



A Model for the Prediction of Mortality and Hospitalization in Chinese Heart Failure Patients

Bo Zhuang^{1†}, Ting Shen^{1†}, Dejie Li¹, Yumei Jiang¹, Guanghe Li¹, Qian Luo¹, Yishan Jin¹, Ziwei Shan¹, Lin Che², Lemin Wang^{1*}, Liang Zheng^{3*} and Yuqin Shen^{1*}

¹ Department of Rehabilitation, Tongji Hospital Affiliated to Tongji University, Tongji University School of Medicine, Shanghai, China, ² Department of Cardiology, Tongji Hospital Affiliated to Tongji University, Tongji University School of Medicine, Shanghai, China, ³ Department of Cardiovascular Medicine, Research Center for Translational Medicine, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China

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*Correspondence:

Lemin Wang
wanglem2003@163.com
Liang Zheng
zhengliang@tongji.edu.cn
Yuqin Shen
sy_1963@126.com

[†]These authors have contributed
equally to this work and share first
authorship

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Background: Although many risk prediction models have been released internationally, the application of these models in the Chinese population still has some limitations.

Aims: The purpose of the study was to establish a heart failure (HF) prognosis model suitable for the Chinese population.

Methods: According to the inclusion criteria, we included patients with chronic heart failure (CHF) who were admitted to the Department of Cardiac Rehabilitation of Tongji Hospital from March 2007 to December 2018, recorded each patient's condition and followed up on the patient's re-admission and death. All data sets were randomly divided into derivation and validation cohorts in a ratio of 7/3. Least absolute shrinkage and selection operator regression and Cox regression were used to screen independent predictors; a nomogram chart scoring model was constructed and validated.

Results: A total of 547 patients were recruited in this cohort, and the median follow-up time was 519 days. The independent predictors screened out by the derivation cohort included age, atrial fibrillation (AF), percutaneous coronary intervention (PCI), diabetes mellitus (DM), peak oxygen uptake (peak VO_2), heart rate at the 8th minute after the cardiopulmonary exercise peaked (HR8min), C-reaction protein(CRP), and uric acid (UA). The C indexes values of the derivation and the validation cohorts were 0.69 and 0.62, respectively, and the calibration curves indicate that the model's predictions were in good agreement with the actual observations.

Conclusions: We have developed and validated a multiple Cox regression model to predict long-term mortality and readmission risk of Chinese patients with CHF.

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Keywords: risk prediction, mortality, hospitalization, heart failure, Chinese population

INTRODUCTION

Heart failure (HF) is a serious manifestation of the late stage of various heart diseases. Its morbidity has an increasing trend, and the mortality and rehospitalization rates remain high, posing a huge economic burden for health care systems (1–3). According to recent studies, the 1-year mortality rate of patients with chronic heart failure (CHF) is 6.4%,

and the combined death or HF hospitalization rate within 1 year is 14.5% (4). Therefore, stratifying patients according to the risk of future results (re-admission and death), and optimizing treatment strategies for patients with different needs would be beneficial to all healthcare systems and patients.

The 2019 American College of Cardiology (ACC) Expert Consensus on HF proposes that the assessment of risk-increasing factors can help guide decision-making for preventive intervention (5). Many risk prediction models have been released internationally (6–10). The 2017 A systems Biology Study to Tailored Treatment in Chronic Heart Failure (BIOSTAT-CHF) research plan included 2,516 HF patients from 69 centers in 11 international centers. It concluded that the strongest predictors of mortality are age, urea nitrogen, N-terminal B-type natriuretic peptide, hemoglobin, and beta blockers. The predictors of hospitalization rate are age, hospitalization history for HF, edema, systolic blood pressure, and estimated glomerular filtration rate (6). In 2019, the Korean Acute Heart Failure registry used 12 predictors to establish a risk score that predicts the risk of HF-specific readmission or death at 30 days after discharge (7). The 2020 Prospective Comparison of angiotensin receptor neprilysin inhibitor (ARNI) with angiotensin-converting enzyme inhibitor (ACEI) to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) model can accurately predict the morbidity and mortality of ambulatory patients with CHF with reduced ejection fraction at 1 and 2 years (8). It can be seen from the above that the current existing forecasting models have the following advantages: Indicators are easily available and not focusing on a single risk factor. However, the application of these models in the Chinese population still has some limitations. Most of these models use static indicators, which are not sufficient to reflect the overall condition of the patients (6–8, 10, 11). Further, most studies have a short follow-up time and cannot judge the long-term prognosis (7, 10, 11). As there are regional differences in the mortality and rehospitalization rates of patients with CHF and scarce data from the Chinese population, the applicability

of the international HF risk prediction model to the Chinese population is controversial (4, 12). Therefore, it is necessary to establish a new HF risk prediction model suitable for the Chinese population.

In this study, we selected individuals with CHF in China as the target population for modeling and conducted relevant cardiopulmonary exercise tests (CPETs) to monitor the respiratory and circulatory parameters of patients under exercise to obtain comprehensive indicators of cardiopulmonary function. According to the literature, CPET parameters are predictors of the prognosis of HF, especially the level of peak oxygen uptake (peak VO_2) (13–15). Of note, our follow-up time is long (the longest follow-up time is as long as 12 years) which is helpful to assess the long-term prognosis of patients with CHF. Our research combines the experimental indicators of cardiopulmonary exercise to propose a long-term prognosis and readmission model for CHF in the Chinese population, which provides a basis for the treatment of clinical CHF and reveals potential targets for interventions to improve prognosis.

