Indian Heart Journal 72 (2020) 93–100

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Original Article

Clinical characteristics and long-term prognosis of ischemic and non-ischemic cardiomyopathy

Zhi-hua Zhang [a, b], Fan-qi Meng [c], Xiao-feng Hou [a], Zhi-yong Qian [a], Yao Wang [a], Yuan-hao Qiu [a], Zhe-yu Jiang [a], An-jie Du [a], Chao-tong Qin [a], Jian-gang Zou [a, *]

[a] Department of Cardiology, The First Affiliated Hospital of Nanjing Medical University, Jiangsu, China
[b] Department of Cardiology, Jiangning Hospital Affiliated to Nanjing Medical University, Jiangsu, China
[c] Department of Cardiology, Xiamen Cardiovascular Disease Hospital, Xiamen, China

ARTICLE INFO

Article history:
Received 29 January 2020
Accepted 19 April 2020
Available online 28 April 2020

Keywords:
Chronic heart failure
Ischemic cardiomyopathy
Non-ischemic cardiomyopathy
The prognosis

ABSTRACT

Objectives: The different etiology of HF has different prognostic risk factors. Prognosis assessment of ICM and NICM has important clinical value. This study is aimed to explore the predicting factors for ICM and NICM.

Methods: 1082 HFrEF patients were retrospectively enrolled from Jan. 01, 2016 to Dec. 31, 2017. On Jan. 31, 2019, 873 patients were enrolled for analysis excluding incomplete, unfollowed, and unexplained data. The patients were divided into ischemic and non-ischemic group. The differences in clinical characteristics and long-term prognosis between the two groups were analyzed, and multivariate Cox analysis was used to predict the respective all-cause mortality, SCD and rehospitalization of CHF.

Results: 873 patients aged 64(53,73) were divided into two groups: ICM (403, 46.16%) and NICM. At the end, 203 died (111 in ICM, 54.68%), of whom 87 had SCD (53 in ICM, 60.92%) and 269 had rehospitalization for HF(134 in ICM, 49.81%). Independent risk factors affecting all-cause mortality in ICM: DM, previous hospitalization of HF, age, eGFR, LVEF; for SCD: PVB, eGFR, Hb, revascularization; for readmission of HF: low T3 syndrome, PVB, DM, previous hospitalization of HF, eGFR. Otherwise; factors affecting all-cause mortality in NICM: NYHA III-IV, paroxysmal AF/AFL, previous hospitalization of HF, β-blocker; for SCD: low T3 syndrome, PVB, nitrates, sodium, β-blocker; for rehospitalization of HF: paroxysmal AF/AFL, previous admission of HF, LVEF.

Conclusions: Both all-cause mortality and SCD in ICM is higher than that in NICM. Different etiologies of CHF have different risk factors affecting the prognosis.

1. Introduction

Chronic heart failure (CHF) is still a problem affecting public health in China and even the world. Epidemiological investigation shows that the prevalence of CHF is about 2% in the world, and the morbidity is still 1/100 per year in people over 65 years old.[1] With the progress of medical technology, the survival of CHF has been improved, but the 5-year livability is still only around 50%,[2,3] and the mortality and rehospitalization are still high.[4] The prevalence of adult HF is about 0.9%[5] in China according to the sample survey in 2003, and the overall incidence is increasing year by year.[6] The majority of deadly patients with heart failure died of malignant ventricular arrhythmia caused by the sudden cardiac death (SCD), the rest died of pump failure.[7] At present, some European studies have found that different etiology of heart failure has different prognosis.[8] Among the heart failure with reduced ejection fraction (HFrEF) patients, about 30%–40% of the patients are non-ischemic,[9] and data from BREATHE indicates that 70% of hospitalized patients are also non-ischemic.[10]

Given the above reasons, it is urgent to identify risk factors associated with the high mortality of HF, thus helping us to further closely monitor and cure these factors. At present, several risk models affecting the prognosis of heart failure have emerged.[11–17] However, in clinical practice, they all have their own limitations. Some models need get peak oxygen consumption (PVO2) during hospitalization, some require electrophysiology study (EPS), and

* *Corresponding author.* Department of Cardiology, the First Affiliated Hospital, Nanjing Medical University, 300 Guangzhou Road, Nanjing, 210029, China. Fax: +00862568136479.
E-mail address: jgzou@njmu.edu.cn (J.-g. Zou).

https://doi.org/10.1016/j.ihj.2020.04.004

others use any invasive examination. Moreover, most of these models failed to incorporate the treatment targets supported by the existing evidence-based medical theories, such as angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blocker (ARB), beta-blockers, and mineralocorticoid receptor antagonist (MRA). At the same time, the derivation of these models was not respectively modeled for the different etiology.

At present, the status of domestic treatment and long-term prognosis are still unclear. In our study, CHF was classified into ischemic cardiomyopathy (ICM) and non-ischemic cardiomyopathy (NICM). We aim to reveal the current treatment status of heart failure in China and the prognosis of different etiology.

2. Methods

1082 patients with HFrEF were enrolled from three level A of the tertiary hospital (the first affiliated hospital of nanjing medical university, xiamen university affiliated hospital of cardiovascular disease, huai'an first people's hospital) from Jan. 1, 2016 to Dec. 31, 2017. All of them were from cardiology department, 411 cases were from nanjing, 531 cases were from xiamen, and the rest were from huai'an.

2.1. Inclusion criteria

To participate in this study, patients must comply with all of the following.

1. Diagnosis of heart failure with reduced EF according to the 2016 European Society of Cardiology (ESC) HF guideline.[18]
2. LVEF < 50% (measured by Simpson's method) after optimised medication including ACEI or ARB, beta-blocker and MRA if available and not contraindicated at least 3 months.

