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ORIGINAL RESEARCH

Web-Based Dynamic Nomogram for Predicting Risk of Mortality in Heart Failure with Mildly Reduced Ejection Fraction

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Purpose: This study aimed to develop an integrative dynamic nomogram, including N-terminal pro-B type natural peptide (NT-proBNP) and estimated glomerular filtration rate (eGFR), for predicting the risk of all-cause mortality in HFmrEF patients.

Patients and Methods: 790 HFmrEF patients were prospectively enrolled in the development cohort for the model. The least absolute shrinkage and selection operator (LASSO) regression and Random Survival Forest (RSF) were employed to select predictors for all-cause mortality. Develop a nomogram based on the Cox proportional hazard model for predicting long-term mortality (1-, 3-, and 5-year) in HFmrEF. Internal validation was conducted using Bootstrap, and the final model was validated in an external cohort of 338 consecutive adult patients. Discrimination and predictive performance were evaluated by calculating the time-dependent concordance index (C-index), area under the ROC curve (AUC), and calibration curve, with clinical value assessed via decision curve analysis (DCA). Integrated discrimination improvement (IDI) and net reclassification improvement (NRI) were used to assess the contributions of NT-proBNP and eGFR to the nomogram. Finally, develop a dynamic nomogram using the "Dynnom" package.

Results: The optimal independent predictors for all-cause mortality (*APSELNH: A: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor-neprilysin inhibitor (ACEI/ARB/ARNI), P: percutaneous coronary intervention/coronary artery bypass graft (PCI/CABG), S: stroke, E: eGFR, L: lg of NT-proBNP, N: NYHA, H: healthcare*) were incorporated into the dynamic nomogram. The C-index in the development cohort and validation cohort were 0.858 and 0.826, respectively, with AUCs exceeding 0.8, indicating good discrimination and predictive ability. DCA curves and calibration curves demonstrated clinical applicability and good consistency of the nomogram. NT-proBNP and eGFR provided significant net benefits to the nomogram.

Conclusion: In this study, the dynamic APSELNH nomogram developed serves as an accessible, functional, and effective clinical decision support calculator, offering accurate prognostic assessment for patients with HFmrEF.

Keywords: heart failure with mildly reduced ejection fraction, all-cause mortality, risk prediction model, risk strategy, dynamic nomogram

Introduction

Heart failure (HF) affects over 60 million patients worldwide, characterized by high morbidity and poor prognosis, making it a global public health priority.[1] Based on left ventricular ejection fraction (EF), the 2021 ESC chronic heart failure guidelines classify HF into three subgroups: HF with reduced EF (HFrEF; EF≤40%), HF with mildly reduced EF (HFmrEF; EF 41-49%), and HF with preserved EF (HFpEF; EF≥50%). HFmrEF, constituting 13-24% of global HF patients,[2,3] is often considered a "gray" area between HFpEF and HFrEF, gaining increasing attention recently. Some reports suggest that the all-cause mortality of HFmrEF is lower than HFrEF and similar to HFpEF,[4,5] while another study

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pooled longitudinal cohort data from four communities and found that HFmrEF had a higher mortality rate than HFrEF and HFpEF.[6] Indeed, as a heterogeneous syndrome, HFmrEF exhibits considerable clinical uncertainty. So far, risk strategies of prognosis for HFmrEF are unclear, treatment options are imperfect, and the long-term prognosis for patients is poor.[7] Accurate risk stratification has become a priority for managing HFmrEF patients.[8]

Clinical predictive models help explore individualized characteristics closely associated with various outcomes for a given disease and are increasingly utilized to support clinical decision-making. However, existing risk models for HF primarily focus on HFpEF and HFrEF, with relatively few risk models targeting HFmrEF currently available.[9–11]

Biomarkers are crucial for assessing HF prognosis. ACC/AHA guidelines recommend using NT-proBNP to guide prognosis stratification in HF (Class IA).[12] Moreover, renal function has a significant value in the prognostic assessment of HFmrEF.[13,14] As a sensitive indicator of renal function, the estimated glomerular filtration rate (eGFR) has been proven closely linked with long-term prognosis in HF.[15,16] However, there is insufficient evidence to support the value of the combination of NT pro-BNP and eGFR in predicting HFmrEF outcomes. Additionally, single clinical predictor might be influenced by etiology and population characteristics, leading to its deviation from clinical practice. Therefore, this study aims to explore the predictive value of eGFR, NT-proBNP, and their coexisting clinical variables for all-cause mortality in HFmrEF, and develop and validate a web-based dynamic nomogram through real-world long-term follow-up data to generate personalized prediction of mortality in HFmrEF patients.

Materials and Methods

Study Population

We enrolled 1250 HFmrEF patients diagnosed and treated at two hospitals in Shanxi Province, China, between March 2014 and March 2019 in this multi-center, prospective cohort study. Among them, 1188 eligible patients were followed up, with 60 patients (5.1%) lost to follow-up, leaving 1128 patients for final analysis (Figure 1). The cohort size of this study conformed to the rule of 10 events per variable.

The inclusion criteria were: ① adult over 18 years old; ② diagnosed with chronic heart failure following guidelines;[17] ③ NYHA class II–IV; ④ echocardiography showing EF of 41%-49%. Exclusion criteria were: ① within the past two months, there were acute cardiovascular events; ② comorbid psychiatric diseases; ③ specific heart diseases including cardiac tumors, myocardial amyloidosis, complex congenital heart disease, hypertrophic cardiomyopathy, and aortic dissection; ④ refusal to participate. The study was based on the statistical analysis of the patients' medical records during their hospitalization and did not involve any interventions for the patients as well as adding additional risks of adverse effects. The researcher explained the purpose of the study to all participants and their families and signed a written informed consent before data collection. Each participant's data in this study has an ID, the researcher will follow strict confidentiality, the study in question is only open to the researcher/ethics committee, and the study complies with the ethical standards set out in the Declaration of Helsinki. Therefore, approval was obtained from the Ethics Committee of Shanxi Medical University, approval number 2013LL128 (Date: December 28, 2013), prior to the commencement of this study.

Follow-up and Endpoint

Dynamic follow-up of patients from two cohorts every 2 months after discharge by telephone until April 1, 2022. The endpoint event was defined as all-cause mortality, including deaths of cardiovascular origin such as fatal myocardial infarction, fatal stroke, death from HF, sudden cardiac death, and non-cardiovascular death.

Data Collection

We extracted data from electronic database of our Major Disease Risk Assessment Laboratory, which each time two trained clinicians double-entered data from the medical record system SXMU&SXGY of hosipitals, including demographic characteristics, comorbidities (such as ischemic heart disease, hypertension, atrial fibrillation (AF), etc), laboratory results, imaging examinations (electrocardiogram, echocardiographic indicators), and therapy measures (medication use, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG)). Urban medical