METHODS

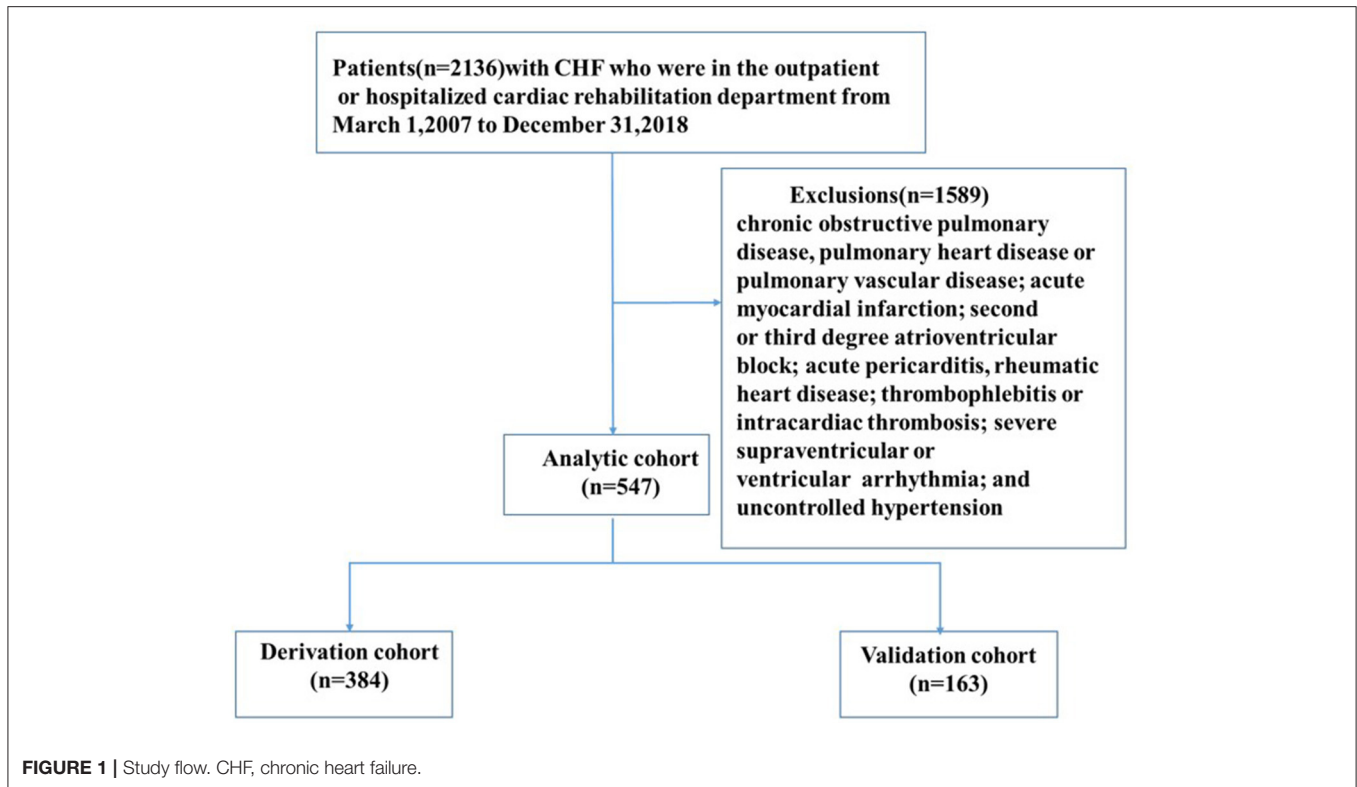
Data Sources and Processing

This study follows the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) report (16). The clinical data of the study were from 2,136 patients with CHF in the Outpatient or Cardiac Rehabilitation Department in Shanghai Tongji Hospital Affiliated to Tongji University from March 1, 2007 to December 31, 2018. The available information includes demographics, medical history, CPET indicators, echocardiography, laboratory testing, and drugs. Other data extracted include the number of hospital admissions, length of stay, and New York Heart Association (NYHA) classification at admission. Inclusion criteria include CHF diagnosed in accordance with the “Chinese Heart Failure Diagnosis and Treatment Guidelines 2018” with a medical history of more than 3 months; age ≥ 18 years; NYHA heart function level 1–3; and ability to cooperate to complete the CPET. Exclusion criteria include chronic obstructive pulmonary disease, pulmonary heart disease or pulmonary vascular disease; acute myocardial infarction; second or third degree atrioventricular block; acute pericarditis, rheumatic heart disease; thrombophlebitis or intracardiac thrombosis; severe supraventricular or ventricular arrhythmia; and uncontrolled hypertension. According to the criteria of acceptance, 1,589 patients were excluded, and 547 patients with HF were finally included (Figure 1). The study was conducted in accordance with the Declaration of Helsinki as revised in 2013 and was approved by the Ethics Committee of Tongji Hospital Affiliated to Tongji University [LL(H)-08-04]. Informed consent was taken from all the patients. Before analysis, the patient’s records/information were anonymized and de-identified.

