Relationship Between Diabetes Mellitus and the Prognosis of Ischemic Heart Failure

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Research

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Abstract

Background: Ischemic heart failure (IHF) is an important type of heart failure (HF). The aim of this study is to analyze the clinical features of IHF, investigate the prognostic value of clinical risk factors, especially DM-related factors, on the IHF patients, so as to provide reference for the high-quality health management of IHF patients.

Methods: A total of 430 IHF patients were divided into comorbid (IHF+ DM) group or IHF group according to whether they had DM in this cross sectional and prospective study. The patients were collected for their clinical information, and were followed up for 3.3 years to record the composite clinical endpoints including all-cause death, stroke, myocardial infarction and decompensated heart failure. The prognostic value of DM-related and other traditional risk factors with IHF were evaluated.

Results: Among 430 patients with IHF, 176 had DM. Compared with the IHF group, the IHF + DM group had higher prevalence of hypertension and overweight, higher levels of FPG and HbA1c, higher proportion of patients in NYHA III – IV grade, larger left ventricular end diastolic diameter (LVEDD) in male group, higher Gensini score and shorter distance of 6-minute walk test (6-MWT). After a median follow-up of 3.3 years, a total of 156 patients (36.3%) had experienced clinical endpoint events. Kaplan Meier analysis showed that the IHF patients with DM history, and higher HbA1c or FPG level would significantly reduce the cumulative survival rates of composite clinical endpoints, as well as the cumulative survival rates of all-cause death and cardiovascular death (all $P < 0.05$). Cox regression analysis indicated that DM history and higher PFG or HbA1c levels were independently associated with the all-cause death, cardiovascular death, and composite endpoints (all $P < 0.05$). The incorporation of diabetes related factors (diabetes history, FPG and HbA1c) significantly increased the area under the receiver operating characteristic (ROC) curve of the risk model established by the traditional risk factors (0.803 vs. 0.775, $P= 0.039$). In addition to DM history, male sex, uric acid ≥ 400 μmol / L, creatinine ≥ 100 μmol / L, Gensini score > 80 and ACEF score were all independent risk factors for the occurrence of composite clinical endpoints in IHF patients.

Conclusion: There existed a high incidence rate of DM in the IHF population. The diabetes related factors (diabetes history, FPG, HbA1c) significantly increased the predictive value of the risk model made by the basic risk factors in predicting the IHF outcomes. DM history, male, uric acid ≥ 400 μmol / L, creatinine ≥ 100 μmol / L, Gensini score > 80 and ACEF score were independent risk factors for the occurrence of composite clinical endpoints in IHF patients.

Background

Heart failure (HF) has become a major worldwide epidemic of cardiovascular disease nowadays [1]. Coronary heart disease (CHD) is one of the most important pathogenic factors of heart failure. The extensive damage of cardiomyocytes and the diffuse lesion of large myocardium caused by myocardial ischemia of CHD eventually lead to the remodeling of cardiac structure and the weakening of the cardiac function, which is precisely the definition of ischemic heart failure (IHF). IHF, characterized by severe coronary artery disease, decreased left ventricular ejection fraction (LVEF) and cardiac enlargement, is distinguished from general HF by its higher mortality rate, greater risk of cardiovascular death and lower long-term survival rate [1].

In the meanwhile, more and more people are suffering from diabetes mellitus (DM). The latest data showed that there had been more than 450 million DM patients worldwide in 2019[2]. DM would cause serious complications in heart, brain, kidney, blood vessels, nerves and so on, which would increase the risk of death directly or indirectly. Cardiovascular disease such as HF, CHD and peripheral arterial disease (PAD) are the most common complications

of DM. DM is not simply a risk factor, it will cause significant heterogeneity in the incidence risk of cardiovascular disease[3].

