Development and validation of a novel nomogram to predict the impact of the polymorphism of the ICAM-1 gene on the prognosis of ischemic cardiomyopathy

Tuersunjiang Naman

First Affiliated Hospital of Xinjiang Medical University

Refukaiti Abuduhalike

First Affiliated Hospital of Xinjiang Medical University

Aihaidan Abudouwayiti

First Affiliated Hospital of Xinjiang Medical University

Juan Sun

First Affiliated Hospital of Xinjiang Medical University

Ailiman Mahemuti (✉ ailiman623@163.com)

First Affiliated Hospital of Xinjiang Medical University

Research Article

Abstract

Object:

The current study investigated the association between polymorphisms of the *ICAM*-1 gene and prognosis of Ischemic cardiomyopathy(ICM), and developed a prognostic nomogram for ICM on the basis of *ICAM-1* gene variants.

Method:

The current study included totally 252 patients with ICM. In addition, PCR-RFLP (polymerase chain reaction-restriction fragment length polymorphism) was used to genotype SNPs in the *ICAM-1* gene in the patients. Later, the nomogram model was built by combining clinical data with *ICAM-1* gene variants. This study used the least absolute shrinkage and selection operator (LASSO) regression model to optimize feature selection into an ICM prognostic model. Furthermore, multivariate Cox-regression was applied to build the prognostic model, which included clinical and gene features chosen by the LASSO regression model. Following that, the receiver operating characteristic (ROC) curve, C-index, calibration plot analyses and decision curve analysis (DCA) were carried out to evaluate the discrimination abilitiy, consistency, and clinical utility of the prognostic model, and the bootstrap method was adopted for internal validation.

Result:

predicting factors rs112872667, treating by PCI or CABG, ventricular arrhythmia, left ventricular end-diastolic diameter (LVDD), use of β-blockers, systolic blood pressure (SBP), heart rate (HR), and serum sodium were incorporated into the prognostic nomogram. The constructed nomogram performed well in discrimination ability, as observed by the time-dependent C-index. Furthermore, as shown by calibration curves, our nomogram's predicted probabilities were highly consistent with measured values. With threshold probabilities, DCA suggested that our nomogram could be useful in the clinic.

Conclusion:

rs112872667 mutation (from CC genotype toCT or TTgenotype) is a protective factor for ICM patients to have a higher survival probability; ICM patients with the mutant genotype (CT or TT) have a lower probability of cardiogenic death than those with the wild genotype (CC).

1. Introduction

Cardiovascular disease (CVD) is still a primarily reason for death worldwide [1]. Ischemic cardiomyopathy (ICM), in particular, is a major cause of global prevalence and death [2]. Furthermore, ICM has been detected as the leading reason for CVDs in the United States and the most common risk factor for HF [3]. In accordance with the global pandemic, around 26 million ICM cases have cardiac insufficiency, costing global health systems more than $30 billion[4, 5]. Furthermore, the mortality rate for cardiac disease cases has been as high as 50% over the last five years[6, 7].

The initial cause of ICM is the development of atherosclerosis in multi-coronary arteries, particularly the diffusive lesions, and reduced or ceased myocardial blood flow that can generate severe myocardial dysfunction, resulting in heart muscle injury [8, 9] and persisting injury.

The content of intercellular adhesion molecule-1(ICAM-1) in blood has previously been proposed as a marker for coronary heart disease(CHD)[2, 10, 11]. *ICAM-1*, an immunoglobulin superfamily member, is highly denoted in leukocytes and endothelial cells, where it functions as a receptor for the leukocyte integrin lymphocyte function-related antigen-1 and Mac-1[8, 12, 13]. *ICAM-1* is an important factor in the pathogenesis of atherosclerosis, exerting critical effects on mononuclear cell recruitment in the vasculature basement membrane[3, 4]. Therefore,*ICAM-1*exerts a vital role in both atherosclerosis and the occurrence of ICM.

As previously reported, ICM refers to a disease featured with high morbidity and mortality, and it is costly to the global health system; thus, there is a need to investigate the causes of ICM, as well as predicting factors that have a prognostic value on the prognosis of ICM, and measures to be taken to reduce morbidity and mortality. Although the *ICAM*-1 gene has been linked to ICM, there is no evidence linking it to long-term ICM prognosis. Therefore, we concentrated on determining the relationship between *ICAM-1* gene polymorphisms(rs112872667, rs12462944, rs2358581, rs281430, rs281434, rs3093030, rs3093032, rs5030348, rs5030377, rs5491, rs62130660, rs923366) and prognosis of ICM. We also developed a new nomogram model for accurately predicting ICM prognosis based on *ICAM-1* gene polymorphisms.

2. Materials And Methods

2.1 Subjects and Study Design

From January 2013 to December 2015, participants were recruited from the First Affiliated Hospital of Xinjiang Medical University. The current work enrolled 324 subjects in total, with 252 of them meeting our study eligibility criteria, including 167 alive and 85 dead (cardiogenic death) subjects (**Figure 1**). Each participant in the current study had previously received coronary angiography in the hospital or during their most recent hospital stay.

The following criteria were used to make the diagnosis of ICM: (1)coronary angiography revealed >50% luminal stenosis in at least one coronary artery of the leading branch or a previous history of coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) (2) N-terminal pro-B-type natriuretic peptide (NT-proBNP)>125ng/mL; (3) nitroglycerin or rest relieved divinable angina; (4) symptoms including dyspnea, shortness of breath, and chest tightness relieved immediately after resting.

Acute decompensated HF; the previous history of unstable hemodynamics; acute myocardial infarction (AMI); liver/kidney/blood/autoimmune diseases; cachexia; noncardiac disorder with a predicted lifespan of <1 year; and those unwilling to participate in this study were excluded.

2.2 Blood Sampling and Laboratory Tests

On the first day of admission, blood was drawn from each ICM patient and analyzed at the Laboratory of the First Affiliated Hospital of Xinjiang Medical University. White blood cell (WBC), hemoglobin, creatinine (CR), platelet (PLT), high/low-density lipoprotein-cholesterol (HDL-C/LDL-C), blood urea nitrogen (BUN), total cholesterol (TC). In addition, triglyceride levels were all measured (TG).

2.3 Isolation of DNA

Following laboratory tests, this work isolated DNA from venous blood. First, blood samples were centrifuged for 10 min at 1500rpm with the Eppendorf high-speed centrifuge using the anticoagulant ethylene diamine tetra acetic acid (EDTA) to separate blood cells and plasma. After that, DNA was extracted from peripheral leukocytes with the use of a whole-blood genome extraction kit (Xiamen Kaishuo Biotechnology Corporation, China) and related protocols. Finally, the extracted DNA sample was stored at 80 °C before genotyping.

2.4 Genotyping of the *ICAM-1* Gene

Of extracted DNA, 1 µL was collected for RNA preparation using specific protocols. Following the detailed instructions, the amplified samples were subjected to SNP genotyping using the SNaPshot multiplex SNP genotyping kit (Application Binary Interface Company, USA).

2.5 Determination of Cardiovascular Risk Factors

Through dividing body weight (kg) by body height squared (m), body mass index (BMI) was calculated. In this study, smokers were defined as those who had smoked for more than 6 months or within the previous 6 months. Drinkers were those who consumed 100 g of alcohol weekly in the previous month. According to the 2018 European Society of Cardiology (ESC)/European Society of Hypertension (EHS) Guidelines [14], hypertension was defined as diastolic blood pressure (DBP)≥90 mmHg, systolic blood pressure (SBP)≥140 mmHg, or use of antihypertensive drugs in the previous two weeks. Diabetes mellitus (DM) was diagnosed based on glucose levels ≥11.1 mmol/L (200 mg/dL) at 2-h after administration of 75 g oral glucose load, fasting plasma glucose levels ≥7.0 mmol/L (126 mg/dL), diabetes or antidiabetic drug use history, and diabetes or antidiabetic drug use history. Atrial tachycardia (AT), atrial premature beat (APB), atrial fibrillation (AF), and atrial flutter were the four types of atrial arrhythmia (AF). Based on the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society [15], ventricular arrhythmia (VA) is referred to as a spectrum that includes ventricular tachycardia (VT), premature ventricular complex (PVC), ventricular fibrillation (VF), and ventricular flutter (VF).

2.6 Study Endpoints in Follow-up

The study's endpoint was cardiogenic death during the hospital stay and after discharge, and we recorded the time length from the first diagnosis of ICM to cardiogenic death as the survival time. The patients and their families were contacted by phone. Data, including the dead cases, were obtained through telephone interviews with family members of the deceased patients or through hospital records. Telephone calls were made three, six, twelve, twenty-four, and sixty months after the initial diagnosis of ICM. Follow-up work was done by trained investigators, and data entry was done by three experienced researchers to ensure data quality. Clinicians trained in systemic data acquisition and event confirmation were in charge of follow-up.