Potential Predictive Variables

Potential predictors include the following characteristics of the patient: demographic characteristics (e.g., gender, age, height, weight, and body mass index), basic heart disease

Abbreviations: ACC, American College of Cardiology; ACEI, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; AHA, American Heart Association; ANOVA, analysis of variance; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor neprilysin inhibitor; BIOSTAT-CHF, Biology Study to Tailored Treatment in Chronic Heart Failure; BNP, B-type natriuretic peptide; CHF, chronic heart failure; CPETs, cardiopulmonary exercise tests; CRP, C-reactive protein; DCM, dilated cardiomyopathy; DM, diabetes mellitus; HBP, high blood pressure; HF, heart failure; HF-ACTION, Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training; HFmrEF, heart failure with a moderately reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFsrEF, heart failure with reduced ejection fraction; HR8min, heart rate at the 8th minute after the cardiopulmonary exercise peaked; HRAT, heart rate at anaerobic threshold; IHD, ischemic heart disease; IQR, interquartile ranges; KM, Kaplan-Meier; LASSO, least absolute shrinkage and selection operator; LVEF, left ventricular ejection fraction; MECKI, The Metabolic Exercise test data combined with Cardiac and Kidney Indexes; MI, myocardial infarction; NYHA, New York Heart Association; PARADIGM-HF, Global Mortality and Morbidity in Heart Failure; PCI, percutaneous coronary intervention; Peak DBP, peak diastolic blood pressure; Peak MBP, peak average blood pressure; Peak VO_2 , peak oxygen uptake; PETCO₂, end-tidal CO₂ pressure; TnI, troponin I; TRIPOD, transparent reporting of a multivariable prediction model for individual prognosis or diagnosis; UA, uric acid; VE/VCO₂, ventilation/carbon dioxide production; VO_2 AT, oxygen consumption at anaerobic threshold; WT, weight.



history (e.g., coronary heart disease, dilated heart disease, and hypertension), other related medical history (e.g., diabetes, hyperlipidemia, and stroke), CPET indicators [e.g., peak VO_2 , end-tidal CO_2 pressure (PETCO_2)], cardiac ultrasonography [e.g., left ventricular ejection fraction (LVEF)], laboratory tests (e.g., blood lipids, and blood potassium), and medications for HF treatment [e.g., angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), angiotensin receptor neprilysin inhibitors (ARNI), β -blockers].

Study Design

A total of 90 variables were included in the study as potential prognostic factors. Patients with readmission or death records mainly for HF during the follow-up were defined as the readmitted or died group. Patients who did not have a readmission or death record during the follow-up were defined as the not readmitted, alive group. This is an open-label design trial. In order to reduce bias, examiners, researchers collecting data on outcome indicators, data managers, and statisticians do not know the patient's name.

Outcomes

Readers should refer to the definitions of key clinical data elements and cardiovascular endpoint events issued by the ACC/American Heart Association (AHA) in conjunction with the US Food and Drug Administration and the Cardiovascular Trial Standard Data Collection Program. The endpoint of this study was the composite endpoint of all-cause death and all-cause

admission. The data from the electronic medical records and our follow-up results were used to measure this result.

Follow-Up

Starting from December 2018, a telephone follow-up or electronic medical record review was conducted every 6 months to collect information on hospitalization or death in the past period, until the patient's first readmission or death or the study was terminated by the follow-up on June 30, 2020. The time of hospitalization or death was recorded by the follow-up staff. A wrong telephone number, lack of response, and refusal to follow up were considered as being lost to follow up.

Statistical Analysis

We used R language [R software (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria)] and SPSS software (version 20.0; IBM Corp, Armonk, NY, USA) for statistical analysis. The measurement data were tested for normal distribution. Normally distributed measurement data were expressed as mean \pm standard deviation. The comparison between two groups was done using an independent sample *t*-test and the comparison between multiple groups using one-way analysis of variance (ANOVA). The least significant difference test was used for multiple comparisons between groups. Non-normal distribution measurement data were expressed as medians and interquartile ranges (IQR) and compared by the non-parametric Mann-Whitney *U*-test. Categorical data were expressed as frequency (percentage), and χ^2 -test was used for comparison between groups. In addition, variables with missing

values <20% were subjected to multiple imputation using the R language mice package. $P < 0.05$ indicates that the difference is statistically significant.

Modeling and Validation

Through random sampling, the entire data set was divided into derivation and validation cohorts in a ratio of 7:3. Least absolute shrinkage and selection operator (LASSO) regression and Cox multivariate analysis were used to screen independent risk factors that could affect the prognosis of CHF, and a nomogram was used to establish a risk prediction model. The C-index values were calculated for the derivation and validation groups. The degree of discrimination was determined and a calibration curve drawn to evaluate the degree of calibration. Finally, the patients were classified into high (greater than the mean risk score) and low

risk (no greater than the mean risk score) categories according to the score, and the Kaplan-Meier (KM) curve was drawn for survival analysis (17).

RESULTS

Study Population and Cohort Characteristics

A total of 547 patients with HF were screened; 18.3% were women; the median age was 63 years; the median follow-up time was 519 days and the loss to follow up rate was 10.79%; The incidence of composite endpoints (all-cause death and all-cause admission) in 1/3/5/10 years were 40.95%, 56.86%, 60.15%, and 63.44%, respectively. Compared with the not readmitted and alive group, the readmitted or died group

TABLE 1 | The characteristics of death or readmission stratification in patients with CHF.