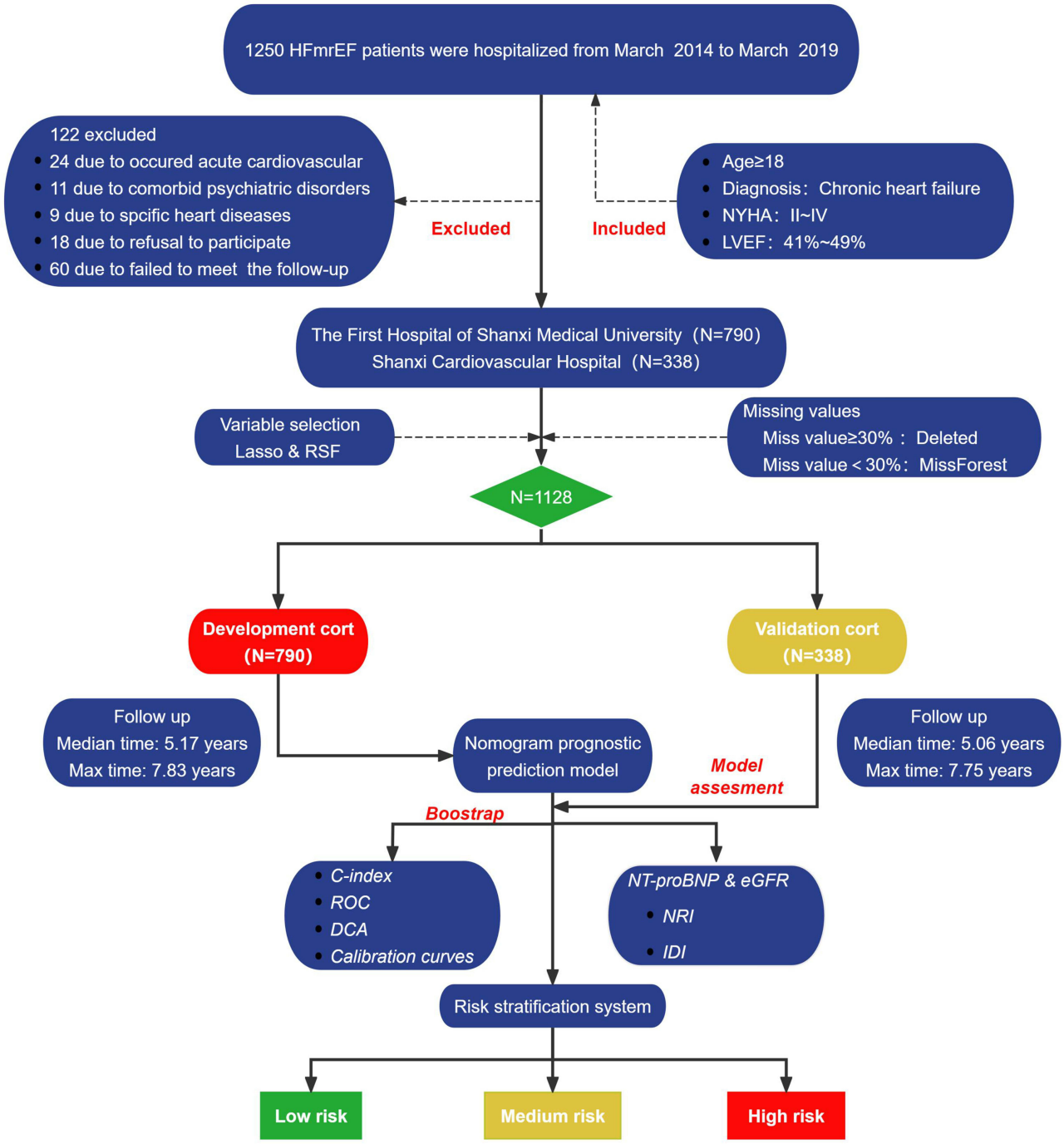

Figure 1 Study design and the workflow diagram.

insurance reimbursement accounts for 80%, while rural medical insurance covers 60%. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[18]

Data Processing and Predictor Selection

This study involved a total of 69 variables. To ensure data quality, we removed 19 variables with a missing rate of >30% and used the MissForest package in R 4.3.1 to fill in the 27 variables with a missing rate of <30%. Specific missing variables are shown in Table S1.

The significant candidate predictors (P<0.05) of all-cause mortality identified by univariate Cox proportional hazards analysis were further selected by The least absolute shrinkage and selection operator (LASSO) regression and Random Survival Forest (RSF). RSF reflects the contribution of each variable to all-cause mortality by calculating the minimum depth reached when running to the final node. Compared to traditional methods, RSF has strong resistance to interference and can reduce the risk of overfitting when dealing with high-dimensional data.[19] LASSO regression reduces the impact of collinearity through L1 regularization, thus lowering model variance and improving accuracy and interpretability.[20] The selected predictors were then subjected to further multivariate analysis.

Development of Nomogram and Risk Stratification System

The Multivariate Cox proportional hazard model identified independent predictors of all-cause mortality, from which a nomogram was developed to predict 1-, 3-, and 5-year all-cause mortality. We calculated the total nomogram point for each patient and utilized X-tile software to determine the optimal critical points for risk stratification, stratifying patients into different groups based on their risk of prognosis.[21] Kaplan-Meier survival curves were plotted to compare survival differences among groups and assess the effectiveness of risk stratification. The Log rank test was used to compare the survival curves.

Model Validation and Performance

Internal validation was performed using the Bootstrap resampling method (repeatedly sampling the original data 1000 times) and plotted calibration curves to assess the consistency of the model. To assess transportability, the final model was validated in an external cohort.

We evaluated the discrimination and stability of the model over time by calculating the time-dependent C-index, with a value closer to 1 indicating better predictive performance. Evaluate the predictive performance using the area under the ROC curve (AUC). To assess the clinical value, decision curve analysis (DCA) was conducted. Calculated net reclassification improvement (NRI) and integrated discrimination improvement (IDI) to evaluate the contribution in the 5-year predictive performance of the nomogram with the additional inclusion of NT-proBNP and eGFR.[22]

Statistical Analysis

The mean±standard deviation (SD) or median (interquartile range) of continuous variables was used to describe them while n (%) described categorical variables. Comparison of baseline characteristics: for continuous variables, independent samples t-tests were used if they conformed to a normal distribution, while the Mann–Whitney U-test was for non-normal distributions; for categorical variables, the chi-square test or Fisher's exact probability method was used.

ROC were fitted and AUCs were calculated to assess the discriminative ability of different predictors for all-cause mortality. Significant variables in the multivariate model were used as covariates, plotted restricted cubic spline (RCS) curves to evaluate the association of eGFR and NT-proBNP with all-cause mortality with 4 knots selected. Finally, the "Dynnom" software package was used to generate interactive dynamic nomogram based on web pages. All tests were two-tailed, and a statistically significant result was considered when $P < 0.05$. We performed statistical analyses using SPSS 25.0 and R 4.3.1.

Results

Baseline Characteristics

Among the 1128 patients enrolled, 790 patients from the First Hospital of Shanxi Medical University were included in the model development cohort, while 338 patients from Shanxi Cardiovascular Hospital were included in the external validation cohort. The median follow-up time for the two cohorts was 5.17 (3.31–6.54) years and 5.06 (3.28–6.39) years, respectively. During this period, 74 patients (9.4%) in the development cohort died, while 33 patients (9.8%) in the validation cohort died. Additionally, most baseline characteristics showed no significant differences between the two cohorts ($P > 0.05$), indicating their balanced distribution (Table S2).