The incidence and recurrence rate of HF were high in DM population, and in turn, a large proportion of HF people were combined with DM[4-7]. However, the effect of diabetes to the clinical outcome of IHF patients has been rarely considered, and the management of the IHF-DM patients is also challenging[8]. Understanding the clinical features and carrying out individualized intervention and treatment according to the risk factors that leads to poor prognosis may be good for the cardiac function, living quality and long life of the IHF population. Therefore, the aim of this study is to analyze the clinical features of IHF, investigate the prognostic value of risk factors on the IHF people, so as to provide reference for the high-quality health management of IHF patients.

Methods

Inclusion and exclusion criteria

IHF patients diagnosed by the Department of cardiovascular of the first medical center of the PLA General Hospital from February 2016 to January 2018 were continuously selected. Inclusion criteria: 1) patients had experienced myocardial infarction or revascularization, or whose stenosis degrees determined by coronary angiography of left main coronary artery or proximal left anterior descending artery or two or three coronary vessels were ≥ 75%; 2) patients had symptoms and signs of HF, and were in New York Heart Association (NYHA) grade II - IV; 3) patients with enlarged heart and with the left ventricular ejection fraction (LVEF) ≤ 40%. Exclusion criteria: 1) patients with HF caused by malignant hypertension, primary cardiomyopathy and complications of CHD (like ventricular septal perforation, papillary muscle dysfunction, etc.), 2) patients with severe heart valve disease, severe arrhythmia, severe hyperthyroidism, end-stage renal failure, advanced cancer or other serious systemic diseases; 3) heart transplant patients or left ventricular assist device recipients; 4) patients without complete data or contact information.

Study population

Firstly, we obtained the baseline information about the sociodemographic and clinical data of 475 IHF patients face-to-face or through the outpatient and inpatient electronic case information system, or conducted questionnaire surveys if necessary. Secondly, we made sure that the severity of coronary artery stenosis of the enrollments had been assessed by coronary angiography, that all had been diagnosed with HF by outpatient or resident physicians and were in NYHA grade II – IV, and that all selected patients' LVEF, left ventricular end diastolic diameter (LVEDD) and other parameters were measured by experienced ultrasound physicians in the PLA General Hospital through PHILPs ie33 color Doppler ultrasound diagnostic instrument, so as to determine whether they had cardiac enlargement or other organic heart diseases. Third and most importantly, we recorded the phone numbers and established a good patient-doctor relationship. Out of the 475 IHF patients, 449 patients met the above inclusion criteria, including 1 patient with heart transplantation, 7 patients with dilated cardiomyopathy, 3 patients with end-stage renal failure, 4 patients with advanced malignant tumors, 3 patients with severe arrhythmia and 1 patient with left ventricular assist device. So finally, 430 IHF patients were included in our study. The informed consent of each patient was obtained and the study was approved by the ethics committee of the PLA General Hospital.

Baseline data collection

We collected the following case information: 1) gender, age, weight, height, education, residence, and other sociodemographic information; 2) systolic blood pressure, diastolic blood pressure and other physiological indexes; 3) history of hypertension, diabetes, hyperlipidemia, stroke, peripheral arterial disease and atrial fibrillation; 4) CHD-related information, NYHA cardiac function grade, 6-minute walk test (6-MWT) results, the left ventricular ejection fraction (LVEF) and LVEDD measured by echocardiography; 5) levels of fasting plasma glucose (FPG), glycosylated hemoglobin A1c (HbA1c), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), hemoglobin, total cholesterol (TC), triglyceride(TG), uric acid (UA), creatinine, the amino terminal pro brain natriuretic peptide (NT-proBNP) and so on. The value of FPG was the average of the 1-3 fasting FPG values that could be obtained. The values of LVEF were determined with the simplified biplane Simpson method. The levels of FPG, HbA1c, HDL-C, LDL-C, TC, TG, UA and creatinine were measured by Corot cobasc501 automatic biochemical analyzer, and the NT-proBNP by Corot Elecsys 2010 automatic electrochemiluminescence immunoanalyzer.