2.7 Statistical Analysis

SPSS25.0 and R 4.2.1 software were used for statistical analysis. Data were classified into two groups: survival (n = 167) and cardiogenic death (n = 85) (**Figure 2**). Using COX-univariable logistic regression analysisi, *P*<0.05 was adopted for detecting statistical significance. Following that, the best predicting factors were chosen using the least absolute shrinkage and selection operator (LASSO) algorithm and adjusted for the decreased high-dimensional

data[16,17]. by enrolling significant factors (P<0.1) from COX-univariable regression. LASSO regression[18] features with non-zero coefficients were chosen.

Following that, COX-multivariate regression was used to develop the prognostic model by incorporating variables from LASSO regression. In addition, the following features were chosen: SE, β, odds ratio (OR), associated 95% confidence interval (CI), and P-value. After analyzing the significance level (two-sided), the model Akaike Information Criterion (AIC) value was determined to optimize the model.

The intersection point was the cutoff value of the total point, and all patients were classified into high- or low-risk groups, and a scatter plot for the corresponding survival time in different samples was plotted.

The survival curves of high and low-risk group patients, as well as the survival curves of wild genotype (CC) and mutant genotype (CT+TT) patients, were plotted using the Kaplan-Meier (KM) method as well as calculated the P-value, and the Hazard-Ratio (HR) were calculated using Cox regression.

2.8 Validation of the Model

Internal validation was carried out with 500 resamples by adopting the Bootstrap method. We later confirmed nomogram discrimination ability by Time-dependent C-index, plotted calibration curve(using the Bootstrap method), and evaluate the clinical effectiveness. At first, the C-index and receiver operating characteristic (ROC) curves were mapped to identify discrimination ability. A value close to 1 indicates improved model performance [19]. Second, calibration plots were created in this work to determine the consistency of predicted and observed values. Furthermore, the 45° diagonal line in the curve suggested that the model performed well in predicting disease incidence. Calibration plots [20] were applied to evaluate calibration ability. Third, decision curve analysis (DCA) [21] was adopted for determining the model's clinical utility on the basis of the net benefits under different threshold probabilities. Furthermore, this study subtracted the proportion of false-positive cases from the proportion of true-positive cases to calculate the net benefit. Then, we weighed the risk of discontinuing interventions against the negative outcomes of unnecessary interventions.

3. Results

The current study included 324 cases in total, with 252 ICM patients included according to the eligibility criteria, of which 167 survived the 60-month follow-up study and 85 died from cardiogenic causes (**Figure 1**).

Patients were categorized into two groups on the basis of 60-month follow-up outcomes: survival(n = 167) and cardiogenic death(n = 85). Univariable Cox-regression was performed on baseline clinical features and genotypes in the survival and death groups. Therefore, there were obvious differences in smoking (P<0.05), complicated with Ventricular arrhythmia (P<0.001), SBP (P<0.001), HR (P<0.001), serum sodium (P<0.001), NT-proBNP(P<0.05), LVDD (P<0.001), treating by CABG or PCI (P<0.001), and using β-Blockers(P<0.001) were significantly different. Meanwhile, age, gender, BMI, alcohol consumption, history of hypertension, history of diabetes, complicated with atrial arrhythmia, diastolic blood pressure, serum potassium, serum calcium, serum chlorine, white blood cell, platelet, hemoglobin, Alanine transaminase(ALT), aspartate aminotransferase (AST), BUN, creatinine(CR), HDL-C, LDL-C, Ejection fraction(EF),using ACEI or ARB, using spironolactone, using antiplatelet aggregation drugs, using statins were not of significant difference(P<0.05) **(Table 1)**.

Table 1 UnivariableCox-regression analysis on clinical data					
Feature	β	SE	Wald	HR(95% CI)	P-value
Age(years)	0.009	0.009	1.196	1.009(0.993−1.027)	0.274
Gender male				1.000	
female	-0.361	0.241	2.241	0.697(0.434−1.118)	0.134
BMI(kg/m^2)	-0.006	0.027	0.047	0.994(0.943−1.048)	0.828
Smoking	0.322	0.217	2.186	1.379(0.901−2.112)	0.139
Drinking	0.277	0.302	0.838	1.319(0.729−2.384)	0.360
Hypertension	0.039	0.219	0.032	1.04(0.667−1.597)	0.857
Diabetes	-0.002	0.233	0.000	0.998(0.632−1.576)	0.993
Atrial arrhythmia	0.098	0.220	0.197	1.102(0.717−1.696)	0.657
Ventricular arrhythmia	0.930	0.234	15.866	2.535(1.604−4.007)	<0.001
SBP(mmHg)	0.047	0.007	52.371	1.049(1.035−1.062)	<0.001
DBP(mmHg)	0.006	0.010	0.349	1.006(0.986−1.026)	0.555
HR(beats/min)	0.100	0.014	49.512	1.105(1.074−1.136)	<0.001
Serum sodium(mmol/L)	-0.061	0.016	13.994	0.941(0.911−0.971)	<0.001
Serum potassium(mmol/L)	-0.013	0.275	0.002	0.987(0.576−1.691)	0.961
Serum calcium(mmol/L)	-0.515	0.499	1.066	0.597(0.224−1.589)	0.302
Serum chlorine(mmol/L)	-0.022	0.021	1.063	0.978(0.939−1.02)	0.303
WBC(10^9/L)	0.050	0.050	0.998	1.052(0.953−1.161)	0.318
PLT(10^9/L)	-0.002	0.001	1.421	0.998(0.996−1.001)	0.233
Hemoglobin (g/L)	0.007	0.006	1.477	1.007(0.996−1.018)	0.224
AST(μg/L)	-0.001	0.003	0.095	0.999(0.992−1.006)	0.758
ALT(μg/L)	-0.002	0.002	0.848	0.998(0.993−1.003)	0.357
CR(μmol/L)	0.000	0.001	0.089	1.000(0.998−1.003)	0.766
BUN(mmol/L)	-0.002	0.002	0.834	0.998(0.994−1.002)	0.361
TC(mmol/L)	-0.009	0.064	0.019	0.991(0.875−1.123)	0.890
TG(mmol/L)	0.250	0.147	2.885	1.284(0.962−1.712)	0.089
HDL-C(mmol/L)	-0.473	0.296	2.553	0.623(0.348−1.113)	0.110
LDL-C(mmol/L)	0.096	0.120	0.640	1.101(0.87−1.393)	0.424
NT-proBNP(ng/L)	0.107	0.033	10.282	1.113(1.042−1.188)	0.001
Ejection fraction(%)	-0.019	0.014	1.785	0.981(0.954−1.009)	0.181

LVED(mm)	0.058	0.013	21.531	1.06(1.034−1.086)	<0.001
Treating by PCI or CABG	-1.107	0.256	18.713	0.33(0.2−0.546)	<0.001
Using ACEI/ARB	-0.386	0.312	1.527	0.68(0.369−1.254)	0.217
β-Blockers	-1.472	0.221	44.192	0.229(0.149−0.354)	<0.001
Spironolactone	-0.233	0.238	0.958	0.792(0.497−1.263)	0.328
Furosemide	0.406	0.220	3.422	1.501(0.976−2.309)	0.064
Antiplatelet aggregation	0.426	0.312	1.865	1.53(0.831−2.819)	0.172
Statins	0.078	0.293	0.070	1.081(0.608−1.92)	0.791

 The Univariable Cox-regression on SNPs (dominant model) in survival versus death groups revealed that rs112872667, rs3093030, rs5030377, and rs5491 were significantly different (P<0.05), whereas differences in rs12462944, rs2358581, rs281430, rs281434, rs281437, rs3093032, rs5030348, rs62130660, rs923366 were not significant (P>0.05)(Table 2).

SNP		β	SE	Wald	HR(95% CI)	P-value
Table 2 Univariable Cox-regression analysis on SNPs in the *ICAM-1* gene						
rs112872667						
Genotype	CC				1.000	
	CT	-0.661	0.256	6.658	0.516(0.312−0.853)	0.010
	TT	-0.825	1.008	0.669	0.438(0.061−3.161)	0.413
Dominant model	CC				1.000	
	CT+TT	-0.670	0.252	7.086	0.512(0.313−0.838)	0.008
rs12462944						
Genotype	GG				1.000	
	GC	-0.429	0.245	3.072	0.651(0.403−1.052)	0.080
	CC	-0.245	0.295	0.688	0.783(0.439−1.396)	0.407
Dominant model	GG				1.000	
	GC+CC	-0.370	0.224	2.735	0.691(0.445−1.071)	0.098
rs2358581						
Genotype	TT				1.000	
	TG	-0.256	0.335	0.584	0.774(0.402−1.492)	0.445
	GG	-0.139	0.332	0.175	0.87(0.454−1.668)	0.676
Dominant model	TT				1.000	
	TG+GG	-0.197	0.312	0.399	0.821(0.446−1.513)	0.528
rs281430						
Genotype	AA				1.000	