Table 1 presents the baseline characteristics of all patients. Among them, 799 (70.8%) were male, with a median age of 68 (59, 76) years, and 664 (58.9%) were NYHA III/IV. Compared to the survival group, the death group had older age, poorer cardiac and renal function, higher proportions of AF, chronic obstructive pulmonary disease, stroke, valvular

Table 1 Baseline Clinical Characteristics Between Groups

Variable	Total (n=1128)	Survival (n=1021)	Death (n=107)	t/χ^2/Z	P value
Age, years	68 (59, 76)	67 (59, 76)	74 (69, 80)	−7.303	<0.001
Gender					
Male	799 (70.8)	734 (71.9)	65 (60.7)	5.820	0.016
Female	329 (29.2)	287 (28.1)	42 (39.3)		
Occupation				12.152	<0.001
Manual workers	382 (33.9)	362 (35.5)	20 (18.7)		
Nonmanual workers	746 (66.1)	659 (64.5)	87 (81.3)		
Healthcare				11.968	0.003
Urban medical insurance	694 (61.5)	625 (61.2)	69 (64.5)		
Rural medical insurance	312 (27.7)	294 (28.8)	18 (16.8)		
Self-paying	122 (10.8)	102 (10.0)	20 (18.7)		
Smoking history	564 (50.0)	511 (50.0)	53 (49.5)	3.684	0.252
Drinking history	278 (24.6)	260 (25.5)	18 (16.8)	3.896	0.048
NYHA				67.504	<0.001
II	464 (41.1)	443 (43.4)	21 (19.6)		
III	420 (37.2)	390 (38.2)	30 (28.0)		
IV	244 (21.6)	188 (18.4)	56 (52.3)		
BMI(kg/m^2)	24.4 (22.2, 26.8)	24.3 (22.2, 26.9)	23.6 (20.9, 25.6)	−3.152	0.002
Heart rate(bpm)	75 (66, 80)	72 (66, 81)	76 (68, 80)	−0.305	0.760
Systolic blood pressure(mmHg)	130 (116, 140)	130 (116, 140)	130 (112, 149)	−0.539	0.590
Diastolic blood pressure(mmHg)	78 (70, 85)	80 (70, 85)	78 (68, 85)	−0.969	0.333
Laboratory indicators					
Lg of NT-proBNP(pg/mL)	3.1±0.5	2.9±0.5	3.6±0.4	9.212	0.002
Cystatin C(mg/L)	1.3±0.8	1.3±0.8	1.6±0.9	5.547	0.019
eGFR[mL/(min·1.73m^2)]	90.9 (69.4, 106.2)	92.7 (72.9, 109.3)	67.2 (51.4, 84.9)	−7.666	<0.001
UA(μmol/L)	382.9±121.0	380±119.9	408±128.9	1.278	0.278
TC(mmol/L)	4.3±1.8	4.3±1.9	4.2±1.4	0.010	0.920
TG(mmol/L)	1.6±0.9	1.6±0.9	1.5±0.6	2.702	0.101
HDLC(mmol/L)	1.0±0.3	1.0±0.3	1.0±0.3	0.582	0.446
LDLC(mmol/L)	2.7±2.3	2.7±2.3	2.6±1.0	0.264	0.608
RDW(%)	14.5 (13.4, 14.8)	13.9 (13.4, 14.7)	14.5 (13.9, 15.5)	−5.042	<0.001
HGB(g/L)	135.5±20.21	136.2±20.2	128.8±18.7	0.046	0.830
ALT(U/L)	26.7 (14.0, 32.3)	20.8 (14.0, 33.0)	18.0 (12.0, 25.0)	−3.007	0.003
AST(U/L)	36.6 (21.0, 39.4)	27.0 (21.0, 41.0)	24.9 (20.0, 35.8)	−1.907	0.057
ALB(g/L)	43.0 (40.0, 46.0)	43.0 (40.0, 46.0)	40.3 (37.2, 43.2)	−5.147	<0.001
TBIL(mmol/l)	17.1 (11.2, 19.5)	14.7 (11.2, 19.4)	16.0 (11.4, 20.5)	−1.239	0.215
K(mmol/l)	4.1 (4.1, 4.4)	4.1 (3.8, 4.3)	4.1 (3.8, 4.4)	−0.552	0.581
Na(mmol/l)	139 (139, 141)	139 (138, 141)	139 (138, 142)	−0.011	0.991
Electrocardiogram					
QRS(ms)	106 (90, 112)	98 (90, 112)	98 (90, 115)	−0.876	0.381
QTC(ms)	445 (418, 468)	440 (418, 468)	448 (422, 477)	−1.451	0.147
Echocardiographic indices					
IVS(mm)	10 (8, 11)	10 (8, 11)	10 (9, 11)	−1.829	0.067
LVDd(mm)	55 (52, 59)	56 (52, 59)	55 (51, 59)	−0.135	0.892
LVPW(mm)	10 (9, 10)	9 (9, 10)	9.0 (9, 11)	−0.838	0.402
Ejection fraction (%)	45 (43, 47)	45 (43, 47)	44 (42, 46)	−1.615	0.106
Comorbidities					
Hypertension	664 (58.9)	591 (57.9)	73 (68.2)	4.276	0.039
Diabetes	372 (33.0)	332 (32.5)	40 (37.4)	1.038	0.308
Stroke	278 (24.6)	225 (22.0)	53 (49.5)	39.426	<0.001
Ischemic heart disease	901 (79.9)	818 (80.1)	83 (77.6)	0.391	0.532

(*Continued*)

Table 1 (Continued).

Variable	Total (n=1128)	Survival (n=1021)	Death (n=107)	t/χ^2/Z	P value
COPD	213 (18.9)	180 (17.6)	33 (30.8)	10.156	<0.001
AF	325 (28.8)	256 (25.1)	69 (64.5)	12.164	<0.001
Hyperlipidemia	211 (18.7)	192 (18.8)	19 (17.8)	0.070	0.791
Valvular heart disease	97 (8.6)	82 (8.0)	15 (14.0)	4.417	0.036
Renal insufficiency	128 (11.3)	103 (10.1)	25 (23.4)	16.969	<0.001
Therapy					
Antiplatelet drug	1033 (91.6)	943 (92.4)	90 (84.1)	8.543	0.003
Vasodilator	769 (68.2)	695 (69.2)	74 (68.1)	0.053	0.818
Beta-blocker	263 (23.3)	242 (23.7)	21 (19.6)	0.900	0.343
ACEI/ARB/ARNI	625 (55.4)	599 (58.7)	26 (24.3)	46.302	<0.001
Statins	1040 (92.2)	947 (92.8)	93 (86.9)	4.586	0.032
Diuretic	911 (80.8)	823 (80.6)	88 (82.2)	0.167	0.683
Cardiotonic	137 (12.1)	120 (11.8)	17 (15.9)	1.552	0.213
PCI/CABG	387 (34.3)	373 (36.5)	14 (13.1)	23.628	<0.001

Abbreviations: NYHA, New York Heart Association; BMI, body mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; UA, uric acid; TC, total cholesterol; TG, triglyceride; HDLC, high-density lipoprotein; LDLC, low-density lipoprotein; RDW, red blood cell distribution width; HGB, hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; TBIL, serum total bilirubin; LA, left atrial diameter; IVS, interventricular septal thickness; LVDD, left ventricular end-diastolic diameter; LVPW, left ventricle post wall; RV, right ventricular end-diastolic diameter; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

disease, lower rates of PCI/CABG treatment, and lower proportions of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor-neprilysin inhibitor (ACEI/ARB/ARNI), statins, and antiplatelet medications.

Identifying Predictors

Univariate Cox analysis identified 20 significant candidate predictors associated with all-cause mortality ($P < 0.05$) (Table S3). To reduce multicollinearity and prevent overfitting, further dimension reduction was performed using LASSO regression and RSF, as shown in Figure S1. The LASSO model achieved optimal fit with $\lambda = 0.007$, resulting in the identification of 13 predictors: age, occupation, healthcare, NYHA, lg of NT-proBNP, Cystatin C, eGFR, ALB, IVS, AF, stroke, ACEI/ARB/ARNI, PCI/CABG. In RSF, with Ntree = 85 and mtry = 3, the out-of-bag error rate was minimized (Error rate = 20.08%). The top 15 valuable predictors in RSF were: lg of NT-proBNP, eGFR, NYHA, age, ACEI/ARB/ARNI, stroke, HGB, healthcare, AF, PCI/CABG, ALB, body mass index (BMI), occupation, antiplatelet, Cystatin C.

Finally, combining the results of both methods, 12 optimal predictors for all-cause mortality were selected for model construction: age, occupation, healthcare, NYHA, lg of NT-proBNP, Cystatin C, eGFR, ALB, AF, stroke, ACEI/ARB/ARNI, PCI/CABG.