Characteristic	Overall (<i>n</i> = 547)	Not readmitted, alive (<i>n</i> = 196)	Readmitted or died (<i>n</i> = 351)	χ^2/Z	<i>p</i>
Time (median [IQR])	519.00 [193.50, 1444.50]	1609.50 [752.75, 2644.25]	262.00 [127.50, 632.50]	-14.470	0.000
Female, <i>n</i> (%)	100 (18.3)	43 (21.9)	57 (16.2)	2.735	0.098
Age (median [IQR])	63.00 [56.00, 69.00]	60.50 [55.00, 68.00]	64.00 [57.00, 70.00]	-3.021	0.003
Smoke, <i>n</i> (%)	329 (60.1)	119 (60.7)	210 (59.8)	0.041	0.839
Alcohol, <i>n</i> (%)	91 (16.6)	32 (16.3)	59 (16.8)	0.021	0.884
IHD, <i>n</i> (%)	333 (60.9)	105 (53.6)	228 (65.0)	6.846	0.009
DCM, <i>n</i> (%)	171 (31.3)	71 (36.2)	100 (28.5)	3.501	0.061
AF, <i>n</i> (%)	81 (14.8)	20 (10.2)	61 (17.4)	5.132	0.023
MI, <i>n</i> (%)	205 (37.5)	47 (24.0)	158 (45.0)	23.749	0.000
PCI, <i>n</i> (%)	225 (41.1)	55 (28.1)	170 (48.4)	21.556	0.000
HBP, <i>n</i> (%)	386 (70.6)	146 (74.5)	240 (68.4)	2.263	0.132
DM, <i>n</i> (%)	158 (28.9)	40 (20.4)	118 (33.6)	10.684	0.001
Height (median [IQR])	168.31 [166.00, 172.00]	168.31 [165.00, 172.00]	168.31 [166.50, 172.00]	-0.005	0.996
WT (median [IQR])	71.97 [65.00, 76.25]	71.97 [65.00, 80.00]	71.97 [65.00, 76.00]	-0.066	0.947
VO ₂ AT (median [IQR])	10.72 [9.10, 12.20]	10.80 [9.50, 12.83]	10.70 [9.00, 12.00]	-2.525	0.012
Peak VO ₂ (median [IQR])	14.66 [12.35, 16.90]	14.80 [12.60, 17.70]	14.40 [12.30, 16.15]	-2.998	0.003
HRAT (median [IQR])	94.00 [85.00, 100.50]	94.50 [86.00, 106.00]	93.00 [84.00, 99.00]	-3.146	0.002
HR8min (median [IQR])	81.00 [81.00, 81.00]	81.00 [81.00, 81.00]	81.00 [81.00, 81.00]	-0.905	0.366
Peak DBP (median [IQR])	81.00 [72.00, 90.00]	81.00 [75.00, 90.00]	81.00 [72.00, 90.00]	-1.380	0.168
Peak MBP (median [IQR])	105.00 [93.83, 114.33]	107.00 [96.00, 115.42]	105.00 [93.33, 113.67]	-2.091	0.037
VE/VCO ₂ (median [IQR])	34.90 [30.65, 39.10]	34.00 [29.26, 38.12]	35.75 [31.50, 40.15]	-3.088	0.002
LVEF (median [IQR])	0.45 [0.36, 0.52]	0.45 [0.38, 0.50]	0.45 [0.36, 0.52]	-0.040	0.968
LVEF group				3.004	0.223
LVEF <0.4, <i>n</i> (%)	170 (31.1)	57 (29.1)	113 (32.2)		
LVEF 0.4–0.49, <i>n</i> (%)	222 (40.6)	89 (45.4)	133 (37.9)		
LVEF ≥0.5, <i>n</i> (%)	155 (28.3)	50 (25.5)	105 (29.9)		
CRP (median [IQR])	6.40 [3.00, 6.40]	6.40 [3.00, 6.40]	6.40 [3.00, 6.40]	-0.562	0.574
BNP (median [IQR])	702.00 [702.00, 702.00]	702.00 [702.00, 702.00]	702.00 [702.00, 702.00]	-0.750	0.453
Tnl (median [IQR])	0.05 [0.01, 0.39]	0.08 [0.01, 0.39]	0.05 [0.01, 0.39]	-1.988	0.047
UA (median [IQR])	432.00 [355.00, 464.00]	432.00 [368.75, 456.00]	432.00 [353.00, 469.50]	-0.244	0.807

Significant values of $P < 0.05$ is indicated in bold.

AF, atrial fibrillation; BNP, B-type natriuretic peptide; CRP, C-reactive protein; DCM, dilated cardiomyopathy; DM, diabetes mellitus; HBP, high blood pressure; HR8min, heart rate at the 8th minute after the cardiopulmonary exercise peaked; HRAT, heart rate at anaerobic threshold; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; Peak DBP, peak diastolic blood pressure; Peak MBP, peak average blood pressure; Peak VO₂, peak oxygen uptake; Tnl, troponin I; UA, uric acid; VE/VCO₂, ventilation/carbon dioxide production; VO₂AT, oxygen consumption at anaerobic threshold; WT, weight.