2.2. Exclusion criteria

Hypertrophic cardiomyopathy;
Rheumatic valvular disease;
Congenital heart disease;
Pulmonary heart disease;
Various types of pericardial diseases;
Acute myocardial infarction within the last 3 months, including ST-segment elevated myocardial infarction (STEMI) and NSTEMI;
Aortic dissection;
Leukemia, lymphoma, aplastic anemia and other serious blood diseases; Autoimmune diseases;
Malignant tumors;
Hormone replacement therapy;
Whether the patient is participating in other interventional clinical trials;
Pregnancy;
Patients who have received cardiac resynchronization therapy with or without implantable cardioverter-defibrillator (CRT-P/D) or ICD, surgical ventricular aneurysm resection, left ventricular reconstruction, heart transplantation or other non-pharmacological treatment to improve cardiac function;
Criteria for the diagnosis of ICM[19]:

1. Previous history of myocardial infarction;
2. Coronary angiography (CAG) confirmed proximal stenosis of left main or left anterior descending (LAD) ≥75%;
3. CAG confirmed that the stenosis of two or more major coronary arteries was ≥75%;
4. History of coronary artery bypass grafting (CABG) or percutaneous transluminal coronary intervention (PCI) for the above three reasons;

Criteria for NICM: meet at least one of the following 1–2 criteria:

1. Failure to meet the diagnostic criteria for ICM;
2. Coronary dual-source CT examination or myocardial nuclide imaging (ECT) examination excluded coronary heart disease (CHD);

2.3. Data collection

Each patient had a profile that included relevant baseline materials, such as Age, Sex, Smoking, Drinking, Blood pressure, Heart rate, NYHA classification, Etiology of heart failure, History of CHF hospitalization; History of syncope; History of sudden death/cardio-pulmonary resuscitation(SCD/CPR); Hypertension; Diabetes mellitus(DM); Chronic obstructive pulmonary disease (COPD);

Auxiliary examination:

(1) Electrocardiogram: LVEF; Left atrial diameter (LAd); Left ventricular diastolic-end diameter (LVDd);
(2) Holter: Left branch bundle block (LBBB); Right branch bundle block (RBBB); QRS duration; Paroxysmalatrial fibrillation or atrial flutter (AF/AFL); PersistentAF/AFL; Frequent premature ventricular beats (PVB); Non-sustained ventricular tachycardia (NSVT);
(3) Laboratory examination: hemoglobin (Hb, unit: g/l); Serum creatine (Scr, unit: mmol/l); Urea nitrogen (BUN, unit: mmol/l); Subclinical hypothyroidism; Low T3 syndrome; Serum sodium (Na+, unit: mmol/l);
(5) Medical treatment: Diuretics; MRA; ACEI/ARB; Beta-blockers; Digoxin. Antiplatelet agents; Anticoagulants; Nitrates; Statins; Calcium antagonist (CCB); Antiarrhythmia drugs
(6) Device implantation and other novel therapy: pacemaker; ICD; CRT/D; Heart transplantation.

2.4. Follow-up and study endpoints

The follow-up visits were conducted on an outpatient basis every 3 months. We got the following information through three ways: regular outpatient visits, telephone visits and family inquiries.

Primary outcome is all-cause mortality and SCD; Secondary endpoint is rehospitalization due to HF. SCD is that occurs within 1 hour of the onset of acute symptoms and is characterized by SCD from cardiac causes or the patient's previous history of no more than cardiac disease occurred within 24 h from the last time he was seen.[20]

2.5. Statistical analysis

All data were performed with a statistical analysis software package (SPSS 21.0 IBM SPSS Inc. Chicago, Illinois, USA). Continuous variables do not conform to the normal distribution by *K–S* test, so they are expressed as median and quartile, and compared by *Non-parametric* test. Categorical variables were expressed as absolute numbers and percentages and analyzed by *Chi-square* tests. Cox regression analysis was used to evaluate the independent

predictors of study outcomes. All variables with a $P < 0.05$ in univariate analysis were entered into a multivariate backwards stepwise regression analysis. Hazard ratios (HR) and 95% confidence intervals (CI) across etiology categories were also estimated in separate group. The *K-M* curve was used with the log-rank test to test for survival differences between groups. $P < 0.05$ was statistically significant.

3. Result

3.1. Clinical features

Among the 1082 HFrEF patients, 123 were of unknown etiology, the remaining was 429 in ICM and 530 in NICM. Detailed baseline characteristics of the population are summarized in Table 1. During the follow-up, 75 patients received non-drug intervention measures within 3 months, 11 was completely lost, and 873 patients were actually enrolled. Among of them, 403 (46.16%) in ICM and 470 (53.84%) in NICM group. The attempt was made to determine the nature of death in every case. 675(77.32%) males, 682(78.12%) NYHAIII-IV, mean LVEF 34(28,40)%, with an average age of 64(53,73) (range:15~92) were actually included in the study.

We can see that the two groups in age, smoking, COPD, hypertension, DM, vital signs (blood pressure, heart rate), AF/AFL, PVB, LBBB, RBBB, NSVT, Scr, Hb, thyroid function and related ultrasonic parameters all have statistical differences ($P< 0.05$); the rest indicators have no medical significance.

3.2. Prognosis of heart failure with different etiology

A total of 873 patients with systolic heart failure were enrolled, 425 were from xiamen cardiovascular hospital, 328 were enrolled in jiangsu provincial people's hospital, and 120 were from huai'an first people's hospital. By the end of follow-up on January 31, 2019, a total of 203(23.25%, ICM 111, NICM 92) patients died, including 87(9.97%, ICM 53, NICM 34) were SCD and 269(30.81%, ICM 134, NICM 135) were rehospitalized for HF. In the two different modes of death, all-cause death and SCD, ICM was higher than NICM($P < 0.05$, see Fig. 1).