Multivariate Cox Proportional Hazard Model for All-Cause Mortality and Discriminatory Role of Predictors

The results of the multivariate Cox proportional hazard model (Table 2) and Forest plot (Figure S2) indicated that self-paying (HR = 4.34, 95% CI: 2.29–8.22; $P < 0.001$), NYHA class IV (HR = 2.91, 95% CI: 1.46–5.80; $P = 0.002$), lg of NT-proBNP (HR = 2.35, 95% CI: 1.40–3.93; $P = 0.001$), combined with stroke (HR = 1.43, 95% CI: 0.64–2.84; $P = 0.002$), eGFR (HR = 0.98, 95% CI: 0.97–0.99; $P = 0.023$), use of ACEI/ARB/ARNI medications (HR = 0.34, 95% CI: 0.20–0.56; $P < 0.001$), and receipt of PCI/CABG treatment (HR = 0.52, 95% CI: 0.27–0.99; $P = 0.048$) were independent predictors of all-cause mortality in HFmrEF ($P < 0.05$).

Table 2 Multivariate Cox Proportional Hazard Analysis for All-Cause Mortality

Variable	HR	95% CI	P value
Age	1.02	1.00–1.05	0.091
Occupation			
Manual workers	Reference		
Nonmanual workers	1.70	0.78–3.69	0.179
Healthcare			
Urban medical insurance	Reference		
Rural medical insurance	1.76	0.75–4.10	0.191
Self-paying	4.34	2.29–8.22	<0.001
NYHA			
II	Reference		
III	1.53	0.78–2.98	0.215
IV	2.91	1.46–5.80	0.002
Lg of NT-proBNP	2.35	1.40–3.93	0.001
eGFR	0.98	0.97–0.99	0.023
Cystatin C	0.64	0.39–1.41	0.076
ALB	0.99	0.95–1.03	0.612
AF	2.16	1.32–3.53	0.053
Stroke	1.43	0.64–2.84	0.002
ACEI/ARB/ARNI	0.34	0.20–0.56	<0.001
PCI/CABG	0.52	0.27–0.99	0.048

Abbreviations: NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; ALB, albumin; AF, atrial fibrillation; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

Figure S3 displays the ROC of the aforementioned predictors for all-cause mortality in HFmrEF. Each predictor demonstrates positive discriminative ability for all-cause mortality. Particularly, lg of NT-proBNP and eGFR rank in the top 2 for predicting all-cause mortality with their ROC curve areas (Figure S3).

Association of NT-proBNP and eGFR with All-Cause Mortality in HFmrEF

The association between levels of NT-proBNP, eGFR and all-cause mortality was evaluated based on a continuous scale with RCS curves (Figure S4). The results indicate nonlinear relationships between lg of NT-proBNP ($P_{nonlinear}$=0.004), eGFR ($P_{nonlinear}$ < 0.001), and all-cause mortality. Patients exhibit a lower risk of all-cause mortality when lg of NT-proBNP falls within the range of 2.14 to 3.07 pg/mL (NT-proBNP: 138 to 1175 pg/mL). Conversely, when lg of NT-proBNP exceeds 3.07 pg/mL (NT-proBNP > 1175 pg/mL), there is a significant increase in the risk of all-cause mortality. For eGFR, mortality risk was elevated when 45 < eGFR < 89 [mL/(min·1.73m²)], and decreased as eGFR levels rose within the range of 89 ≤ eGFR ≤ 125 [mL/(min·1.73m²)].

Development of the Nomogram and Stratification System for Mortality Risk

Based on the multivariate model, the nomogram for prediction of 1-, 3-, and 5-year mortality comprises 7 predictors. Each predictor is assigned a corresponding point, with the total point being the sum of points from the 7 variables, corresponding to the survival rate of patients with different survival periods.

For convenient risk management and stratified guidance of patients, we conducted risk scoring using nomogram and determined optimal risk stratification thresholds (point 1 = 219.5, point 2 = 304.2) using X-tile software (Figure S5). All patients were categorized into low (point < 219.5), middle (219.5 ≤ point ≤ 304.2), and high-risk groups (point > 304.2). Through Log rank testing, significant differences (P < 0.05) in prognostic survival rates were observed among risk groups (Figure 2). The nomogram incorporating this risk stratification is shown in Figure 3.

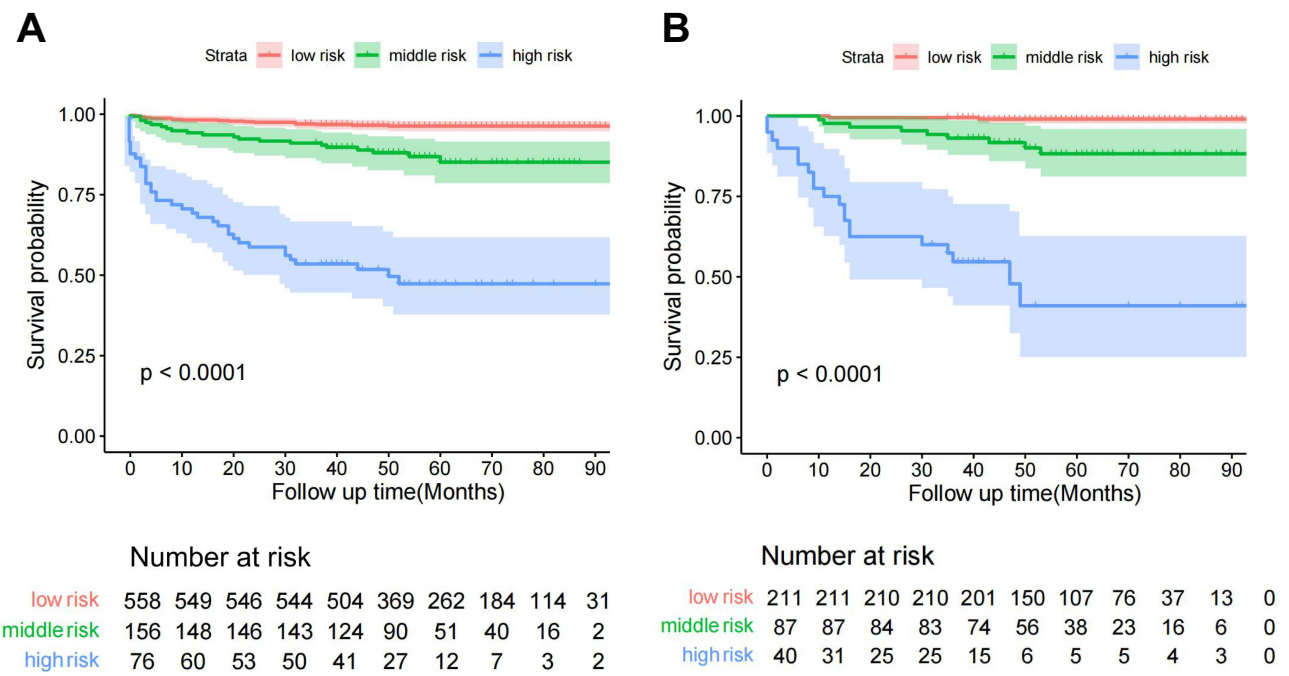

Figure 2 Kaplan-Meier curves of all-cause mortality events in different risk groups. (**A**) development cohort, (**B**) validation cohort.