	AG	0.364	0.237	2.359	1.439(0.904−2.291)	0.125
	GG	1.134	0.407	7.755	3.109(1.399−6.907)	0.005
Dominant model	AA				1.000	
	AG+GG	0.440	0.231	3.619	1.552(0.987−2.442)	0.057
rs281434						
Genotype	AA				1.000	
	AG	0.215	0.383	0.316	1.24(0.586−2.625)	0.574
	GG	-0.094	0.399	0.055	0.911(0.417−1.989)	0.814
Dominant model	AA				1.000	
	AG+GG	0.085	0.372	0.052	1.088(0.525−2.256)	0.820
rs281437						
Genotype	CC				1.000	
	CT	0.429	0.231	3.447	1.536(0.976−2.416)	0.063
	TT	-11.972	230.987	0.003	0.000(00.0−2.613E+191)	0.959
Dominant model	CC				1.000	
	CT+TT	0.280	0.231	1.469	1.324(0.841−2.083)	0.225
rs3093030						
Genotype	CC				1.000	
	CT	-0.745	0.250	8.860	0.475(0.291−0.775)	0.003
	TT	-0.498	0.361	1.908	0.608(0.300−1.232)	0.167
Dominant model	CC				1.000	
	CT+TT	-0.681	0.224	9.229	0.506(0.326−0.785)	0.002

rs3093032						
Genotype	CC				1.000	
	CT	0.100	0.278	0.129	1.105(0.641−1.903)	0.719
	TT	-11.013	209.002	0.003	0.00(0.0−1.319E+173)	0.958
Dominant model	CC				1.000	
	CT+TT	0.008	0.278	0.001	1.008(0.585−1.737)	0.976
rs5030348						
Genotype	AA				1.000	
	AG	-0.169	0.274	0.382	0.844(0.493−1.444)	0.536
	GG	-0.066	0.300	0.048	0.936(0.52−1.687)	0.826
Dominant model	AA				1.000	
	AG+GG	-0.131	0.256	0.262	0.877(0.531−1.449)	0.609
rs5030377						
Genotype	AA				1.000	
	AG	-0.797	0.241	10.937	0.451(0.281−0.723)	0.001
	GG	-0.443	0.381	1.352	0.642(0.304−1.355)	0.245
Dominant model	AA				1.000	
	AG+GG	-0.725	0.221	10.703	0.485(0.314−0.748)	0.001
rs5491						
Genotype	AA				1.000	
	AT	0.521	0.229	5.165	1.683(1.074−2.637)	0.023
Rs62130660						

Genotype	TT				1.000	
	TG	-0.274	0.260	1.109	0.76(0.457−1.266)	0.292
	GG	1.305	0.384	11.531	3.687(1.736−7.829)	0.001
Dominant model	TT				1.000	
	TG+GG	-0.018	0.231	0.006	0.982(0.624−1.544)	0.937
rs923366						
Genotype	CC				1.000	
	CT	0.086	0.266	0.106	1.09(0.648−1.835)	0.745
	TT	-0.280	0.336	0.699	0.755(0.391−1.458)	0.403
Dominant model	CC				1.000	
	CT+TT	-0.018	0.256	0.005	0.983(0.595−1.622)	0.945

3.1 Clinical Features

Based on univariable Cox-regression on clinical features and gene polymorphism analysis, 16 features of $P<0.1$ were contained in LASSO regression analysis, and SNP variables were incorporated based on P-values obtained from the dominant model. By analyzing the 252 study participants, sixteen variables were reduced to nine variables **(Figure 3 A and B)**. Furthermore, non-zero coefficients were added to the LASSO model.

3.2 Individualized Prognostic Model Establishment

First and foremost, the prognostic model was created **(Table 3, Model 1)**. The model AIC value was determined to be 762.492, with a C-Index value of 0.8657(95%CI: 0.8278−0.8916;$P<0.001$). Following that, a simple model **(Table 3, Model2)** was created through optimizing Model 1 on the basis of the AIC value. Model 2 had an AIC value of 760.518 and a C-index value of 0.8651(95%CI: 0.8295−0.8901, $P<0.001$). Model1's AIC and C-index values were not obviously different from Model2's ($P>0.05$); thus, Model2 was deemed to be the best model. Multivariable Cox-regression on the prognostic model **(Table 3, Model 2)** revealed that rs112872667 polymorphism, PCI or CABG treatment, complication with ventricular arrhythmia, use of β-blockers, SBP, HR, Serum sodium,and LVDD were independent prognostic factors of cardiogenic death probability($P<0.05$). The rs112872667 mutation (CC to CT+TT) is a survival factor for ICM patients; ICM patients with the mutant genotype of CT or TT had a lower risk of cardiogenic death than patients with the genotype CC (HR:0.397, 95%CI: 0.237−0.663, $P<0.001$).

Table 3Parameters of the prognostic model

Variables		Model1				Model2			
		β	SE	HR(95% CI)	P	β	SE	HR(95% CI)	P
Treating by PCI or CABG		-1.258	0.324	0.284(0.150–0.537)	<0.001	-1.259	0.324	0.284 (0.150–0.536)	<0.001
Ventricular arrhythmia		0.930	0.267	2.534(1.501–4.278)	0.001	0.939	0.261	2.557 (1.533–4.266)	<0.001
β-Blockers		-0.667	0.266	0.513(0.305–0.865)	0.012	-0.663	0.264	0.516 (0.307–0.866)	0.012
rs112872667	CC			1.000				1.000	
	CT+TT	-0.881	0.38	0.415(0.197–0.872)	0.020	-0.924	0.262	0.397 (0.237–0.663)	<0.001
rs5030377	AA			1.000					
	AG+GG	-0.056	0.35	0.946(0.476–1.878)	0.873				
SBP(mmHg)		0.023	0.007	1.023(1.009–1.037)	0.001	0.023	0.007	1.023 (1.009–1.037)	0.001
HR(beats/min)		0.037	0.019	1.038(1.001–1.077)	0.047	0.038	0.018	1.039 (1.003–1.076)	0.035
Serum sodium(mmol/L)		-0.035	0.019	0.966(0.930–1.003)	0.068	-0.036	0.018	0.965 (0.931–1.000)	0.048
LEVD(mm)		0.098	0.016	1.103(1.068–1.139)	0.000	0.098	0.016	1.103 (1.068–1.139)	<0.001
AIC		762.492				760.518			
C-index (95% CI)		0.8657(0.8278–0.8916)				0.8651(0.8295–0.8901)			

The model (Model2) nomogram, including these variables, was established**(Figure 4).**

3.3 NomogramValidation

Based on the discrimination ability, ime-dependent concordance index (C-index), calibration curve, DCA, this study validated our constructed nomogram.

The constructed prognostic nomogram had a high discrimination capacity (**Figure 5 A**). The 1-year, 3-year, and 5-year AUCs were 0.912, 0.906, and 0.916, separately. Our constructed nomogram had higher accuracy in predicting ICM based on the model's time-dependent C-index and C-index developed using the bootstrap method (**Fig5 B**).

The calibration plot, created using the bootstrap method, revealed a high degree of consistency in predicted and measured probabilities (**Figure 6 A, B, and C**).

As demonstrated in DCA, using our constructed nomogram to predict cardiogenic death probability yielded a greater net benefit than the "treat none" or "treat all" strategies, demonstrating favorable nomogram clinical utility (**Figure 6 D, E, and F**).

3.4follow-up study of the patients

Using a cutoff value of total points 153.139, all patients were categorized into high- and low-risk groups(**Fig7 A**),model sensitivity was 88.58%, specificity was 81.62%, positive/negative predictive values (PPV/NPV) were 74% and 92.37%, respectively, accuracy was84.2%,and displayed survival status distribution between two risk groups(**Fig7 B**).

We developed a Kaplan-Meier survival curve in two risk groups (**Fig 8**), and the survival status was notably different in both groups (P<0.001; HR = 22.213;95%, CI:10.223−48.264).

We discovered that the rs112872667 mutation is a novel factor related with the prognosis of ICM patients. All patients were classified into two groups based on wild genotype (CC) and mutant genotype (CT+TT). Based on the KM curve and Cox regression analyses, ICM group with wild genotype CC had an increased cardiogenic mortality during follow-up compared to mutant genotype (CT or TT) (P = 0.007, HR = 0.510;95%CI:0.311−0834)(**Figure** 9).

4. Discussion

The current unicentric follow-up study developed a clinically useful new nomogram tool for predicting ICM prognosis; the variables listed below in this nomogram were identified as related factors of ICM patient prognosis: Complications with ventricular arrhythmia, high Systolic blood pressure, fast heart rate, low serum sodium, and large left ventricular end-diastolic diameter(LVDD) are risk factors of having high survival probability during the follow-up period, and mutation of rs112872667 (from CC to CT + TT), PCI or CABG, and use of β-blockers are protective factors of having high survival probability during the follow-up period.

Nomograms are extensively applied as prognostic tools in medicine today. Nomograms rely on user-friendly digital interfaces to achieve enhanced accuracy and to simplify understanding prognosis for better predicting clinical prognosis in CVDs[22, 23]. The current study first created a nomogram for predicting ICMc prognosis.