3.3. Treatment of patients with different etiology of ICM and NICM

As can be seen from the figure, ACEI/ARB, anticoagulant drug dabigatran and heart transplantation showed no significant difference between the two groups, and the remaining drug treatments such as Diuretics; MRA; Beta-blockers; Digoxin; Warfarin; Nitrates; Statins; CCB and Antiarrhythmia drugs were significantly different($P< 0.05$). Throughout the follow-up, 7 patients with completely lost follow-up were excluded in ICM, leaving 422 patients, 3(0.7%) patients with heart transplantation; 14(3.3%) with CRT/CRTD; 8(1.9%) with other non-drug treatments such as valve replacement, ICD, pacemaker, CABG, RFCA, left ventricular

Table 1
Clinical characteristics in patients with CHF.

Variables	Unclear etiology group(n = 123)	etiology groups		*P*	*P'*
		ICM (n = 429)	NICM (n = 530)		
Age (years)	70(53,78)	69(61,77)	60(48,68)	0.004	0.000
Male gender, n (%)	74(60.2)	344(80.2)	401(75.7)	0.000	0.055
Medical history, n (%)					
Smoking	56(45.5)	228(53.1)	244(46.0)	0.445	0.032
Alcohol abuse	47(38.2)	220(51.3)	275(51.9)	0.005	0.897
COPD	9(7.3)	45(10.5)	30(5.7)	1.000	0.007
Hypertension	60(48.8)	263(61.3)	207(39.1)	1.000	0.000
DM	32(26.0)	162(37.8)	78(14.7)	0.444	0.000
Previous HF hospitalization	54(43.9)	226(52.7)	291(54.9)	0.044	0.515
Syncope	6(4.9)	17(4.0)	16(3.0)	0.437	0.478
SCD/PCR	2(1.6)	8(1.9)	3(0.6)	0.652	0.072
CAG + CTCA	6(4.9)	372(86.7)	316(59.6)	0.000	0.000
Vital signs on admission					
SBP (mmHg)	130(116,145)	130(117,145)	121(109,137)	0.051	0.000
DBP (mmHg)	82(72,93)	77(68,86)	80(70,89)	0.006	0.010
HR (bpm)	89(75,101)	80(70,91)	86(73,100)	0.007	0.000
NYHA III-IV	113(91.9)	325(75.8)	422(79.6)	0.000	0.159
Holter, n (%)					
AF/AFL	39(31.7)	79(18.4)	178(33.6)	0.282	0.000
PVB	41(33.3)	107(24.9)	190(35.8)	0.606	0.000
NSVT	33(26.8)	104(24.2)	210(39.6)	0.218	0.000
LBBB	14(11.4)	49(11.4)	85(16.0)	0.488	0.049
RBBB	12(9.8)	35(8.2)	22(4.2)	0.115	0.013
QRS duration (ms)	110(86,140)	110(91,132)	115(99,130)	0.347	0.114
Echocardiography data					
LVEF (%)	32(27,38)	37(31,42)	31(26,37)	0.038	0.000
LVEF≤35%(%)	44(9.9)	187(33.5)	371(66.5)	0.207	0.000
LAd (mm)	46(42,50)	42(39,46)	45(41,50)	0.004	0.000
LVDd (mm)	64(59,68)	60(56,66)	67(62,73)	0.810	0.000
Laboratory data					
BUN (mmol/l)	7.18(5.84,9.75)	7.01(5.56,8.93)	6.92(5.57,8.75)	0.177	0.608
Scr (umol/l)	95.90(76.65,122.92)	94.40(77.00,119.20)	89.80(75.10,107.65)	0.160	0.002
Na+ (mmol/l)	140.22(137.29,142.00)	140.02(137.73,141.91)	140.10(137.98,142.48)	0.673	0.131
Hb(g/l)	137(119,153)	131(118,142)	139(129,150)	0.705	0.000
Subclinical hypothyroidism	4(3.3)	8(1.9)	8(1.5)	0.201	0.013
Low T3 syndrome	8(6.5)	33(7.7)	26(4.9)	0.201	0.013

P indicates unclear etiology group vs. etiology group; *P'* indicates ICM vs. NICM. < 0.05 has significance.

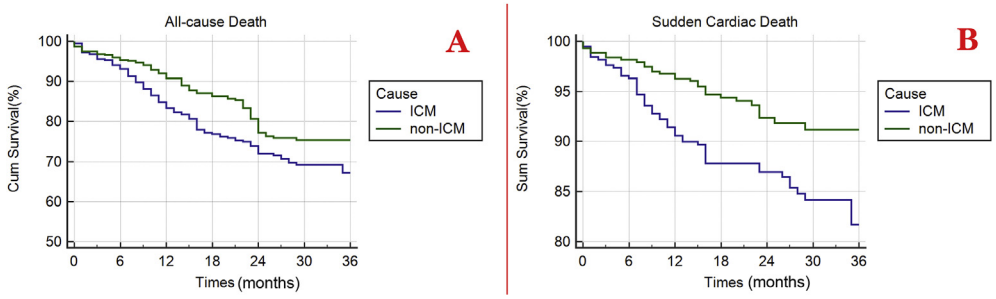

Fig. 1. Kaplan–Meier curves for the probability of all-cause mortality and SCD in patients with CHF-REF according to etiology. Patients of ICM were more susceptible to all-cause mortality and SCD compared those with NICM. Log-rank test, $P<0.001$. *Abbreviations:* ICM, ischemic cardiomyopathy; NICM, non-ischemic cardiomyopathy.

shunt and ventricular aneurysm resection. In NICM, excluding 4 patients with lost follow-up, the remaining 526 patients, 5(1%) patients with heart transplantation; 51(9.7%) with CRT/CRTD; 10(1.9%) other non-drug treatments. Meanwhile, DCM of whom is 483(91.8%), the other cause for the rest patients is high alcoholic cardiomyopathy; arrhythmia cardiomyopathy; Hypertensive cardiomyopathy; anemic cardiomyopathy; hyperthyroidism cardiomyopathy, etc. Based on a small number of these cases, we are temporarily unable to further analysis the prognosis. Because the etiology is clear, they can be through rectifying causes such as correction of anemia, hyperthyroidism, stop drinking, control of blood pressure and heart rate, further improving its prognosis. Existed research has shown that in patients with alcoholic cardiomyopathy after six months of absence from alcohol, can make the heart cavity narrow, cardiac function improved significantly. (see Fig. 2)

3.4. Independent predictors of all-cause mortality of heart failure with different etiology

Significant predictors for all-cause mortality, combining LVEF, people-accepted commonly predictive variable on prognosis of CHF, were all entered into multivariate regression analysis, the results showed sorting by strength as follows: In ICM, DM, previous HF hospitalization, age, eGFR, LVEF; In NICM, NYHA class III-IV, paroxysmal AF/AFL, isosorbide mononitrate, previous HF hospitalization, beta-blockers; As shown in Table 2.