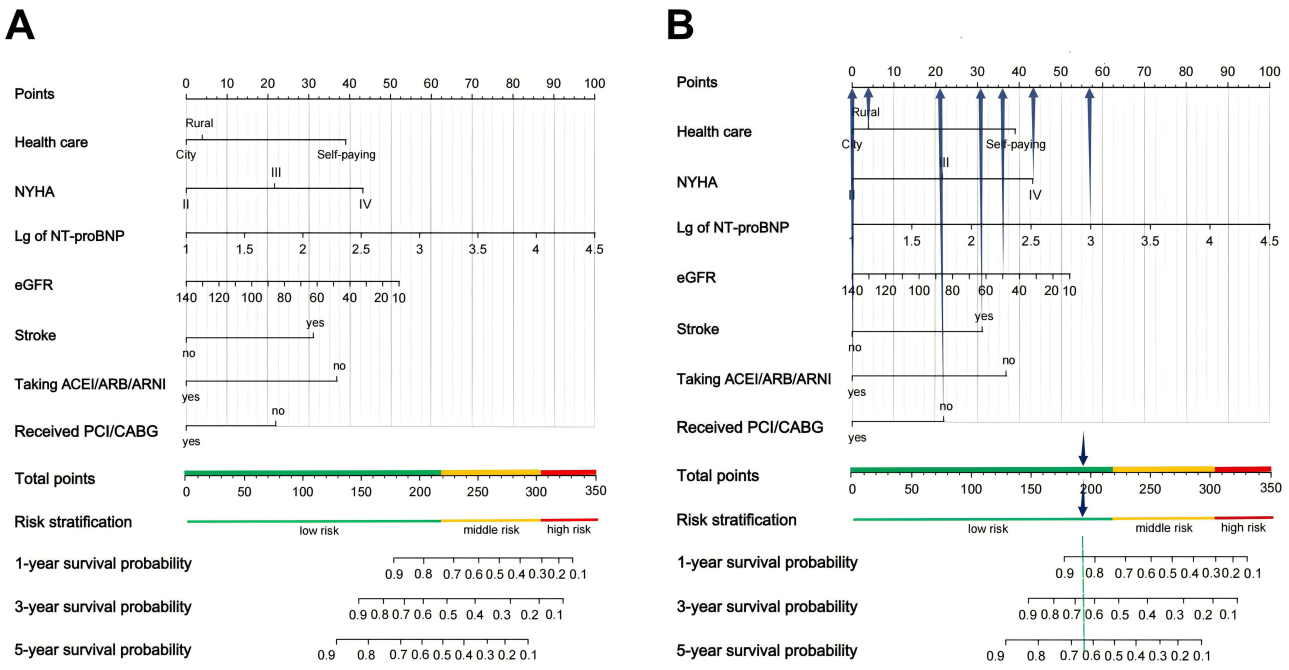

Figure 3 The APSELNH nomogram for all-cause mortality risk in HFmrEF. (**A**) Each clinical predictor corresponds to a specific point, from which a vertical line is drawn to the point axis above. The points of each predictor located on the point axis are then summed to obtain the total point. Based on the total point, vertical lines are drawn downwards on the survival axis to determine the corresponding risk classification and survival probabilities for the patient. (**B**) To illustrate the use of the nomogram, take patient 60 as an example. This patient is covered by rural medical insurance, NYHA class IV, with lg of NT-proBNP: 3 pg/mL, eGFR: 50 [ml/(min ·1.73m^2)], combined with stroke, regular ACEI/ARB/ARNI medications, and not treated with PCI/CABG. The total point on the nomogram is 194, indicating a low-risk classification, with corresponding 1-, 3-, and 5-year survival rates of approximately 83%, 68%, and 65%, and respective mortality rates of approximately 17%, 32%, and 35%.

Performance, and Validation of the Nomogram

The discrimination of HFmrEF outcomes was evaluated using a time-dependent analysis. The C-index of the nomogram in the development and validation cohorts were 0.858 (95% CI: 0.817–0.899) and 0.826 (95% CI: 0.803–0.867) respectively, consistently exceeding 0.8 over time, indicating its utility in predicting long-term mortality risk (Figure 4).

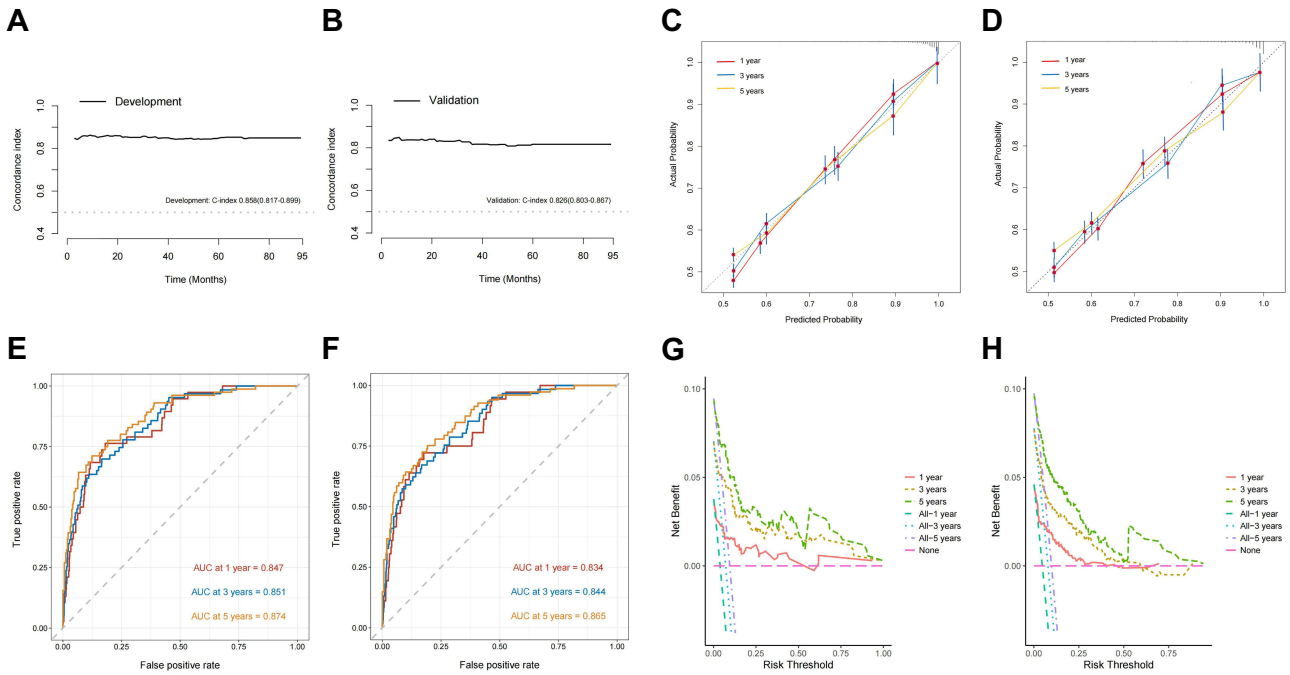

Figure 4 Performance and validation of the nomogram. Time-dependent C-index of the development cohort (**A**) and validation cohort (**B**). The Bootstrap calibration curves for predicting outcomes of HFmrEF in the development (**C**) and validation (**D**) cohorts are presented. The prediction curves closely align with the diagonal line, indicating proximity between predicted probabilities and observed values. ROC curves for predicting outcomes of HFmrEF in the development (**E**) and validation (**F**) cohorts are also shown. The area under the ROC curve (AUC) ranges from 0.8 to 0.9, indicating good predictive performance of the nomogram for 1-, 3-, and 5-year all-cause mortality. Decision curve analysis (DCA) curves for predicting outcomes of HFmrEF in the development (**G**) and validation (**H**) cohorts are displayed. The vertical dashed line on the left represents "all interventions", the horizontal dashed line represents "no interventions" and the curve represents the nomogram. The DCA curves indicate that adopting the threshold probability under the nomogram strategy for HFmrEF patients significantly increases the net benefit of 1-, 3-, and 5-year all-cause mortality.