We validated this predictive nomogram using discrimination, calibration, and DCA. Based on AUC values and the time-dependent concordance index (C-index), our constructed nomogram demonstrated favorable discrimination capacity, as displayed in Fig. 5 (**A and B**). Later, the nomogram calibration curves (Fig. 6A, B, **and C**) were drawn, indicating good consistency between predicted and real values. DCA is a novel test for evaluating a nomogram[24]. According to Fig. 6(**D, E,F**), the DCA demonstrated that using this nomogram to predict the probability of cardiogenic death provides additional benefits over the "treat-none" and "treat-all" strategies, as well as good clinical utility.

We discovered a new predictor factor that can predict the prognosis of ICM and has not been reported in previous studies, which is: variation of rs112872667 in the *ICAM-1* gene correlated with ICM prognosis, mutation of

rs112872667(from CC to CT + TT) is the protective factor of ICM patients on having higher survival probability,CT + TT genotype of ICM patients have lower cardiogenic death probability than those patients with CC genotype, Cardiogenic death is 0.397-fold more likely in patients with the CT + TT genotype than in patients with the CC genotype.

Although soluble *ICAM-1* (s*ICAM-1*) level has previously been linked to ICM and atherosclerosis severity[25], inhibiting *ICAM-1* level can delay atherosclerosis development in apolipoprotein E knockout mice, the relationship of *ICAM-1* gene polymorphism with ICM patient prognosis remains unknown. Therefore, our findings are novel and will significantly impact on accurately predicting the prognosis of ICM patients.

Single nucleotide polymorphism is a type of DNA variation that occurs in an individual[26]. It is the cause of a wide range of individuals, including differences in drug response and complexity in diseases including coronary artery disease and other disorders.

The SNP may occur in the coding region and play the role of Synthetic other kind of amino acid. If the mutation occurs in the noncoding regions they may perform various functions, such as regulating the expression of various genes and proteins. Thus, understanding gene variation and its role can help us understand the mechanism of disease and the relationship between gene variation and disease, allowing us to take effective measures to prevent disease progression or treat disease.

ICAM-1 gene can be found on chromosome 19 (Chr19:10,271,120−10,286,615;15.495 kbp) (Fig. 10A), and it contains 7 exons separated by 6 introns[27], and rs112872667 SNP is found in *ICAM-1* gene(intron2) (Fig. 10B).

The rs112872667 SNP has a C allele gene and a CC wild-type gene; the allele gene C and T frequencies are 0.94890 and 0.05110 respectively globally, while they are 0.889 and 0.111 respectively in Asian populations. Mutations to CT and TT genotypes are possible in the CC genotype.

According to previous research, 50% of SNPs occur within noncoding regions[28], rs112872667 SNP is also located in noncoding regions of *ICAM-1* gene(intron2), and it shows association with the prognosis of ICM patients, but the mechanism of how rs112872667 play a role on the prognosis of ICM is unclear.

Regardless of How the mechanism is, the mutation rs112872667 is associated with the prognosis of ICM. Based on Cox regression and K-M survival analyses of 60-month follow-up data, ICM cases carrying the CC genotype had an elevated risk of cardiogenic mortality compared to cases carrying the CT + TT genotype(Fig. 9). Perhaps it influences the function of other related genes, or the mutation of rs112872667 is a marker for activating the body's self-protective system to extend survival time. This implies that the pathological mechanisms underlying this correlation should be clarified in future research.

Such findings provide a foundation for developing novel effective SNP markers in medical tests, the prediction of personalized prognosis of ICM patients, and providing safe, personalized treatment. This will provide the medical field with a new tool.

This work does, however, have some limitations. At first, the present unicentric study had a small sample size. As a result, more studies with larger sample sizes and multi-center cohorts are needed for further validation. Second, while our model underwent internal validation using the bootstrap method, its generalizability (external validity) remains unknown. Third, in addition to rs112872667, multiple variables were identified as being related factors for the prognosis of ICM patients; these variables may be confounding factors for the accurate description of the relevant degree of rs112872667 with ICM prognosis. This was the first study to establish a link between the rs112872667

polymorphism and ICM prognosis. More research is needed to control additional variables by matching those between survival and death groups and to describe the relevance degree more accurately than this.

To summarize, this study discovered that the rs112872667 polymorphism of the *ICAM-1* gene was related to the prognosis of ICM patients. The rs112872667 mutation is a protective factor for having a high survival probability of ICM. The cardiogenic death probability of patients carrying the mutant genotype(CT + TT) is 0.397-fold that of patients carrying the wild genotype(CC). namely, the wild genotype(CC)has high probablitiy of cardiogenic death during the follow-up period, thus, clinicians have to pay great attention on managing the ICM patients who carried the CC genotype by strictly controlling all of the risk factors to improve the prognosis. And we created a prognostic model that included *ICAM-1* polymorphism and clinical variabless; our model was useful in identifying high and low-risk patients on the prognosis of ICM patients, and it assisted in managing and treating ICM cases individually to improve the prognosis and reduce mortality.

Declarations

Ethics approval and consent to participate

The present work gained approval from Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University (Approval No. 2021D01D17). Informed consent was obtained from all the participants. This study was conducted in accordance to relevant guidelines and regulations.

Consent for publication

Individuals who participated into the present work provided informed consents for publishing identifiable data and images contained in the present manuscript.

Competing interests

All authors claimed that there existed no competing interest.

Author's contributions

Tuersunjiang Naman and Refukaiti Abuduhalike carried out the experiments, analyzed the data, and wrote this paper, which should be considered co-first author. Aihaidan Abudouwayiti and Juan Sun did the data collection and follow-up and did extensive literature review. Ailiman MaheMuti was responsible for the study design, revising the manuscript and streamlining the study. The above authors approved the final version for submission.

Funding

Acknowledgments

Availability of data and materials

Data supporting our results can be obtained from dbSNP at: https://www.ncbi.nlm.nih.gov/SNP/snp_viewTable.cgi?handle=LXJMU

References

1. Yang L, Wang L, Deng Y, et al. Serum lipids profiling perturbances in patients with ischemic heart disease and ischemic cardiomyopathy [J]. Lipids Health Dis, 2020, 19(1): 89.

2. Moroni F, Gertz Z, Azzalini L. Relief of Ischemia in Ischemic Cardiomyopathy [J]. Curr Cardiol Rep, 2021, 23(7): 80.

3. Divoky L, Maran A, Ramu B. Gender Differences in Ischemic Cardiomyopathy [J]. Curr Atheroscler Rep, 2018, 20(10): 50.

4. Braunwald E. The war against heart failure: the Lancet lecture [J]. The Lancet, 2015, 385(9970): 812–824.

5. Virani S S, Alonso A, Benjamin E J, et al. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association [J]. Circulation, 2020, 141(9): e139-e596.

6. Lund L H, Savarese G. Global Public Health Burden of Heart Failure [J]. Cardiac Failure Review, 2017, 03(01).

7. Roth G A, Mensah G A, Johnson C O, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: Update From the GBD 2019 Study [J]. J Am Coll Cardiol, 2020, 76(25): 2982–3021.

8. Hobby A R H, Berretta R M, Eaton D M, et al. Cortical bone stem cells modify cardiac inflammation after myocardial infarction by inducing a novel macrophage phenotype [J]. Am J Physiol Heart Circ Physiol, 2021, 321(4): H684-H701.

9. Zhao T T, Wasti B, Xu D Y, et al. Soluble epoxide hydrolase and ischemic cardiomyopathy [J]. Int J Cardiol, 2012, 155(2): 181–7.

10. Benjamin E J, Blaha M J, Chiuve S E, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association [J]. Circulation, 2017, 135(10): e146-e603.

11. Luo J Y, Ma Y T, Xie X, et al. Association of intercellular adhesion molecule1 gene polymorphism with coronary heart disease [J]. Mol Med Rep, 2014, 10(3): 1343–8.

12. Groenewegen A, Rutten F H, Mosterd A, et al. Epidemiology of heart failure [J]. Eur J Heart Fail, 2020, 22(8): 1342–1356.

13. Sekulic M, Zacharias M, Medalion B. Ischemic Cardiomyopathy and Heart Failure [J]. Circ Heart Fail, 2019, 12(6): e006006.

14. Heizhati M, Wang L, Yao X, et al. Prevalence, awareness, treatment and control of hypertension in various ethnic groups (Hui, Kazakh, Kyrgyz, Mongolian, Tajik) in Xinjiang, Northwest China [J]. Blood Press, 2020, 29(5): 276–284.

15. Al-Khatib S M, Stevenson W G, Ackerman M J, et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society [J]. J Am Coll Cardiol, 2018, 72(14): e91-e220.

16. Friedman J, Hastie T, Tibshirani R. Regularization Paths for Generalized Linear Models via Coordinate Descent [J]. Journal of statistical software, 2010, 33(1): 1–22.