3.5. Independent predictors of SCD in CHF with different etiology

In our study, we find that in ICM, heart rate, NYHA class III-IV, frequent PVB, revascularization, LVEF, eGFR, Hb, digoxin were statistical significance in single-variable analysis, after a multi-factor regression PVB and renal insufficiency will increase the incidence of SCD, and revascularization and Hb can reduce the occurrence of SCD. In NICM, low T3 syndrome increased the risk of SCD by more than three times, and PVB and nitrates increased two times. However, beta-blockers and Na^+ reduced the risk of SCD($P < 0.05$). Results are shown in Table 3.

3.6. Independent predictors of heart failure rehospitalization in ICM and NICM

Independent predictors of rehospitalization due to HF with different etiology were also different. In ICM group, independent risk factors for heart failure rehospitalization: low T3 syndrome, frequent PVB, DM, Previous HF hospitalization, eGFR. Meanwhile, In NICM patients, Independent risk factors that affect heart failure rehospitalization: paroxysmal AF/AFL, previous hospitalization of HF, LVEF. The results are shown in Table 4.

3.7. Independent predictors of all-cause mortality and SCD

Using the same method, according to the strength role of predictors for all-cause mortality in order, our results show: NYHA class III-IV (HR = 2.154), low T3 syndrome (HR = 1.842), previous

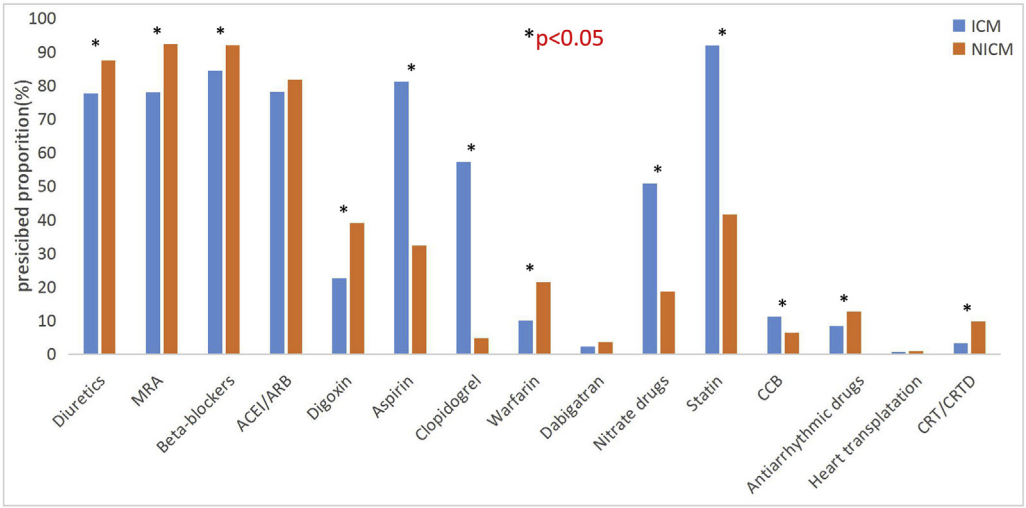

Fig. 2. Treatment of patients with different etiology of NICM and ICM: Note that the significant differences at discharge drug therapies between the two groups.

Table 2
Predictors of all-cause mortality across etiology categories-results of separate COX analysis.

ICM					NICM				
Variables	Univariable	*P*	Multivariable	*P*	Variables	Univariable	*P*	Multivariable	*P*
	HR(95%CI)		HR (95%CI)			HR (95%CI)		HR (95%CI)	
Age (years)	1.039 (1.019−1.059)	<0.0001	1.036 (1.014−1.059)	0.001	Age (years)	1.024 (1.010−1.040)	0.001		
Advanced NYHA class III-IV	2.931 (1.610−5.335)	<0.0001			SBP (mmHg)	0.989 (0.979−0.998)	0.020		
Previous HF hospitalization	1.803 (1.227−2.648)	0.003	1.664 (1.120−2.473)	0.012	Advanced NYHA class III-IV	4.593 (1.864−11.316)	0.001	2.603 (0.999−6.782)	0.05
Revascularization	0.596 (0.410−0.866)	0.007			Previous HF hospitalization	3.115 (1.896−5.118)	<0.0001	1.834 (1.010−3.329)	0.046
Diabetes mellitus	1.474 (1.015−2.139)	0.041	1.776 (1.180−2.673)	0.006	Af/AFL				
LVEF	0.977 (0.953−1.002)	0.070	0.968 (0.944−0.993)	0.014	Paroxysmal	3.314 (1.763−6.227)	<0.0001	2.124 (1.000−4.509)	0.05
eGFR	0.983 (0.976−0.989)	<0.0001	0.987 (0.979−0.994)	0.001	Persistent	1.467 (0.927−2.319)	0.101		
Na^+ (mmol/l)	0.952 (0.910−0.995)	0.030			Frequent PVB	1.583 (1.029−2.433)	0.036		
Hemoglobin (g/l)	0.990 (0.981−0.999)	0.024			Non-sustained VT	1.655 (1.090−2.512)	0.018		
Low T3 syndrome	2.093 (1.141−3.841)	0.017			Hypertension	0.619 (0.394−0.973)	0.038		
Diuretics	1.951 (1.131−3.365)	0.016			COPD	2.808 (1.491−5.286)	0.001		
Beta-blocker	0.619 (0.396−0.966)	0.035			LVEF	0.990 (0.963−1.018)	0.469		
ACEI/ARB	0.605 (0.407−0.900)	0.013			eGFR	0.989 (0.982−0.996)	0.002		
					Hemoglobin (g/l)	0.986 (0.976−0.996)	0.005		
					Low T3 syndrome	3.737 (1.912−7.303)	<0.0001		
					Beta-blocker	0.300 (0.179−0.503)	<0.0001	0.395 (0.195−0.799)	0.01
					ACEI/ARB	0.438 (0.271−0.707)	0.001		
					Digoxin	1.658 (1.096−2.508)	0.017		
					Isosorbide mononitrate	1.930 (1.222−3.049)	0.005	1.872 (1.109−3.162)	0.019