Calibration curves demonstrated a good fit between predicted and observed values after 1000 rounds of Bootstrap resampling. ROC analysis was performed on the model, and the AUCs in the development cohort were as follows: 1 year: 0.847, 3 years: 0.851, 5 years: 0.874. In the validation cohort, the AUCs were 0.834, 0.844, and 0.865, respectively. Additionally, in both cohorts, the DCA curves showed clinical net benefits across a broad range of threshold probabilities, indicating good clinical applicability of the model. These findings demonstrate the significant value of the nomogram model in predicting the long-term prognosis of HFmrEF patients (Figure 4).

Further analysis of the predictive value of NT-proBNP and eGFR revealed that independently adding NT-proBNP or eGFR to the baseline model resulted in notable improvements as indicated by IDI and NRI. Moreover, the combination of NT-proBNP and eGFR showed the most significant improvement in the predictive performance for 5-year all-cause mortality of the baseline model (Table 3).

Table 3 Add NT-proBNP and eGFR to Nomogram Integrated Discrimination Improvement and Net Reclassification Improvement for 5-Year All-Cause Mortality

Model	Predictors	IDI (95% CI)	P value	NRI (95% CI)	P value
Development					
NYHA, Stroke,	+NT-proBNP	0.109 (0.019–0.227)	<0.001	0.294 (0.172–0.464)	<0.001
ACEI/ARB/ARNI,	+eGFR	0.045 (0.008–0.086)	0.020	0.229 (0.049–0.361)	0.028
PCI/CABG, Healthcare	+NT-proBNP, eGFR	0.128 (0.017–0.218)	<0.001	0.321 (0.168–0.423)	<0.001
Validation					
NYHA, Stroke,	+NT-proBNP	0.057 (0.008–0.086)	0.008	0.096 (0.011–0.182)	0.028
ACEI/ARB/ARNI,	+eGFR	0.045 (0.006–0.083)	0.048	0.675 (−1.471–1.890)	0.446
PCI/CABG, Healthcare	+NT-proBNP, eGFR	0.110 (0.023–0.199)	0.015	0.196 (0.028–0.352)	0.045

Abbreviations: NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

Development of the Web-Based Dynamic Nomogram

For the convenience of clinical practitioners, we developed a web-based decision support tool called APSELNH (A: ACEI/ARB/ARNI medicines, P: PCI/CABG therapy, S: stroke, E: eGFR, L: lg of NT-proBNP, N: NYHA, H: healthcare) (Figure S6). By accessing the online platform (https://apselnh.shinyapps.io/APSELNH/), clinicians can input the 7 predictive variables and follow-up time to generate individualized survival predictions.

Discussion

HFmrEF is a heterogeneous syndrome with wide variation in patient survival time. However, there is currently limited research on the prognosis of HFmrEF and a lack of effective risk stratification tools to guide clinical management. This study developed a dynamic nomogram combining NT-proBNP, eGFR, and other clinical characteristics (NYHA, healthcare, stroke, PCI/CABG, ACEI/ARB/ARNI) to assess the prognosis of HFmrEF patients and achieve risk stratification. The nomogram, derived from real-world patient cohorts and externally validated, provides an accurate individualized prediction of all-cause mortality risk. To our knowledge, this represents one of the few studies focusing on predicting the prognostic risk of HFmrEF.

Predictors of All-Cause Mortality in HFmrEF

NT-proBNP reflects left ventricular wall stress and is not only recognized as an essential diagnostic marker for HF but also holds significant value in assessing its prognosis. Previous assessments of NT-proBNP in predicting HF prognosis have mainly focused on HFrEF and HFpEF. In recent years, Lam et al[23] found that NT-proBNP independently predicted mortality of HFmrEF. Reports by Richenbacher et al[24] also indicated significant benefits of NT-proBNP-guided treatment in improving the prognosis of HFmrEF patients. However, most studies have analyzed NT-proBNP as a continuous variable, lacking effective clinical prognostic thresholds for practical application in HFmrEF. In this study, after excluding confounding factors, we found NT-proBNP levels exceeding 1175 pg/mL significantly increased the risk of all-cause mortality in HFmrEF patients, providing a reference for early identification of patients with poor prognosis. When NT-proBNP levels were between 138–1175 pg/mL, patients exhibited a lower risk of all-cause mortality. Similar results were observed in another study, where participants with lower NT-proBNP levels during follow-up had significantly better prognoses.[25] This may be due to the cardioprotective effects of NT-proBNP through stimulation of urine and sodium excretion and antihypertensive effects.[26]

NT-proBNP monitors cardiac function through left ventricular filling pressure and wall stress. When cardiac output decreases in HF patients, renal blood flow also decreases, leading to deterioration of renal function. Decreased eGFR is a sensitive indicator of renal impairment. Therefore, the combined utility of eGFR and NT-proBNP may have potential value in identifying long-term prognosis in HF patients. Lin et al[27] found that higher eGFR was associated with reduced long-term all-cause mortality risk in HFmrEF patients. Their study cohort was similar to ours in age (65 vs 67), gender ratio, and main etiology (ischemic heart disease), but they did not further investigate the cutoff value of eGFR for predicting mortality. In our study, after adjusting for NYHA, NT-proBNP, and other confounding factors, eGFR levels below 89 [mL/(min·1.73m²)] increased the risk of all-cause mortality in patients. HF itself can lead to renal impairment, and compared to HFpEF and HFrEF, HFmrEF patients are more likely to have comorbidities such as hypertension and diabetes that impair renal function.[28,29] Renal dysfunction exacerbates existing HF through mechanisms such as fluid and sodium retention, electrolyte imbalance, and sympathetic nervous system activation. Our results and previous studies support the inclusion of eGFR in prognostic models. Combining NT-proBNP and eGFR in the nomogram provides greater clinical value than assessing them separately.

In addition to the above two predictors, NYHA is a recognized independent predictor of all-cause mortality in HFmrEF,[30,31] ranking third in our model. Furthermore, patients with concomitant stroke had a 43% increased risk of mortality (HR=1.43, 95% CI: 0.64–2.84), which complements the findings of Yang et al.[32] They found that in patients with HFpEF and HFrEF, those with concurrent stroke are more likely to experience cardiovascular adverse events. Abnormal activation of the hypothalamus-pituitary-adrenal axis and significantly elevated catecholamine levels are observed in stroke, which may induce hypoxia and cardiomyocyte apoptosis through actions on α and β-adrenergic

receptors in the heart, leading to cardiac dysfunction.[33] Additionally, healthcare status is also a valuable prognostic factor, as it may reflect the impact of economic status on patient treatment compliance.[34]

Regarding treatment, the 2023 ESC heart failure guidelines[35] recommend the use of ACEI/ARB/ARNI to reduce mortality and readmission risk in HFmrEF patients (Class IIb). This may be due to the ability of these medicines to improve ischemic heart disease and reverse ventricular remodeling. It is worth noting that coronary artery lesions occur more frequently in HFmrEF than in HFpEF and HFrEF, and ischemic heart disease caused by coronary artery lesions is also more common in HFmrEF.[24] Research has demonstrated that revascularization can enhance myocardial ischemia, hinder myocardial remodeling, increase myocardial tolerance to future cardiovascular events, and is a crucial method of alleviating symptoms and enhancing prognosis in patients.[36] Our study also found that patients had a better prognosis after receiving PCI/CABG treatment. Our nomogram incorporates the aforementioned treatment measures.