TABLE 2 | Analysis of risk events indicators in chronic heart failure patients.

Indicators	Univariate analysis		Multivariable analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age	1.03 (1.02–1.04)	0.000	1.03 (1.01–1.04)	0.000
AF	1.80 (1.30–2.49)	0.000	1.60 (1.12–2.29)	0.009
MI	1.73 (1.34–2.24)	0.000	1.26 (0.72–2.20)	0.417
PCI	1.70 (1.31–2.20)	0.000	1.81 (1.02–3.18)	0.041
DM	1.56 (1.18–2.05)	0.002	1.41 (1.06–1.88)	0.020
Height	1.01 (0.99–1.03)	0.175	1.01 (1.00–1.03)	0.124
Peak VO ₂	0.93 (0.90–0.97)	0.000	0.95 (0.91–0.99)	0.012
HR8min	1.05 (1.02–1.08)	0.004	1.06 (1.03–1.10)	0.000
Peak DBP	0.99 (0.98–1.00)	0.008	1.00 (0.98–1.02)	0.696
Peak MBP	0.99 (0.98–1.00)	0.010	0.99 (0.98–1.01)	0.538
CRP	1.03 (1.01–1.05)	0.000	1.04 (1.02–1.05)	0.000
BNP	1.00 (1.00–1.00)	0.003	1.00 (1.00–1.00)	0.108
TnI	0.93 (0.83–1.05)	0.243	0.92 (0.81–1.04)	0.187
UA	1.00 (1.00–1.00)	0.016	1.00 (1.00–1.00)	0.005

Significant values of $P < 0.05$ is indicated in bold.

AF, atrial fibrillation; BNP, b-type natriuretic peptide; CRP, c-reactive protein; DM, diabetes mellitus; HR8min, heart rate at the 8th minute after the cardiopulmonary exercise peaked; MI, myocardial infarction; PCI, percutaneous coronary intervention; Peak DBP, peak diastolic blood pressure; Peak MBP, peak average blood pressure; Peak VO₂, peak oxygen uptake; TnI, troponin I; UA, uric acid.

had the following characteristics: (i) older subjects; (ii) a high proportion of patients with a history of ischemic heart disease (IHD) (65%), atrial fibrillation (AF) (17.4%), myocardial infarction (MI) (45%), percutaneous coronary intervention (PCI) (48.4%), and diabetes mellitus (DM) (33.6%) ($P < 0.05$); (iii) lower oxygen consumption at anaerobic threshold (VO₂ AT), peak VO₂, heart rate at anaerobic threshold (HRAT), and peak average blood pressure (Peak MBP); (iv) higher ventilation/carbon dioxide production (VE/VCO₂) slope; (v) lower levels of biochemical indicator, troponin I (TnI) (Table 1).

Risk Model Development and Validation

Using computer-generated random numbers, the majority (70%) of the cohort were randomly assigned to the derivation cohort ($n = 384$), and the remaining 30% were assigned to the validation cohort ($n = 163$). There was no significant difference in the characteristics between the derivation and validation groups (Supplementary Table 1). After 90 variables entered LASSO regression screening, 14 variables [age, AF, MI, PCI, DM, height, peak VO₂, heart rate at the 8th minute after the cardiopulmonary exercise peaked (HR8min), peak diastolic blood pressure (peak DBP), peak MBP, c-reactive protein (CRP), b-type natriuretic peptide (BNP), TnI, uric acid (UA)] were obtained (Supplementary Figures 1A,B), and eight variables were retained after univariate analysis, multivariable analysis, and stepwise regression (Table 2; Supplementary Table 2).

In univariate regression analysis, 12 variables were significantly related to the prognosis of heart failure (the composite endpoint of death and rehospitalization). In the multivariate Cox regression analysis, the regression coefficients of the indicators in Table 3, and construct the prognostic