Note: the MDRD formula calculated eGFR = 186*(Scr)-1.154*(age)-0.203*(0.742 female). eGFR was the estimated glomerular filtration rate. Scr was serum creatinine in mg/dl. Age is measured in years.

Table 3
Predictors of sudden cardiac death across etiology categories-results of separate COX analysis.

ICM					NICM				
Variables	Univariable	P	Multivariable	P	Variables	Univariable	P	Multivariable	P
	HR(95%CI)		HR (95%CI)			HR (95%CI)		HR(95%CI)	
Heart rate (bpm)	1.019 (1.004−1.034)	0.015			DBP (mmHg)	0.973 (0.949−0.998)	0.033		
Advanced NYHA class III-IV	5.635 (1.756−18.087)	0.004			Previous HF hospitalization	3.678 (1.502−9.005)	0.004		
Revascularization	0.473 (0.277−0.806)	0.006	0.515 (0.293−0.907)	0.021	Af/AFL				
Frequent PVB	2.180 (1.246−3.815)	0.006	2.023 (1.131−3.616)	0.017	paroxysmal	5.063 (1.992−12.866)	0.001		
LVEF	0.962 (0.929−0.997)	0.032			persistent	1.092 (0.453−2.634)	0.844		
eGFR (ml/min)	0.983 (0.973−0.992)	<0.0001	0.989 (0.978−1.000)	0.047	Frequent PVB	2.955 (1.441−6.058)	0.003	2.694 (1.034−7.017)	0.043
Hemoglobin (g/l)	0.985 (0.972−0.997)	0.016	0.987 (0.974−1.000)	0.048	Non-sustained VT	3.340 (1.609−6.935)	0.001		
Digoxin	2.114 (1.170−3.821)	0.013			LVEF	0.961 (0.915−1.010)	0.119		
					eGFR(ml/min)	0.978 (0.965−0.991)	0.001		
					Na+	0.873 (0.806−0.944)	0.001	0.874 (0.783−0.974)	0.015
					Low T3 syndrome	5.577 (2.100−14.809)	0.001	3.541 (1.105−11.349)	0.033
					β-blockers	0.291 (0.119−0.713)	0.007	0.347 (0.122−0.982)	0.046
					COPD	3.117 (1.086−8.950)	0.035		
					Isosorbide mononitrate	2.694 (1.282−5.662)	0.009	2.381 (1.066−5.321)	0.034

Table 4
Predictors of rehospitalization due to HF across etiology categories-results of separate COX analysis.

ICM					NICM				
Variables	Univariable	P	Multivariable	P	Variables	Univariable	P	Multivariable	P
	HR (95%CI)		HR (95%CI)			HR (95%CI)		HR (95%CI)	
Previous HF hospitalization	1.561 (1.105–2.207)	0.012	1.477 (1.032–2.114)	0.033	SBP (mmHg)	0.992 (0.984–1.000)	0.047		
Af/AFL					Previous HF hospitalization	1.747 (1.200–2.545)	0.004	1.484 (1.000–2.202)	0.050
paroxysmal	1.953 (1.046–3.644)	0.036			Af/AFL				
persistent	1.581 (1.003–2.492)	0.048			paroxysmal	1.894 (1.030–3.481)	0.040	1.956 (1.023–3.739)	0.042
Frequent PVB	1.670 (1.143–2.442)	0.008	1.618 (1.098–2.384)	0.015	persistent	1.065 (0.718–1.580)	0.755		
Diabetes mellitus	1.611 (1.136–2.284)	0.007	1.615 (1.128–2.314)	0.009	Frequent PVB	1.550 (1.071–2.245)	0.020		
LVEF	0.983 (0.962–1.005)	0.126			Non-sustained VT	1.648 (1.152–2.357)	0.006		
eGFR	0.986 (0.980–0.992)	<0.0001	0.989 (0.983–0.996)	0.001	LVEF	0.971 (0.948–0.994)	0.015	0.973 (0.947–0.999)	0.040
Low T3 syndrome	2.450 (1.369–4.384)	0.003	2.051 (1.125–3.740)	0.019	LBBB	1.563 (1.015–2.406)	0.043		
Digoxin	1.526 (1.039–2.242)	0.031			eGFR	0.991 (0.985–0.997)	0.004		
Aspirin	0.660 (0.439–0.993)	0.046			Na+ (mmol/l)	0.951 (0.912–0.990)	0.016		
Statin	0.446(0.270–0.734)	0.002			ACEI/ARB	0.598 (0.386–0.927)	0.021		
					Isosorbide mononitrate	1.517 (1.012–2.275)	0.044		
					QRS duration (ms)	1.007 (1.002–1.013)	0.006		

hospitalization history of heart failure (HR = 1.771), DM (HR = 1.556), frequent PVB (HR = 1.406), age (HR = 1.020), eGFR (HR = 0.988), beta-blockers (HR = 0.623) are shown in Supplement Table 1. Independent risk factors for SCD: frequent PVB (HR = 2.103), nitrates (HR = 1.851), DM (HR = 1.801), eGFR (HR = 0.990), and LVEF (HR = 0.967) were shown in Supplement Table 2.