Application Value of Nomogram Model in HFmrEF

Personalized risk stratification management could allow the direction of treatment intensity and follow-up frequency, aiming to delay the progression of HF, and reduce HF readmission and mortality rates, while minimizing unnecessary interventions in those at low risk (rationalizing the allocation of healthcare resources). Predictive models are effective support tools for risk stratification of HF patients. Risk models such as the Seattle HF model,[37] the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk model,[38] and the AHA Get With The Guidelines-Heart Failure (GWTH-HF) model[39] primarily focus on the entire HF population or predominantly on HFpEF and HFrEF subgroups, with AUC or C-index below 0.8. Although a simple model developed by Wang et al[40] based on 9 common clinical variables can be used for the assessment of HFmrEF prognosis, however, the model was not predominantly derived from patients with HFmrEF and was only internally validated. Therefore, existing risk models lack specificity for the HFmrEF and have not demonstrated good predictive performance.

This study developed and evaluated the long-term prognostic performance of the nomogram model based on long-term longitudinal follow-up data (median follow-up time of 5.17 years, maximum 7.83 years). The model demonstrated excellent performance in discrimination, accuracy, and clinical applicability after internal validation [C-index: 0.858, AUC: 0.847 (1 year)-0.851 (3 years)-0.874 (5 years)]. It is worth noting that to further validate the model's generalizability, we tested the final model in an external cohort and observed satisfactory results [C-index: 0.826, AUC: 0.834 (1 year)-0.844 (3 years)-0.865 (5 years)].

During the process of feature variable selection, due to the multidimensionality and complexity of clinical data, issues such as collinearity and overfitting often arise.[41] With the development of computer science, researchers have increasingly used methods such as LASSO regression, random forests (RF), naive Bayes, support vector machines, etc., to construct survival models.[42] Angraal et al[43] reported that the RF model performed best in predicting a 3-year mortality rate in HFpEF patients, with an AUC of 0.72 (95% CI: 0.69~0.75) and a Brier score of 0.17. Zhao et al[44] reported that the LASSO-Cox model was the best predictive model for a 1-year mortality rate in HFmrEF patients, with a C-index of 0.77 (95% CI: 0.64–0.89). Our model incorporates a large number of candidate variables, and the combination of LASSO regression and RSF effectively overcomes collinearity and overfitting issues encountered by traditional methods in handling high-dimensional indices. In addition, poor interpretability is a major obstacle to the clinical application of models built on machine learning techniques, known as "black boxes." Therefore, this study introduces a nomogram to achieve the visualization of the model.

This study has several limitations. Firstly, the inclusion of HF patients from China limits the generalizability of the conclusions, and further validation through expanding the scope of the study is needed. Secondly, the study focused on patients already hospitalized, excluding those who may be at risk of hospitalization or death due to HF. From a preventative perspective, this population also deserves attention, and we will further explore these aspects in future studies. Thirdly, some predictive parameters related to mortality were not included, such as troponin I/T, arterial blood gas analysis, CHA_2DS_2-VASc score,[45] etc. All of these parameters are important prognostic indicators in patients with heart failure but were tested only in selected patients, with a >50% missing rate for each indicator.

Conclusion

This study identified 7 optimal predictors of all-cause mortality in HFmrEF patients: NT-proBNP, eGFR, NYHA classification, stroke, healthcare, ACEI/ARB/ARNI medications, and PCI/CABG treatment. Based on these predictors, we developed and validated a web-based APSELNH nomogram online calculator using long-term follow-up data. It is worth mentioning that the combined use of NT-proBNP and eGFR significantly enhances the nomogram's predictive ability for long-term prognosis. Calculating their cutoff values helps in early identification of high-risk patients. In summary, the web-based APSELNH online risk calculator provides a convenient and rapid tool to assist clinicians in the risk stratification of patients, thereby guiding risk management strategy.

Data Sharing Statement

The original contributions presented in the study are included in the article. For further information, please contact the corresponding authors.

Ethics Approval and Informed Consent

This study was conducted in accordance with the principles outlined in the Helsinki Declaration, and the research protocol has been approved by the Ethics Committee of Shanxi Medical University (Date December 28, 2013/No. 2013LL128). Written informed consent was obtained from all participating researchers prior to the start of the study.

Consent for Publication

All authors have approved the manuscript for publication.

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Author Contributions

All authors have made a substantial contribution to the work reported, be it in conception, design, execution, acquisition of data, analysis, and interpretation, or all of these; have been involved in drafting, revising, or critically appraising the article; have given final approval for the version to be published; have agreed on the journal to which the article will be submitted; and agree to accept responsibility for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

References

1. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599–3726. doi:10.1093/eurheartj/ehab368
2. Nauta JF, Hummel YM, Van Melle JP, et al. What have we learned about heart failure with mid-range ejection fraction one year after its introduction? *Eur J Heart Fail*. 2017;19(12):1569–1573. doi:10.1002/ejhf.1058
3. Tsuji K, Sakata Y, Nochioka K, et al. Characterization of heart failure patients with mid-range left ventricular ejection fraction—a report from the CHART −2 Study. *Eur J Heart Fail*. 2017;19(10):1258–1269. doi:10.1002/ejhf.807
4. Wehner GJ, Jing L, Haggerty CM, et al. Routinely reported ejection fraction and mortality in clinical practice: where does the nadir of risk lie? *Eur Heart J*. 2020;41(12):1249–1257. doi:10.1093/eurheartj/ehz550