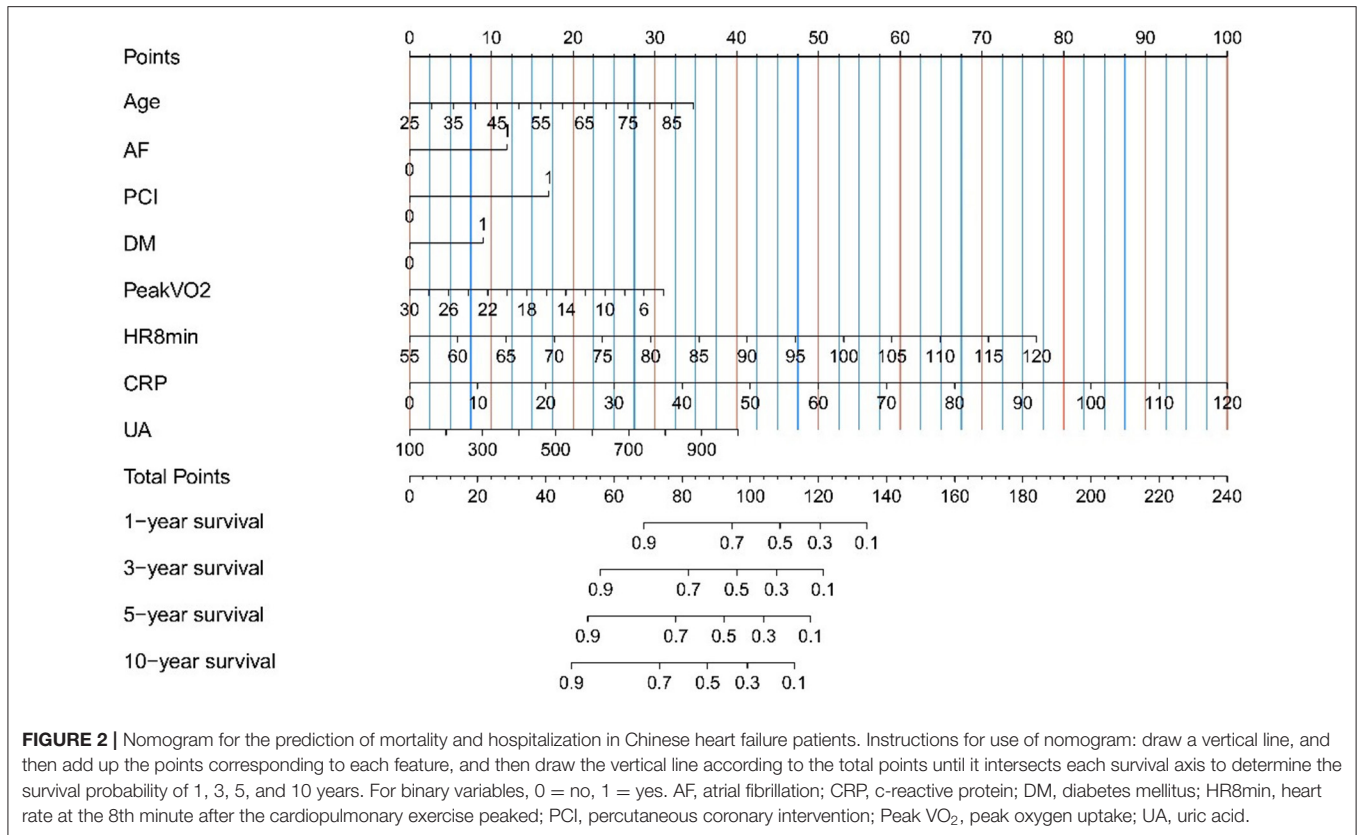
TABLE 3 | The selected variables for model construction.

Factors	Coefficient	HR (95%CI)	P
Age	0.025	1.03 (1.01–1.04)	0.000
AF	0.560	1.75 (1.24–2.47)	0.001
PCI	0.803	2.23 (1.68–2.96)	0.000
DM	0.423	1.53 (1.16–2.02)	0.003
Peak VO ₂	−0.056	0.95 (0.91–0.98)	0.005
HR8min	0.056	1.06 (1.02–1.09)	0.001
CRP	0.039	1.04 (1.03–1.05)	0.000
UA	0.002	1.00 (1.00–1.00)	0.000

AF, atrial fibrillation; CRP, c-reactive protein; DM, diabetes mellitus; HR8min, heart rate at the 8th minute after the cardiopulmonary exercise peaked; PCI, percutaneous coronary intervention; Peak VO₂, peak oxygen uptake; UA, uric acid.

risk proportion model [the calculation formula is $h(t,x) = h_0(t)\exp(0.025\text{Age} + 0.560\text{AF} + 0.803\text{PCI} + 0.423\text{DM} - 0.056\text{Peak VO}_2 + 0.056\text{HR8min} + 0.039\text{CRP} + 0.002\text{UA})$] according to the multivariate Cox regression coefficients of the eight indicators (18). Factors—age, AF, PCI, DM, peak VO₂, HR8min, CRP, and UA—that were independently associated with a higher likelihood of readmission or death were construct a risk scoring model, which was expressed in the form of a nomogram (Tables 2, 3; Figure 2; Supplementary Figure 2).

The AUC of the prediction model is shown in Supplementary Figure 3. To evaluate the effectiveness of risk prediction for the composite endpoint of heart failure death and readmission. The sensitivity, specificity, positive predictive value, and negative predictive value of the training group's prediction model are shown in Supplementary Table 3.



In the derivation and validation cohorts, the calculated model discrimination C-index values were 0.69 (95%CI 0.65–0.72) and 0.62 (95%CI 0.57–0.67), respectively, and the model’s discrimination ability was moderate. The calibration chart shows that the occurrence of end-point events at 1 year/3 years/5 years/10 years was in good agreement with the actual observations (Supplementary Figure 4).

Based on the score calculated by the nomogram, the derivation cohort was divided into two groups, high- and low- risk groups, and KM curve survival analysis was performed. The results of the LogRank method showed that the KM curves of the high-risk and low-risk groups were significantly different in the three cohorts (derivation group, validation group, and the whole group). In the derivation group, the risk of rehospitalization or death at 1 year/3 years/5 years/10 years was 69.5, 87.8, 92.7, and 100% for the high-risk group and 32.5, 61.9, 75.8, and 95.7% for the low-risk group, respectively (Figure 3; Supplementary Figure 5).