3.8. Independent predictors of heart failure rehospitalization

The same way was used to analyze risk factors affecting heart failure rehospitalization, the order is as follows: Dabigatran (HR = 2.127), low T3 syndrome (HR = 2.081), subclinical hypothyroidism (HR = 1.572), frequent PVB (HR = 1.480), previous hospitalization history of HF (HR = 1.414), eGFR (HR = 0.993), and LVEF (HR = 0.983), as shown in Supplement Table 3.

4. Discussion

Our study was a multicenter, retrospective, observational clinical study involving nearly 900 inpatients. According to our clinical experience, we collected risk variables that may affect the prognosis of HF, including drug therapy and the variables in previous models, to explore the predictive factors for all-cause death, SCD, and rehospitalization of CHF. Compared with previous research models,[21–23] our study has the following characteristics: first, the selected patients were all from Asian, including all NYHA grades and ages HFrEF patients, which truly represented the “real world” in China; Secondly, we enrolled more than 40 risk variables, and even further refined factors to better understand the critical cutoff; Thirdly, all variables included were non-invasive and easy to obtain data in clinical practice. In addition, drug treatments were all from the discharge medication of inpatients after stable condition, so it was less disturbed by the other medical institutions. Finally, our research explored the prognosis of different etiology of heart failure.

Our study showed that ICM group were older than NICM and had more risk factors for atherosclerosis, such as smoking, COPD, hypertension and DM. On the other hand, NICM patients showed faster heart rate, AF/AFL, NSVT, LBBB and PVB in Holter. Compared with ICM, diameter of each cardiac cavity was higher in echocardiography, accompanied by lower LVEF and SBP at admission in NICM. In laboratory examination, eGFR, low T3 syndrome and Hb all had statistical significances ($P < 0.05$).

In terms of drug therapy, patients with CHF all received standardized therapy, 768 (80.1%) of which received ACEI/ARB, 851 (88.7%) received beta-blockers and 823 (85.8%) administrated MRA. In NICM, diuretics, MRA, beta-blockers, digoxin and warfarin account for a larger proportion than ICM, respectively, 87.4%, 92.3%, 92.3%, 39.1% and 21.5%. All the drugs mentioned above had significant differences in medical statistics between groups. Considering the following factors: with larger cardiac cavity, lower EF and more AF/AFL patient in NICM, water and sodium storage were severe, so diuretics and MRA were used frequently. Moreover, the usage rate of controlling the HR and anticoagulant was also higher. We also found that ICM was higher in the comparison of all-cause mortality and SCD. The prognostic factors of HF were different between two groups.

Age, NYHA III-IV, previous HF hospitalization history, paroxysmal AF/AFL, DM, and renal function index (BUN, eGFR) were candidate variables in previous prognostic models of heart failure.[21–30] Our results showed that all these variables could increase the risk for all-cause mortality(HR>1), which was consistent with the previous models. At the same time, we found that the paroxysmal AF/AFL can increase the risk for all-cause

mortality(HR = 2.063), but not for persistent, the phenomenon was considered connecting with unstable cardiac electrical activity. In paroxysmal AF/AFL patients, heart rhythm was shifted between the sinus rhythm and AF/AFL, easily induced atrial thrombosis embolism occurs even in death. Existing study[31] have found that about 13%–30% of patients with heart failure who have no previous thyroid disease will show low T3, normal T4 and TSH levels, which we call "low T3 syndrome". This study suggested that low T3 syndrome is associated with worsening cardiac function, myocardial remodeling, and cardiovascular outcomes. This was also demonstrated in our study, low T3 syndrome was shown to increase the risk of all-cause death and heart failure rehospitalization (HR = 1.842 vs. 2.081), consistent with previous study.[32]

In previous studies,[33,34] LVEF reduction was considered to be the major risk factor for all-cause mortality and SCD, and European guidelines also considered LVEF≤35% as the main indication for ICD/CRT-D implantation for primary prevention of heart failure.[35] Although the patients with LVEF≤35% is currently considered to be an important risk factor for predicting SCD, we also found in other study[34] that LVEF >35% also had a higher incidence of SCD. In our study, it showed that LVEF had no predictive value for all-cause mortality in the total population of heart failure, but showed positive results in the occurrence of SCD and rehospitalization due to HF. Subsequently, we further refined the LVEF, namely ≤35% and >35%, and obtained the same result as that without stratification through regression analysis. According to the classification of etiology, COX regression analysis was respectively conducted for the corresponding study endpoints, and the results showed that LVEF had the probability of increasing the risk of all-cause mortality in ICM, but in readmission for heart failure in NICM.

In the study, we also found that complete or partial revascularization was predictive of SCD in ICM(HR = 0.515), which could reduce the risk of SCD. This variable is relatively rare in previous research models. Our study included it and showed that it has independent predictive value. It was considered to be related to the opening of coronary vessels to increase myocardial oxygen supply. Previous study have found that ICM patients have a high incidence of SCD,[36] revascularization can save more dying myocardium and reduce scar formation, thereby reducing the occurrence of SCD.

Another positive research variable is the nitrate drugs, we found that it can make all-cause mortality and SCD in NICM significantly increased (HR = 1.872 vs. 2.381). However, the prediction value is not reflected in ICM, and the mechanism is still unclear, but it provided a basis for us to weigh the advantages and disadvantages and make further decisions when using the drug in future.

Consistent with previous studies, renal function is also an important predictor of mortality.[37–40] We used eGFR, corrected for age and gender, more objective, to replace creatinine level. The results showed that renal deterioration significantly increased the risk of all-cause mortality, SCD, and heart failure rehospitalization for ICM (0.987, 0.989, 0.989).

Age is another important risk variable associated with study outcome, and previous studies[15,16,41,42] have reported that advanced age is an important risk predictor in patients with HFrEF. We also concluded that the risk of all-cause mortality increases with the advanced age in ICM group.