17. Wang H, Zhang L, Liu Z, et al. Predicting medication nonadherence risk in a Chinese inflammatory rheumatic disease population: development and assessment of a new predictive nomogram [J]. Patient Prefer Adherence, 2018, 12: 1757–1765.

18. Kidd A C, Mcgettrick M, Tsim S, et al. Survival prediction in mesothelioma using a scalable Lasso regression model: instructions for use and initial performance using clinical predictors [J]. BMJ Open Respir Res, 2018, 5(1): e000240.

19. Harrell F E. Evaluating the yield of medical tests [J]. JAMA: The Journal of the American Medical Association, 1982, 247(18): 2543–2546.

20. Kramer A A, Zimmerman J E. Assessing the calibration of mortality benchmarks in critical care: The Hosmer-Lemeshow test revisited [J]. Crit Care Med, 2007, 35(9): 2052–6.

21. Kerr K F, Brown M D, Zhu K, et al. Assessing the Clinical Impact of Risk Prediction Models With Decision Curves: Guidance for Correct Interpretation and Appropriate Use [J]. J Clin Oncol, 2016, 34(21): 2534–40.

22. Wei L, Champman S, Li X, et al. Beliefs about medicines and non-adherence in patients with stroke, diabetes mellitus and rheumatoid arthritis: a cross-sectional study in China [J]. BMJ Open, 2017, 7(10): e017293.

23. Zhang J Y, Zhao Q, Liu F, et al. Genetic Variation of Migration Inhibitory Factor Gene rs2070766 Is Associated With Acute Coronary Syndromes in Chinese Population [J]. Front Genet, 2021, 12: 750975.

24. Mo S, Dai W, Xiang W, et al. Predictive factors of synchronous colorectal peritoneal metastases: Development of a nomogram and study of its utilities using decision curve analysis [J]. Int J Surg, 2018, 54(Pt A): 149–155.

25. Kitagawa K, Matsumoto M, Sasaki T, et al. Involvement of ICAM-1 in the progression of atherosclerosis in APOE-knockout mice [J]. Atherosclerosis, 2002, 160(2): 305–310.

26. Shastry B S. SNPs: impact on gene function and phenotype [J]. Methods Mol Biol, 2009, 578: 3–22.

27. Sun Y H, Yang S F, Liu Y F, et al. Single-Nucleotide Polymorphisms and Haplotypes of Intercellular Adhesion Molecule-1 in Uterine Cervical Carcinogenesis in Taiwanese Women [J]. Reprod Sci, 2016, 23(3): 401–8.

28. Halushka M K, Fan J B, Bentley K, et al. Patterns of single-nucleotide polymorphisms in candidate genes for blood-pressure homeostasis [J]. Nat Genet, 1999, 22(3): 239–47.
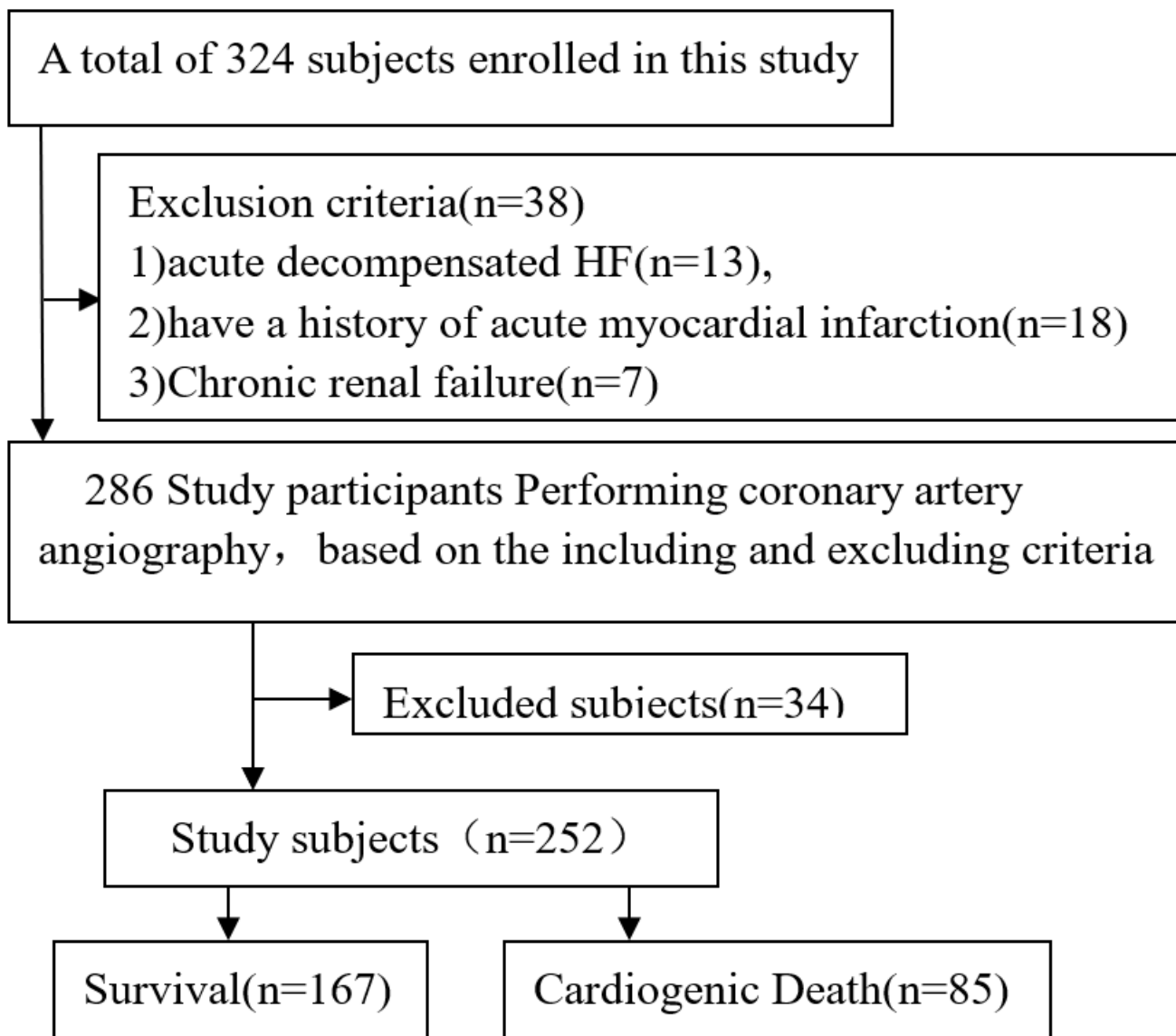
Figures

Figure 1

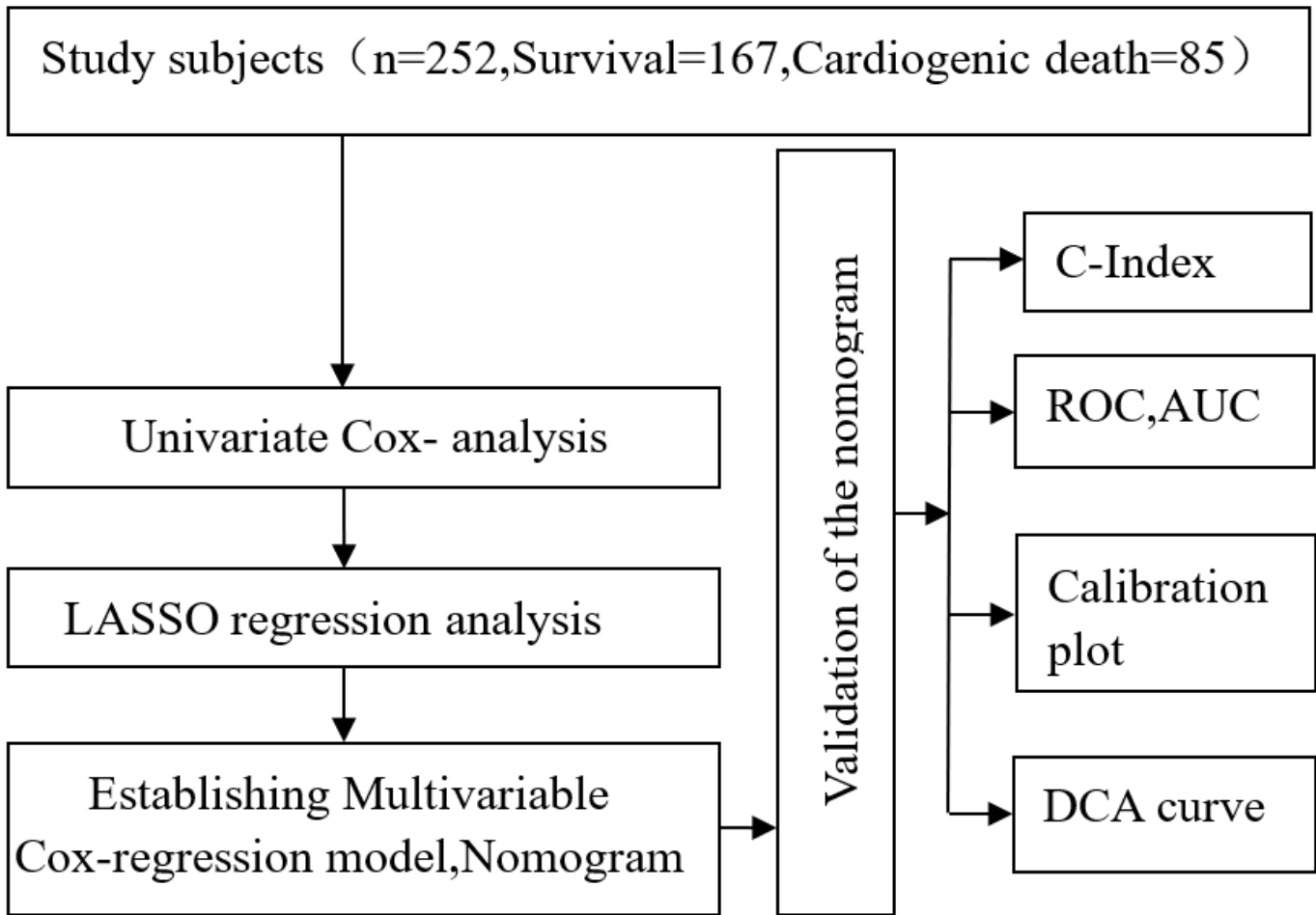Flowchart showing subject selection and grouping