DISCUSSION

In this study, we selected simple parameters based on clinical conditions, laboratory indicators, cardiopulmonary exercise tests, and other measurements, and developed a new prediction model based on the Chinese HF population, which can assess the risk of readmission or death of patients with CHF. The C index values of the derivation cohort and validation cohorts were 0.69 (95%CI 0.65–0.72) and 0.62 (95%CI 0.57–0.67), respectively,

which indicate moderate levels of predictive ability. Our C-index values are high among those from previously published HF risk prediction models (19). Moreover, the calibration curve at 1 year/3 years/5 years/10 years showed good consistency. Compared with the traditional HF risk prediction model, our model has some advantages for CHF patients in China: (i) it adds relevant CPET indicators; (ii) has a long follow-up time, and (iii) the target population is based on the Chinese population. This model can comprehensively assess the long-term prognosis of patients with HF and provide data for the Chinese population for inclusion in the world’s CHF prognosis assessment.

In our cohort study, it was observed that patients with CHF who were hospitalized or who died were older, had more complications, and had poorer exercise endurance. The indicators included in the model were age, AF, PCI, DM, peak VO₂, HR8min, CRP, and UA. As a protective factor, peak VO₂ has been used as a tool to assess the severity of the disease, judge the short-term and long-term prognosis of patients with HF, and select patients for heart transplantation (20, 21). Lewis and Zlotoff (22) summarized the application of risk stratification based on cardiopulmonary exercise experiments in the management of advanced HF. They showed that exercise response patterns are predictive: Peak oxygen consumption can predict the lifespan of ordinary people, and CPET can effectively divide patients into high-risk and low-risk categories of HF events (22). Of note, as the peak VO₂ index can be improved by exercise (23), this model evaluation encourages high-risk

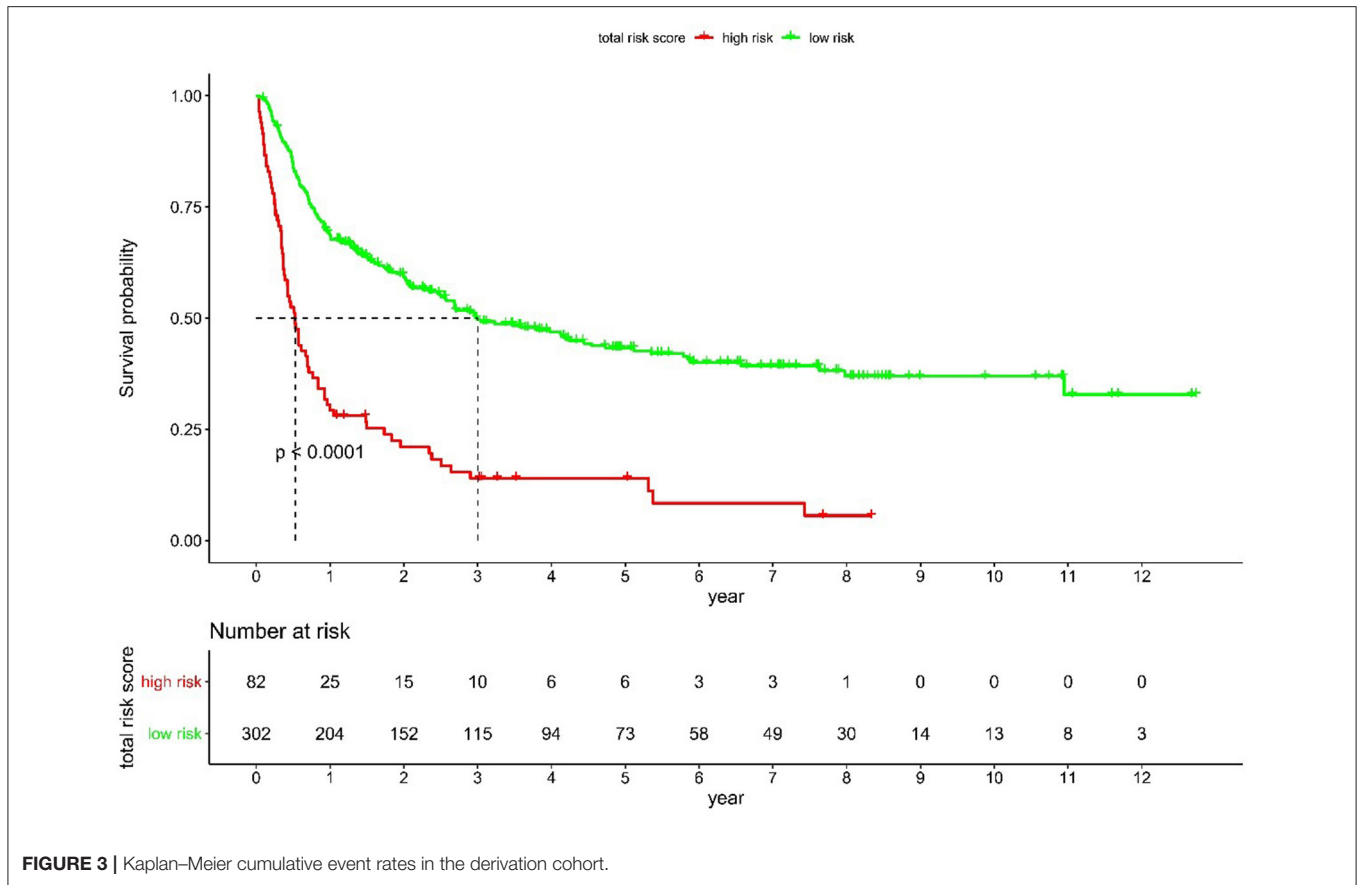


FIGURE 3 | Kaplan–Meier cumulative event rates in the derivation cohort.