DM is also associated with the prognosis of CHF. Previous studies have found that patients with HFrEF associated with DM have poor prognosis,[25,43,44] especially in the patients with a high proportion of ICM. Our research also revealed a significant increase in ICM in all-cause mortality and rehospitalization due to HF with diabetes (HR = 1.776 vs. 1.615), which may be associated with diabetes-related complications.

Among the ECG-related indicators, QRS duration showed positive results in single-variable COX analysis of study endpoints in NICM, but the prediction value disappeared after multi-variable regression. In the study of DEFINITE,[45] it was also concluded that the QRS duration had no correlation with the total mortality in NICM. Meanwhile, the study manifested QRS morphology such as LBBB or RBBB has significant differences between the two groups. LBBB is higher and RBBB is lower in NICM compared with ICM. Besides, further analysis concluded it has no impact on MACE outcomes. In addition, Brembilla[46] also found no association between bundle branch block and the occurrence of SCD in patients with heart failure, which is consistent with our results.

5. Conclusions

Both all-cause mortality and SCD in ICM group is higher than that in NICM group. Different etiology of heart failure has different risk factors affecting the prognosis.

6. Limitations

The research also has the following limitations. First, the sample size of the study was small and the follow-up time was short (873 patients were followed up for 22 months in the middle stage); Secondly, some other important indicators, such as BMI, troponin T, and late gadolinium enhancement(LGE) technique in cardiac nuclear magnetic resonance, are missing to assess the degree of myocardial fibrosis; Third, the study was limited to Asia, exactly, China; Fourthly, risk stratification and modeling of positive predictors were not carried out; Fifth, HF is limited to patient with reduced left ventricular ejection fraction, and further research is needed on EF retention. Finally, since a large part of our follow-up was obtained through telephone interviews and family inquiries, there was no doubt at the end-point of all-cause mortality, but there may be difference in the judgment of SCD and rehospitalization of heart failure.

Funding support

This study was sponsored partly by the grant of clinical frontier technology from Jiangsu Science and Technology Agency (BE2016764).

Conflicts of interest

There is no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2020.04.004.

References

1. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. *Heart*. 2007;93(9):1137–1146.
2. Writing Group M, Mozaffarian D, Benjamin EJ, et al. Executive summary: heart disease and stroke statistics–2016 update: a report from the American heart association. *Circulation*. 2016;133(4):447–454.
3. Roger VL, Weston SA, Redfield MM, et al. Trends in heart failure incidence and survival in a community-based population. *Jama*. 2004;292(3):344–350.
4. Sakata Y, Shimokawa H. Epidemiology of heart failure in Asia. *Circ J : official journal of the Japanese Circulation Society*. 2013;77(9):2209–2217.
5. Jiang H, Ge J. Epidemiology and clinical management of cardiomyopathies and heart failure in China. *Heart*. 2009;95(21):1727–1731.
6. Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. *Nat Rev Cardiol*. 2011;8(1):30–41.
7. Ye S, Grunnert M, Thune JJ, et al. Circumstances and outcomes of sudden unexpected death in patients with high-risk myocardial infarction: implications for prevention. *Circulation*. 2011;123(23):2674–2680.