Figure 2

Flowchart showing the establishment and validation of the model
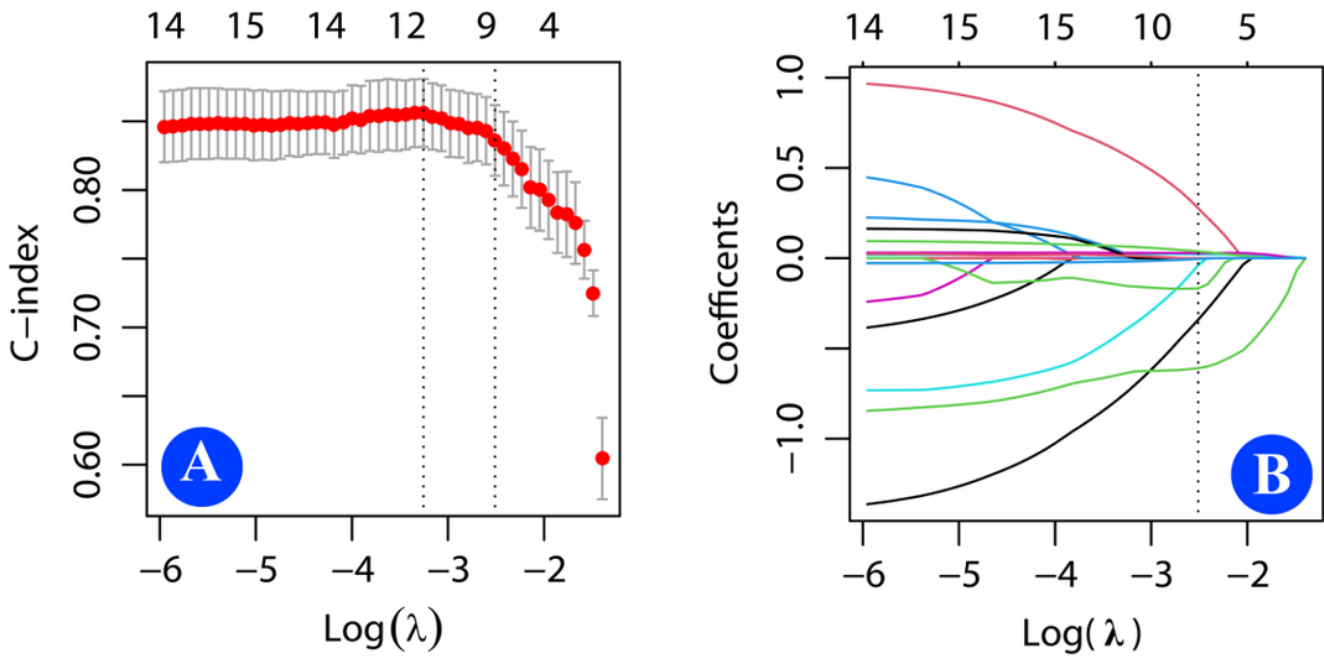
Figure 3

Selected features based on the LASSO model. (A) 10-fold cross-validation was carried utto select the tuning parameter (λ) based on the LASSO model based on the minimum criteria. A plot of the C-index as a function of log(λ). The minimum criteria were applied to draw dotted vertical lines connecting the optimal points, where the standard error of the minimum criteria is 1 (1- SE criteria). λ= 0.081 was chosen (1- SE criteria) by performing 10-fold cross-validation. (B) LASSO coefficients for these 17 selected features. A plot showing the coefficient as a function of the log(λ) sequence. The 10-fold cross-validation was performed to select the tuning parameter (λ) with the use the LASSO model, with the optimal λ eliciting the 10 non-zero coefficients.
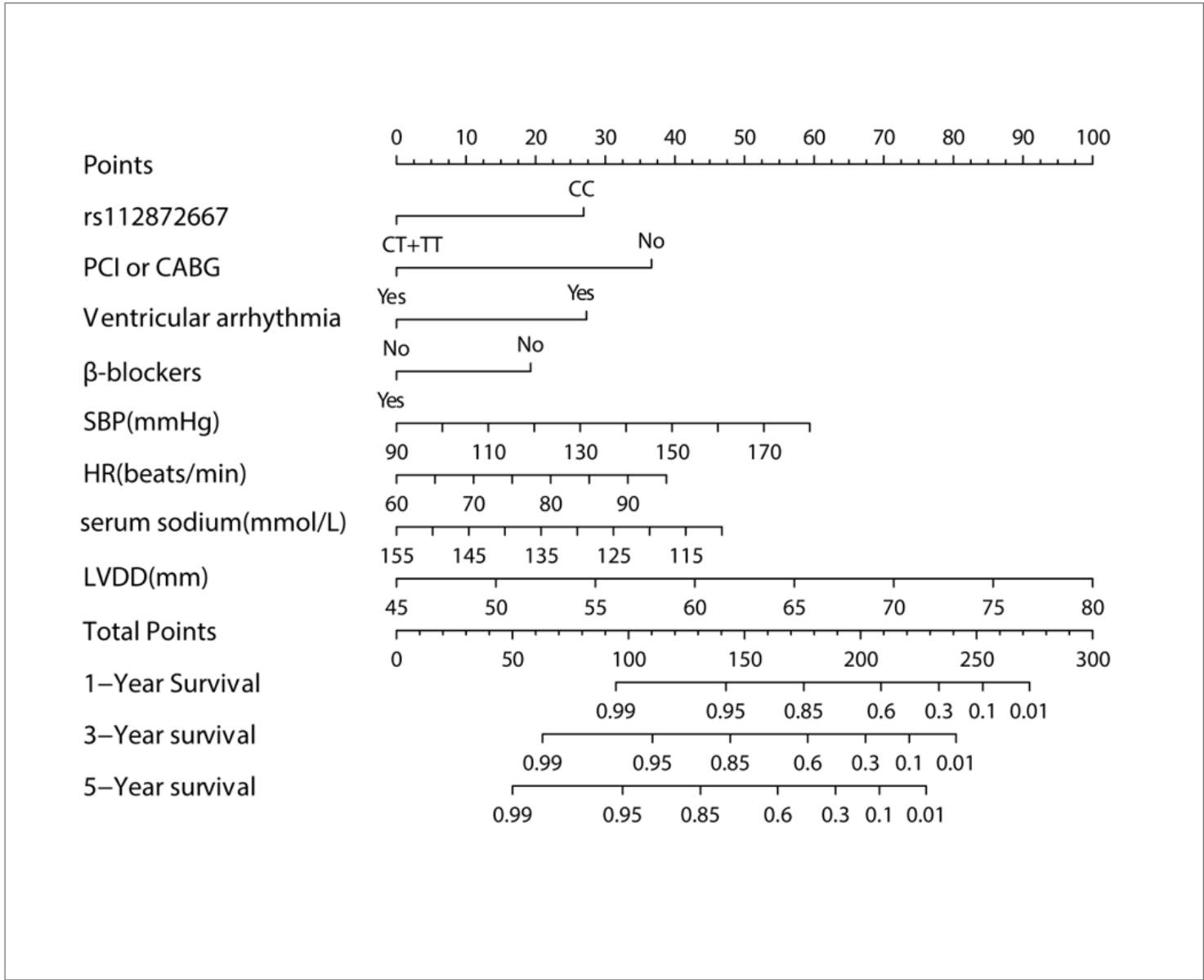
Figure 4