5. Raja DC, Samarawickrema I, Das S, et al. Long-term mortality in heart failure with mid-range ejection fraction: systematic review and meta-analysis. *ESC Heart Fail*. 2022;9(6):4088–4099. doi:10.1002/ehf2.14125
6. Bhambhani V, Kizer JR, Lima JAC, et al. Predictors and outcomes of heart failure with mid-range ejection fraction. *Eur J Heart Fail*. 2018;20 (4):651–659. doi:10.1002/ejhf.1091
7. Farré N, Lupon J, Roig E, et al. Clinical characteristics, one-year change in ejection fraction and long-term outcomes in patients with heart failure with mid-range ejection fraction: a multicentre prospective observational study in Catalonia (Spain). *BMJ Open*. 2017;7(12):e018719. doi:10.1136/bmjopen-2017-018719
8. Savarese G, Stolfo D, Sinagra G, et al. Heart failure with mid-range or mildly reduced ejection fraction. *Nat Rev Cardiol*. 2022;19(2):100–116. doi:10.1038/s41569-021-00605-5
9. Kasahara S, Sakata Y, Nochioka K, et al. The 3A3B score: the simple risk score for heart failure with preserved ejection fraction - A report from the CHART-2 study. *Int J Cardiol*. 2019;284:42–49. doi:10.1016/j.ijcard.2018.10.076
10. Gao Y, Bai X, Lu J, et al. Prognostic value of multiple circulating biomarkers for 2-year death in acute heart failure with preserved ejection fraction. *Front Cardiovasc Med*. 2021;8:779282. doi:10.3389/fcvm.2021.779282
11. Lv H, Yang X, Wang B, et al. Machine learning-driven models to predict prognostic outcomes in patients hospitalized with heart failure using electronic health records: retrospective study. *J Med Internet Res*. 2021;23(4):e24996. doi:10.2196/24996
12. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128(16):1810–1852. doi:10.1161/CIR.0b013e31829e8807
13. Löfman I, Szummer K, Dahlström U, et al. Associations with and prognostic impact of chronic kidney disease in heart failure with preserved, mid-range, and reduced ejection fraction. *Eur J Heart Fail*. 2017;19(12):1606–1614. doi:10.1002/ejhf.821
14. Meijs C, Brugts JJ, Lund LH, et al. Identifying distinct clinical clusters in heart failure with mildly reduced ejection fraction. *Int J Cardiol*. 2023;386:83–90. doi:10.1016/j.ijcard.2023.05.024
15. Inker LA, Shaffi K, Levey AS. Estimating glomerular filtration rate using the chronic kidney disease-epidemiology collaboration creatinine equation: better risk predictions. *Circ Heart Fail*. 2012;5(3):303–306. doi:10.1161/CIRCHEARTFAILURE.112.968545
16. Kingery JR, Yango M, Wajanga B, et al. Heart failure, post-hospital mortality and renal function in Tanzania: a prospective cohort study. *Int J Cardiol*. 2017;243:311–317. doi:10.1016/j.ijcard.2017.05.025
17. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136(6):e137–e161. doi:10.1161/CIR.0000000000000509
18. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604. doi:10.7326/0003-4819-150-9-200905050-00006
19. Dietrich S, Floegel A, Troll M, et al. Random survival forest in practice: a method for modelling complex metabolomics data in time to event analysis. *Int J Epidemiol*. 2016;45(5):1406–1420. doi:10.1093/ije/dyw145
20. Wang Q, Qiao W, Zhang H, et al. Nomogram established on account of lasso-cox regression for predicting recurrence in patients with early-stage hepatocellular carcinoma. *Front Immunol*. 2022;13:1019638. doi:10.3389/fimmu.2022.1019638
21. Camp RL, Dolled-Filhart M, Rimm DL. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. *Clin Cancer Res*. 2004;10(21):7252–7259. doi:10.1158/1078-0432.CCR-04-0713
22. Pencina MJ, D'Agostino RB Sr, Demler OV. Novel metrics for evaluating improvement in discrimination: net reclassification and integrated discrimination improvement for normal variables and nested models. *Stat Med*. 2012;31(2):101–113. doi:10.1002/sim.4348
23. Pencina MJ, D'Agostino RB, Demler OV. Mortality associated with heart failure with preserved vs. reduced ejection fraction in a prospective international multi-ethnic cohort study. *Eur Heart J*. 2018;39(20):1770–1780. doi:10.1093/eurheartj/ehy005
24. Rickenbacher P, Kaufmann BA, Maeder MT, et al. Heart failure with mid-range ejection fraction: a distinct clinical entity? Insights from the trial of intensified versus standard medical therapy in elderly patients with congestive heart failure (TIME-CHF). *Eur J Heart Fail*. 2017;19 (12):1586–1596. doi:10.1002/ejhf.798
25. Savarese G, Hage C, Orsini N, et al. Reductions in N-terminal pro-brain natriuretic peptide levels are associated with lower mortality and heart failure hospitalization rates in patients with heart failure with mid-range and preserved ejection fraction. *Circ Heart Fail*. 2016;9(11):e003105. doi:10.1161/CIRCHEARTFAILURE.116.003105
26. Booth RA, Hill SA, Don-Wauchope A, et al. Performance of BNP and NT-proBNP for diagnosis of heart failure in primary care patients: a systematic review. *Heart Fail Rev*. 2014;19(4):439–451. doi:10.1007/s10741-014-9445-8
27. Lin Y-P, Huang W-T, Lee W-L, et al. A higher estimated glomerular filtration rate is associated with better survival in subjects with coronary artery disease and heart failure with a mildly reduced ejection fraction. *Int Heart J*. 2023;64(5):816–822. doi:10.1536/ihj.23-207
28. Ostrominski JW, Vaduganathan M, Selvaraj S, et al. Dapagliflozin and apparent treatment-resistant hypertension in heart failure with mildly reduced or preserved ejection fraction: the deliver trial. *Circulation*. 2023;148(24):1945–1957. doi:10.1161/CIRCULATIONAHA.123.065254
29. Schupp T, Abumayyaleh M, Weidner K, et al. Prognostic implications of type 2 diabetes mellitus in heart failure with mildly reduced ejection fraction. *J Clin Med*. 2024;13(3):742. doi:10.3390/jcm13030742
30. Bonsu KO, Owusu IK, Buabeng KO, et al. Clinical characteristics and prognosis of patients admitted for heart failure: a 5-year retrospective study of African patients. *Int J Cardiol*. 2017;238:128–135. doi:10.1016/j.ijcard.2017.03.014
31. Soufi MK, Almahmoud MF, Kadri AN, et al. Heart failure with stable mildly-reduced ejection fraction: prognosis and predictors of outcomes. *Curr Probl Cardiol*. 2023;48(5):101631. doi:10.1016/j.cpcardiol.2023.101631
32. Yang M, Kondo T, Butt JH, et al. Stroke in patients with heart failure and reduced or preserved ejection fraction. *Eur Heart J*. 2023;44 (31):2998–3013. doi:10.1093/eurheartj/ehad338
33. Du Y, Demillard LJ, Ren J. Catecholamine-induced cardiotoxicity: a critical element in the pathophysiology of stroke-induced heart injury. *Life Sci*. 2021;287:120106. doi:10.1016/j.lfs.2021.120106
34. Tian J, Ding F, Wang R, et al. Dynamic trajectory of a patient-reported outcome and its associated factors for patients with chronic heart failure: a growth mixture model approach. *Risk Manag Healthc Policy*. 2022;15:2083–2096. doi:10.2147/RMHP.S384936

35. McDonagh TA, Metra M, Adamo M, et al. 2023 focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2023;44(37):3627–3639. doi:10.1093/eurheartj/ehad195
36. Wang Z, Jin L, Zhou W, et al. A single-center observational study on the efficacy of percutaneous coronary intervention for ischemic heart failure: a cohort study. *Medicine*. 2018;97(13):e0238. doi:10.1097/MD.0000000000010238
37. Levy WC, Mozaffarian D, Linker DT, et al. The Seattle heart failure model: prediction of survival in heart failure. *Circulation*. 2006;113 (11):1424–1433. doi:10.1161/CIRCULATIONAHA.105.584102
38. Wong CM, Hawkins NM, Petrie MC, et al. Heart failure in younger patients: the meta-analysis global group in Chronic Heart Failure (MAGGIC). *Eur Heart J*. 2014;35(39):2714–2721. doi:10.1093/eurheartj/ehu216
39. Peterson PN, Rumsfeld JS, Liang L, et al. A validated risk score for in-hospital mortality in patients with heart failure from the American Heart Association get with the guidelines program. *Circ Cardiovasc Qual Outcomes*. 2010;3(1):25–32. doi:10.1161/CIRCOUTCOMES.109.854877
40. Wang C, Han S, Tong F, et al. Risk prediction model of in-hospital mortality in heart failure with preserved ejection fraction and mid-range ejection fraction: a retrospective cohort study. *Biomarker Med*. 2021;15(14):1223–1232. doi:10.2217/bmm-2021-0025
41. Friedrich S, Groll A, Ickstadt K, et al. Regularization approaches in clinical biostatistics: a review of methods and their applications. *Stat Methods Med Res*. 2023;32(2):425–440. doi:10.1177/09622802221133557
42. Wang Z, Wang B, Zhou Y, et al. Weight-based multiple empirical kernel learning with neighbor discriminant constraint for heart failure mortality prediction. *J Biomed Inform*. 2020;101:103340. doi:10.1016/j.jbi.2019.103340
43. Angraal S, Mortazavi BJ, Gupta A, et al. Machine learning prediction of mortality and hospitalization in heart failure with preserved ejection fraction. *JACC Heart Fail*. 2020;8(1):12–21. doi:10.1016/j.jchf.2019.06.013
44. Zhao H, Li P, Zhong G, et al. Machine learning models in heart failure with mildly reduced ejection fraction patients. *Front Cardiovasc Med*. 2022;9:1042139. doi:10.3389/fcvm.2022.1042139
45. Sonaglioni A, Lonati C, Rigamonti E, et al. CHA_2DS_2-VASc score stratifies mortality risk in heart failure patients aged 75 years and older with and without atrial fibrillation. *Aging Clin Exp Res*. 2022;34(7):1707–1720. doi:10.1007/s40520-022-02107-x