8. Pecini R, Moller DV, Torp-Pedersen C, Hassager C, Kober L. Heart failure etiology impacts survival of patients with heart failure. *Int J Cardiol*. 2011;149(2):211–215.
9. Douglas LMM. *Heart Failure: A Companion to Braunwald's Heart Disease*. 3 ed. Philadelphia: Saunders; 2011.
10. investigators B. Rationale and design: BREATHE registry–I Brazilian registry of heart failure. *Arq Bras Cardiol*. 2013;100(5):390–394.
11. Aaronson KD, Schwartz JS, Chen TM, Wong KL, Goin JE, Mancini DM. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. *Circulation*. 1997;95(12):2660–2667.
12. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. *Jama*. 2003;290(19):2581–2587.
13. Fonarow GC, Adams Jr KF, Abraham WT, et al. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. *Jama*. 2005;293(5):572–580.
14. Varadarajan P, Pai RG. Prognosis of congestive heart failure in patients with normal versus reduced ejection fractions: results from a cohort of 2,258 hospitalized patients. *J Card Fail*. 2003;9(2):107–112.
15. Brophy JM, Dagenais GR, McSherry F, Williford W, Yusuf S. A multivariate model for predicting mortality in patients with heart failure and systolic dysfunction. *Am J Med*. 2004;116(5):300–304.
16. Kearney MT, Nolan J, Lee AJ, et al. A prognostic index to predict long-term mortality in patients with mild to moderate chronic heart failure stabilised on angiotensin converting enzyme inhibitors. *Eur J Heart Fail*. 2003;5(4):489–497.
17. Bouvy ML, Heerdink ER, Leufkens HG, Hoes AW. Predicting mortality in patients with heart failure: a pragmatic approach. *Heart*. 2003;89(6):605–609.
18. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37(27):2129–2200.
19. Felker GM, Shaw LK, O'Connor CM. A standardized definition of ischemic cardiomyopathy for use in clinical research. *J Am Coll Cardiol*. 2002;39(2):210–218.
20. European Heart Rhythm A, Heart Rhythm S, Zipes DP, et al. ACC/AHA/ESC 2006 guidelines 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 and the European society of cardiology committee for practice guidelines (writing committee to develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death). *J Am Coll Cardiol*. 2006;48(5):e247–e346.
21. Senni M, Parrella P, De Maria R, et al. Predicting heart failure outcome from cardiac and comorbid conditions: the 3C-HF score. *Int J Cardiol*. 2013;163(2):206–211.
22. Barlera S, Tavazzi L, Franzosi MG, et al. Predictors of mortality in 6975 patients with chronic heart failure in the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico-Heart Failure trial: proposal for a nomogram. *Circ Heart Fail*. 2013;6(1):31–39.
23. Agostoni P, Corra U, Cattadori G, et al. Metabolic exercise test data combined with cardiac and kidney indexes, the MECKI score: a multiparametric approach to heart failure prognosis. *Int J Cardiol*. 2013;167(6):2710–2718.
24. 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.
25. Pocock SJ, Wang D, Pfeffer MA, et al. Predictors of mortality and morbidity in patients with chronic heart failure. *Eur Heart J*. 2006;27(1):65–75.
26. Komajda M, Carson PE, Hetzel S, et al. Factors associated with outcome in heart failure with preserved ejection fraction: findings from the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE). *Circ Heart Fail*. 2011;4(1):27–35.
27. Vazquez R, Bayes-Genis A, Cygankiewicz I, et al. The MUSIC Risk score: a simple method for predicting mortality in ambulatory patients with chronic heart failure. *Eur Heart J*. 2009;30(9):1088–1096.
28. Collier TJ, Pocock SJ, McMurray JJ, et al. The impact of eplerenone at different levels of risk in patients with systolic heart failure and mild symptoms: insight from a novel risk score for prognosis derived from the EMPHASIS-HF trial. *Eur Heart J*. 2013;34(36):2823–2829.
29. O'Connor CM, Whellan DJ, Wojdyla D, et al. Factors related to morbidity and mortality in patients with chronic heart failure with systolic dysfunction: the HF-ACTION predictive risk score model. *Circ Heart Fail*. 2012;5(1):63–71.
30. Senni M, Santilli G, Parrella P, et al. A novel prognostic index to determine the impact of cardiac conditions and co-morbidities on one-year outcome in patients with heart failure. *Am J Cardiol*. 2006;98(8):1076–1082.
31. Iervasi G, Pingitore A, Landi P, et al. Low-T3 syndrome: a strong prognostic predictor of death in patients with heart disease. *Circulation*. 2003;107(5):708–713.
32. Ning N, Gao D, Triggiani V, et al. Prognostic role of hypothyroidism in heart failure: a meta-analysis. *Medicine*. 2015;94(30):e1159.
33. Koutalas E, Kanoupakis E, Vardas P. Sudden cardiac death in non-ischemic dilated cardiomyopathy: a critical appraisal of existing and potential risk stratification tools. *Int J Cardiol*. 2013;167(2):335–341.
34. Goldberger JJ, Cain ME, Hohnloser SH, et al. American heart association/american college of cardiology foundation/heart rhythm society scientific statement on noninvasive risk stratification techniques for identifying patients at risk for sudden cardiac death: a scientific statement from the American heart association council on clinical cardiology committee on electrocardiography and arrhythmias and council on epidemiology and prevention. *Heart Rhythm*. 2008;5(10):e1–e21.
35. Russo AM, Stainback RF, Bailey SR, et al. ACCF/HRS/AHA/ASE/HFSA/SCAI/SCCT/SCMR 2013 appropriate use criteria for implantable cardioverter-defibrillators and cardiac resynchronization therapy: a report of the American college of cardiology foundation appropriate use criteria task force, heart rhythm society, American heart association, American society of echocardiography, heart failure society of America, society for cardiovascular angiography and interventions, society of cardiovascular computed tomography, and society for cardiovascular magnetic resonance. *J Am Coll Cardiol*. 2013;61(12):1318–1368.
36. Frazier CG, Alexander KP, Newby LK, et al. Associations of gender and etiology with outcomes in heart failure with systolic dysfunction: a pooled analysis of 5 randomized control trials. *J Am Coll Cardiol*. 2007;49(13):1450–1458.
37. Klein L, Massie BM, Leimberger JD, et al. Admission or changes in renal function during hospitalization for worsening heart failure predict postdischarge survival: results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF). *Circ Heart Fail*. 2008;1(1):25–33.
38. Cowie MR, Komajda M, Murray-Thomas T, Underwood J, Ticho B, Investigators P. Prevalence and impact of worsening renal function in patients hospitalized with decompensated heart failure: results of the prospective outcomes study in heart failure (POSH). *Eur Heart J*. 2006;27(10):1216–1222.
39. Pfister R, Diedrichs H, Schiedermair A, et al. Prognostic impact of NT-proBNP and renal function in comparison to contemporary multi-marker risk scores in heart failure patients. *Eur J Heart Fail*. 2008;10(3):315–320.
40. Krumholz HM, Chen YT, Vaccarino V, et al. Correlates and impact on outcomes of worsening renal function in patients > or =65 years of age with heart failure. *Am J Cardiol*. 2000;85(9):1110–1113.
41. Eichhorn EJ. Prognosis determination in heart failure. *Am J Med*. 2001;110(Suppl 7A):14S–36S.
42. Rich MW, McSherry F, Williford WO, Yusuf S, Digitalis Investigation G. Effect of age on mortality, hospitalizations and response to digoxin in patients with heart failure: the DIG study. *J Am Coll Cardiol*. 2001;38(3):806–813.
43. Domanski M, Krause-Steinrauf H, Deedwania P, et al. The effect of diabetes on outcomes of patients with advanced heart failure in the BEST trial. *J Am Coll Cardiol*. 2003;42(5):914–922.
44. Das SR, Drazner MH, Yancy CW, Stevenson LW, Gersh BJ, Dries DL. Effects of diabetes mellitus and ischemic heart disease on the progression from asymptomatic left ventricular dysfunction to symptomatic heart failure: a retrospective analysis from the Studies of Left Ventricular Dysfunction (SOLVD) Prevention trial. *Am Heart J*. 2004;148(5):883–888.
45. Kadish A, Dyer A, Daubert JP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med*. 2004;350(21):2151–2158.
46. Brembilla-Perrot B, Alla F, Suty-Selton C, et al. Nonischemic dilated cardiomyopathy: results of noninvasive and invasive evaluation in 310 patients and clinical significance of bundle branch block. *Pacing Clin Electrophysiol : PACE (Pacing Clin Electrophysiol)*. 2008;31(11):1383–1390.