HF patients to undergo exercise-based cardiac rehabilitation. Therefore, we believe that during continuous exercise, with the improvement of exercise endurance, the risk score may continue to improve, and finally improve the long-term prognosis.

In addition, we noted that the risk factors that affect the prognosis also include heart rate (specific time), CRP, and UA, which is consistent with the risk factors mentioned in the current study (24–30). Heart rate is a determinant of myocardial oxygen demand, coronary blood flow, and myocardial function, and is the key to adapting cardiac output to metabolic demands. An elevated heart rate can predict adverse outcomes in patients with CHF, which may be related to neurohormonal activation (24). Inflammation plays a key role in the etiology and progression of atherosclerosis. Studies have shown that in patients undergoing PCI for the first ST elevation myocardial infarction, there is a clear relationship between the in-hospital CRP plasma concentration and the development of HF after infarction (25). Uric acid can affect cardiovascular disease through platelet aggregation and endothelial inflammation activation. The change in serum uric acid levels in the hospital can predict adverse outcomes in patients with HF (26, 31).

There are other combined CPET HF risk scores, whose predictive accuracy is variable, depending on population selection, treatment, event selection, and follow-up time (32–35). The 2012 Heart Failure: A Controlled Trial Investigating

Outcomes of Exercise TraiNing (HF-ACTION) predictive risk score model is the first risk predictive model for HF patients caused by systolic insufficiency. It analyzes multiple candidate variables, including demographics, medical history, laboratory values, CPET exercise parameters, quality of life, and the level of depression (32). The HF-ACTION represents heart failure with reduced ejection fraction (HFrEF) patients, and its score contains indicators that are easily available. However, the limitation is that patients with preserved systolic function are excluded, and the representativeness of people from outside the United States are limited. Our study included patients with heart failure with a moderately reduced ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF), and included the Chinese population for modeling, which has good applicability to the Chinese population. At the same time, the indicators we included are easily available clinically. In 2013, the Metabolic Exercise test data combined with Cardiac and Kidney Indexes (MECKI) score combined CPET indicators with established clinical, laboratory and echocardiography parameters, and finally included six indicators of hemoglobin, Na⁺, modification of diet in renal disease, LVEF, peak VO₂, and VE/VCO₂ slope (33). These continuous variables define the MECKI score, identify the risk of cardiovascular death and heart transplantation, and have been validated in different settings (34). However, it is mainly used for white people, and its applicability to the Chinese

population is unknown. In 2020, Pugliese et al. identified five independent predictors including peak oxygen consumption, which can determine the increased risk of adverse events in patients with HF with preserved ejection fraction (35). However, the sample size of that study is small, the follow-up time is short, and its applicability in Chinese population needs to be investigated.

Although there are many HF risk prediction models in the world, a model based on Chinese population data is an unmet need. On the one hand, our current model highlights the importance of CPET in risk scoring, helps optimize the risk stratification and management of HF patients, and supports cardiac rehabilitation programs. On the other hand, the indicators included in our model are simple and easy to obtain, which helps its vigorous promotion in primary hospitals.

Our study has the following limitations: First, as all the patients are from Shanghai Tongji Hospital, this is a single-center study with regional limitations and an insufficient sample size. Our future research will include people from other parts of China and expand the sample size of the research. Second, the included population comprises people who are around 60 years old, which may limit the generality of our model. However, compared with younger patients, older patients tend to have a higher risk of death and readmission. Third, there is currently a lack of external verification. At the same time, there is also a lack of comparison data with other international forecasting models in the same Chinese cohort. In the future, we will promote this model, conduct external verification, compare it with other international models in the same Chinese cohort, and continue to improve the model to provide a theoretical basis for treatment decisions for Chinese HF patients. Finally, the loss to follow-up rate in this study exceeded 5%. The main reasons include patients' lack of attention to the study, poor compliance, and insufficient communication skills of the follow-up staff. Moreover, due to the long follow-up time (the longest follow-up time is up to 12 years), the patient's telephone number and place of residence have changed, resulting in a high rate of loss to follow-up. In the future follow-up, we will strengthen patient education, increase doctor-patient contact, and conduct communication training for follow-up personnel, so as to reduce the rate of loss to follow-up as much as possible.

CONCLUSIONS

In this study, a scoring model for CHF in China was constructed based on CPET indicators. This model can evaluate the long-term risk of death or rehospitalization due to CHF and provide decision-making basis for clinicians, patients, and their families.

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Clinical Perspectives

Clinicians use this model to assess the prognosis of patients with heart failure and identify high-risk patients, so as to better guide the implementation of treatment plans.

Translational Outlook

Although there are many models for evaluating the mortality and hospitalization risk of patients with heart failure, this study combines the experimental indicators of cardiopulmonary exercise to propose a long-term prognosis and readmission model for chronic heart failure in the Chinese population, laying the foundation for more accurate risk stratification in the future.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Tongji Hospital Affiliated to Tongji University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BZ and TS prepared the manuscript and all the authors participated in the clinical and related research. All authors gave final approval and agreed to be accountable for the integrity and accuracy of all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fcvm.2021.761605/full#supplementary-material>

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