Nomogram for evaluation of ICM survival rate. The nomogram was constructed on the basis of genomic and clinical variables, such as polymorphism of rs112872667, treatment by PCI or CABG, complications with ventricular arrhythmias, use of β-blockers, SBP, HR, serum sodium, and LVDD.
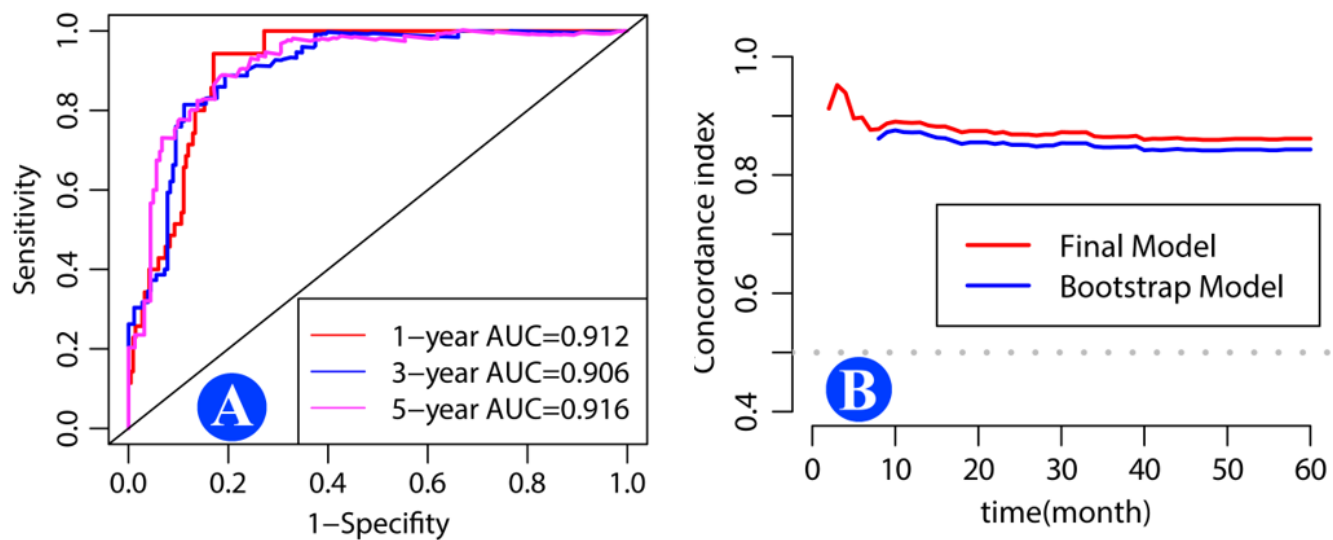
Figure 5

A: Receiver operating curve of 1-year,3-year,5-year.B:Concordance index (C-index) developed by model and bootstrap method.
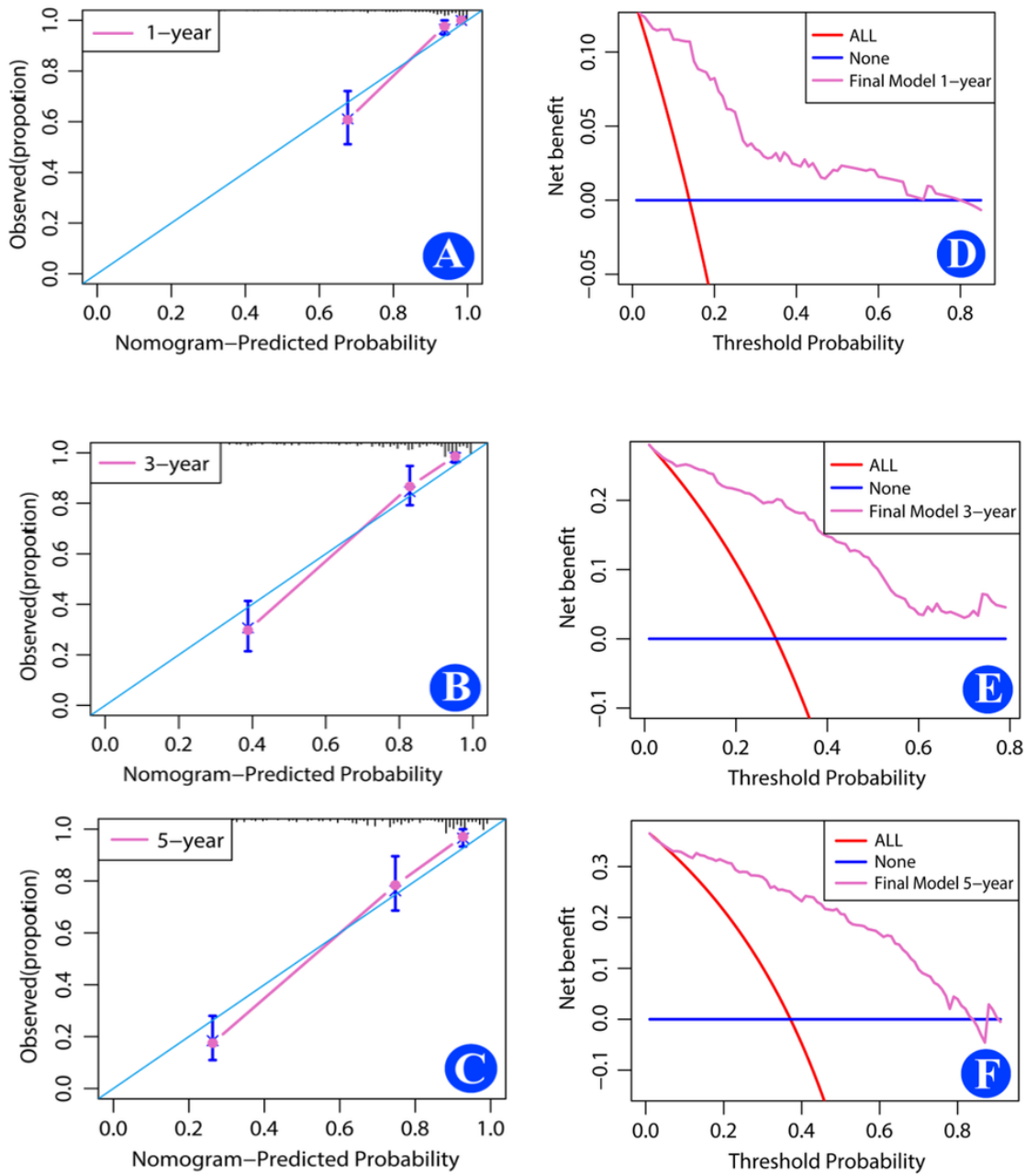
Figure 6

Calibration plot of (A: 1-, B: 3-, C: 5-year survival). DCA for nomogram(**D:** for 1-, **E:** for 3-, F: for 5-year survival). The x-axis shows the threshold probabilities, the values at which the expected benefit of treatment is equal to the "no treatment" strategy. The y-axis indicates net benefits calculated through the subtraction of false-positive rates from true-positive patient rates. Then, the risk of abandoning interventions in comparison with unneeded interventions' negative outcomes was weighed.
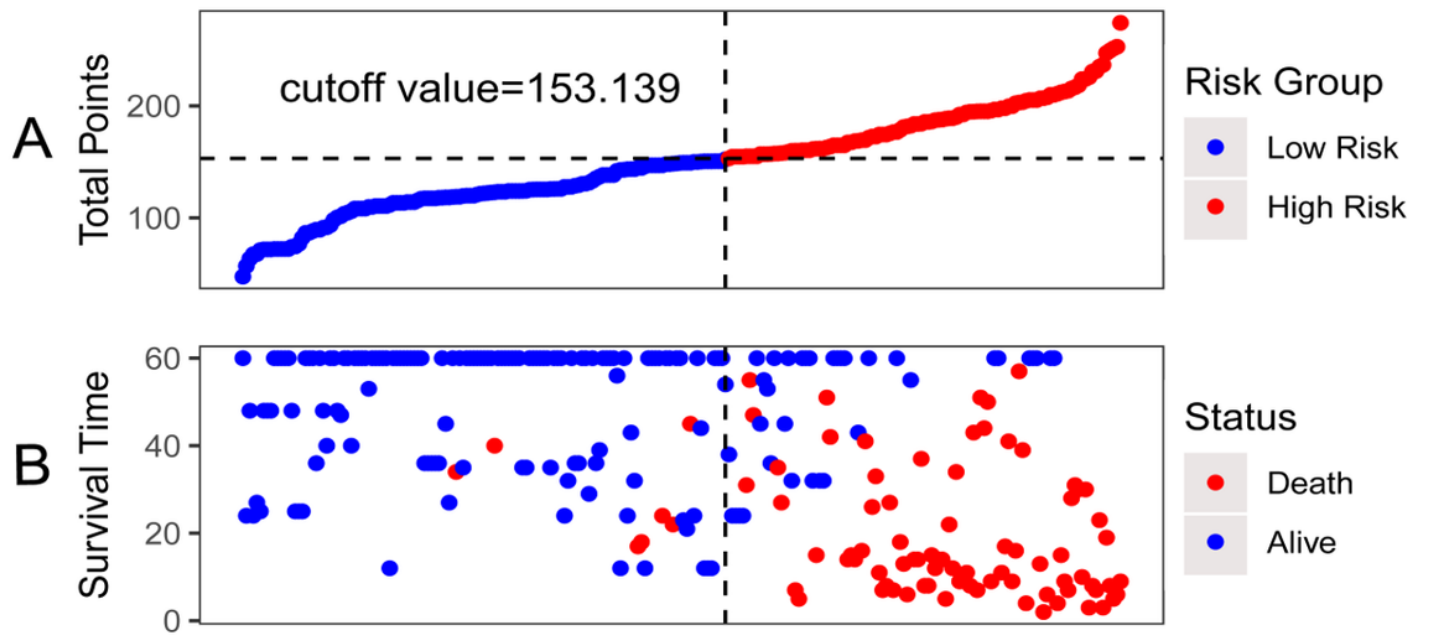
Figure 7

