover, a retrospective study demonstrated that myocardial scar was independently associated with an increased risk of a composite of all-cause death, heart transplantation, acute coronary syndrome, hospitalization for HF, and late revascularization.[18] This study also showed that rest scar burden was an independent predictor of the prognosis of AHF with an HR (95% CI) of 1.03 (1.01–1.06). Each increase in rest scar burden by 1% significantly increased the risk of all-cause mortality by 3%; thus, rest scar burden was included in the clinical prediction model. These findings indicated the clinical impact of rest scar burden on the long-term prognosis of patients with AHF and its clinical utility for stratifying them into different prognostic groups. Further studies determining our findings would be of interest.

In total, we identified five independent predictors (including DBP, VHD, CRT, NT-proBNP, and rest scar burden) of all-cause mortality in patients with AHF and developed a clinical prediction model for early identification and appropriate management of AHF, particularly in high-risk individuals. Cross-validation and bootstrap validation confirmed the favourable discrimination and calibration of the nomogram model, together with a high net benefit. The web-based DVCNS heart prognostic nomogram provided clinicians with a simple and visualized tool for clinical use.

Limitations

This study has several limitations. First, we enrolled only 147 patients with AHF who received ECG-gated rest SPECT MPI in a single institution, and therefore, these findings might have limited generalizability and differ in individual countries or race/ethnicity. The relatively high model performance might be partly attributed to it. Second, most patients (83%) had a LVEF of $<$40%, suggesting that the nomogram might be more applicable to HF patients with low ejection fraction. Third, although numerous confounding covariates were adjusted for in this study, a proportion of clinically relevant indicators were still missing, such as body mass index and soluble growth stimulation expressed gene 2 protein. Fourth, we focused solely on baseline clinical characteristics without considering alterations in levels of prognostic indicators during the follow-up period, which might provide additional information for the prognosis of patients with AHF. Finally, although the nomogram has been internally validated by cross-validation and bootstrap validation, further research is required for external validation.

Conclusions

In conclusion, this study found that DBP, VHD, CRT, NT-proBNP, and rest scar burden as measured by SPECT MPI were independent prognostic factors for the risk of all-cause mortality in AHF patients. Based on these predictors, we developed a nomogram to estimate the probabilities of all-cause death at 1, 3, and 5 years. The use of the proposal nomogram in the form of an online calculator can stratify patients into different prognostic groups, thus helping to guide treatment decisions.

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Conflict of interest

The authors declared no conflicts of interest.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for reporting cohort studies checklist.

Table S2. Proportion of missing data for potential predictors in the cohort before multiple imputation (n = 147).

Table S3. The least absolute shrinkage and selection operator (LASSO) coefficient profiles of the 51 features.

Appendix S1. Approved file of the Institutional Review Board of the First Affiliated Hospital of Nanjing Medical University.

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