A:Division of two risk groups based on threshold total point. **B**:Survival status distribution between two risk groups.
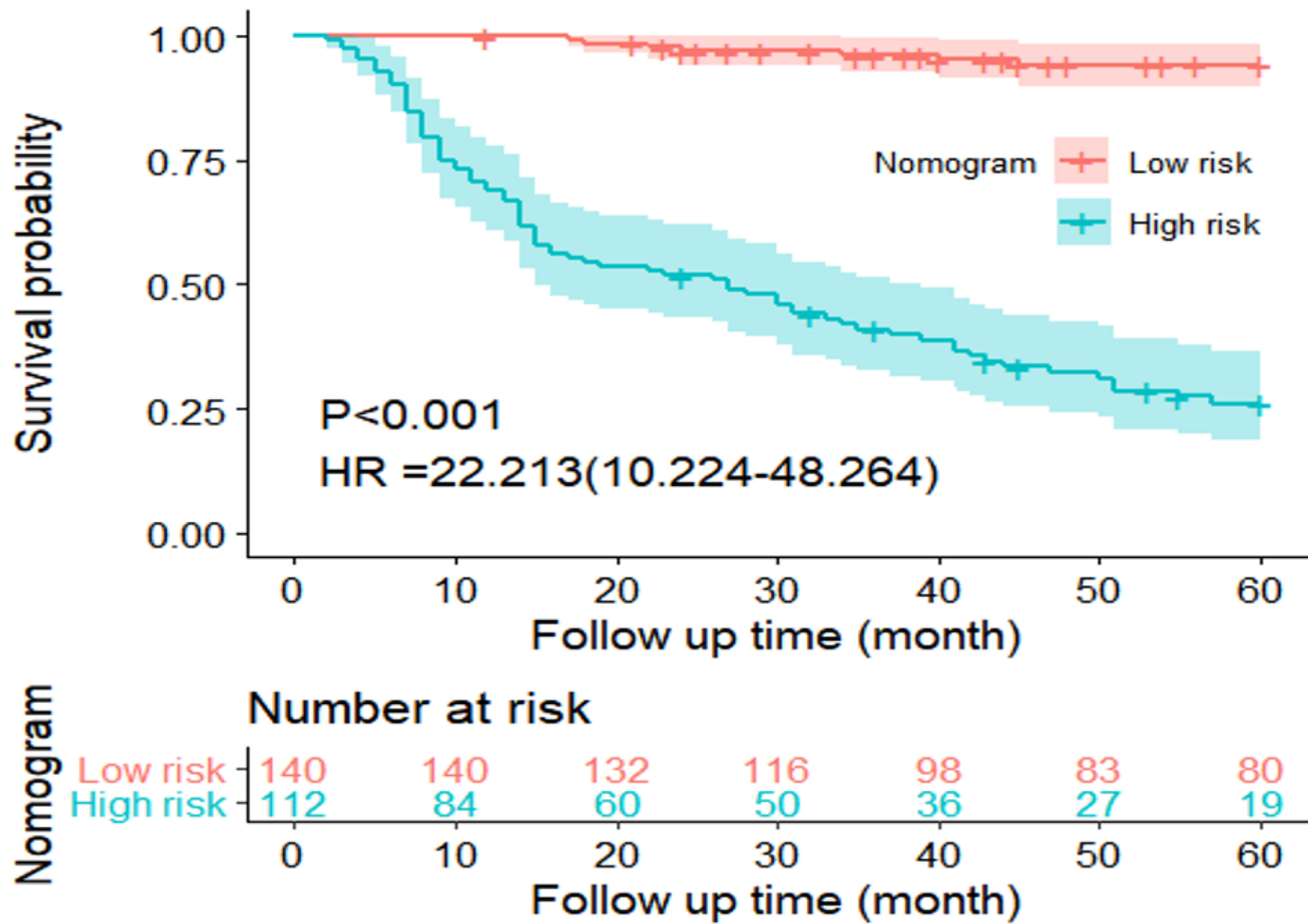
Figure 8

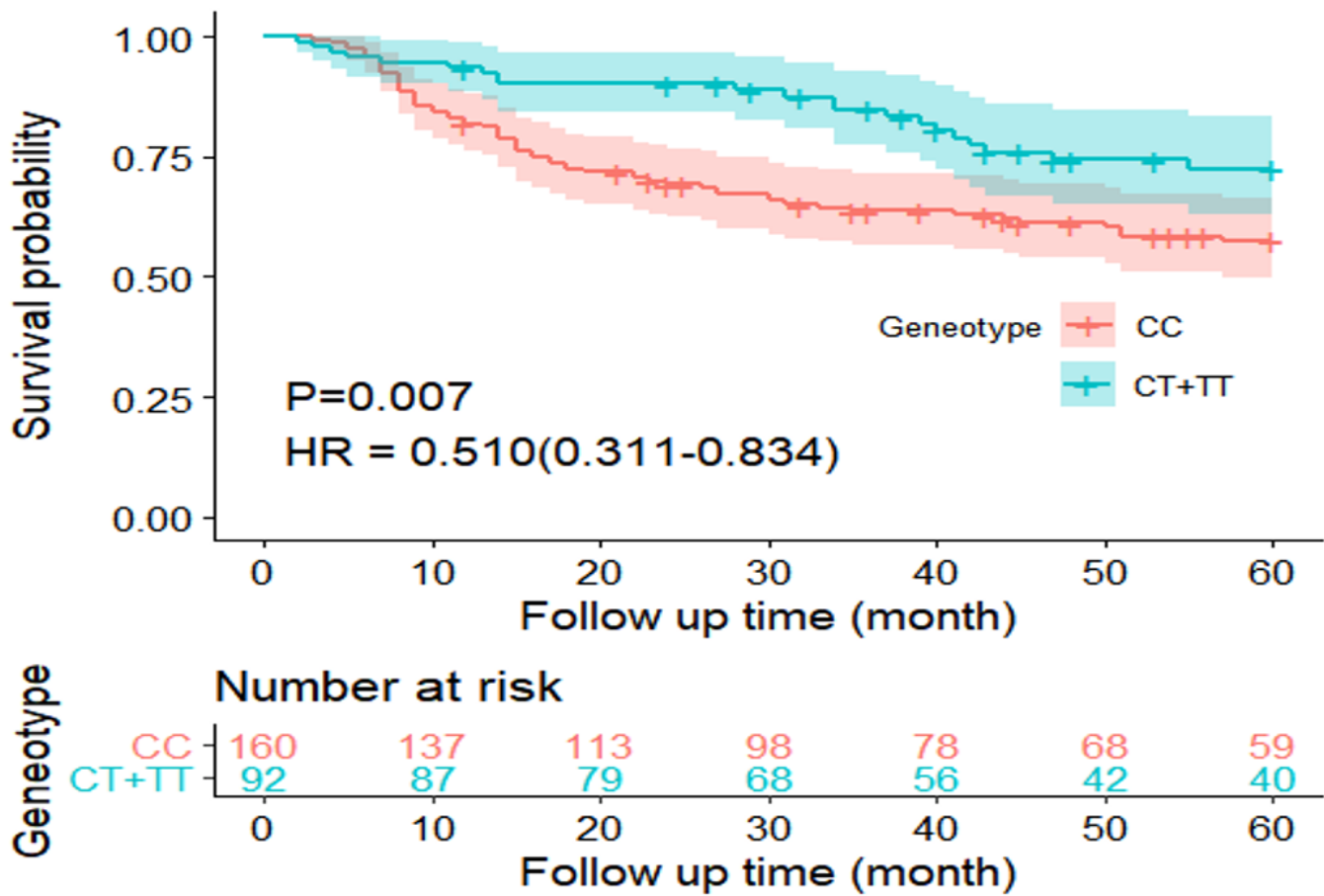Survival curve showing high- and low-risk group patients of ICM.

Figure 9

Survival curve for ICM patients ofCC and CT+TT genotypes within SNP rs112872667.