Follow-up method and study endpoints

By April 2020, three experienced doctors and medical students had followed up the enrollments every six months to one year by consulting outpatient, emergency and readmission electronic medical records or by telephone interview. The adverse endpoint events during the follow-up period were recorded in detail. Survival time: the duration from enrollment to death or to the time when other non-death clinical endpoint events occur. If one patient experienced both non-death end events and death events, the survival time was recorded as the duration from one's enrollment to when the death event occurred. Those who were lost to follow-up were treated as deleted cases.

All-cause death and adverse cardiovascular and cerebrovascular events, including cardiovascular death, ischemic or hemorrhagic stroke, nonfatal myocardial infarction and decompensation of heart failure (readmission for heart failure or atrial fibrillation with a rapid ventricular rate) were considered as clinical endpoints. And cardiovascular death was defined as death caused by cardiac diseases such as myocardial infarction. Stroke was defined as neurological dysfunction caused by cerebral ischemia lasting for more than 1 day, excluding transient ischemic attack (TIA) with complete remission of symptoms within 1 day. Decompensation of heart failure was defined as seeing a doctor due to the onset of heart failure symptoms (rapid atrial fibrillation with a ventricular rate of more than 100 beats / min was also recorded in this event).

Related definitions

DM was defined as fasting plasma glucose (FPG) ≥ 7 mmol/L, or random blood glucose ≥ 11.1 mmol/L, or previously had been treated by hypoglycemic therapy. Age, creatinine and ejection fraction (ACEF) score: ACEF score = age (years) / LVEF (%) + 1 (creatinine > 2mg / dl)[9]

Statistical analysis

SPSS 24.0 (IBM, USA) was used to analyze the data. The centralized and discrete trend of continuous variables was described in the form of mean ± standard deviation (x ± s) or median and quartiles [M (Q1, Q3)]. The comparison between the two groups of continuous variables was performed by student's t test or Mann-Whitney rank sum test. Categorical variables were described as rates or percentages. Chi-square test or Mann-Whitney rank sum test was used to compare the rates between two or more groups. Kaplan-Meier method was used to draw the survival curves of IHF / IHF + DM groups, different-FPG-level groups and different-HbA1c-level groups. The difference of cumulative survival rate among groups was compared by log-rank test. Cox regression analyze was used to explore the risk factors of adverse endpoints of the IHF patients during the follow-up period. The Schoenfeld residual method was

used to test whether the continuous variables comply with the equal proportional risk assumption, while the survival curve method was used to test the classified variables. Among the continuous variables, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), hemoglobin, UA, creatinine, FPG and HbA1c were transformed into categorical variables according to their clinical significance; LVEF, 6-MWT and Gensini score were transformed into categorical variables according to their median levels; and NT-proBNP was converted to the base 10 logarithm to facilitate statistical analysis. Cox multivariate regression method was used to explored the predictive ability of diabetes history, FPG and HbA1c to the adverse endpoints of IHF population. A Cox multivariate regression model was established to determine the independent risk factors of compound clinical endpoints in patients with IHF. R software (http://www.R-project.org) and Yier statistical software http://www.empowerstats.com) were used to compare the two ROC curves that represent the predictive models established before and after diabetes-related factors' incorporation. The difference was considered statistically significant when $p < 0.05$.

Results

Patient characteristics

A total of 430 IHF patients (312 males) were included in the study. Among them, 62.8% (270 cases) were over 60 years old, 26.1% (112 cases) were over 75 years old, 62.3% (268 cases) were overweight (24 kg/m^2 ≤ BMI), and 44.7% (192 cases) used to smoke. 60.2% (259 cases) had a history of hypertension, 24.7% (106 cases) had a history of hyperlipidemia, 8.1% (35 cases) had a history of PAD, 10.5% (45 cases) had a history of stroke, 24% (103 cases) of atrial fibrillation, and 40.9% (40.9% cases) of diabetes mellitus. The usage of angiotensin converting enzyme inhibitor (ACEI) / angiotensin receptor blocker (ARB), β receptor blockers, mineralocorticoid receptor antagonists (MRA) and statins accounting for 62.1%, 79.5%, 42.5% and 91.0% of the IHF patients respectively, as shown in Table 1. The IHF patients were divided into IHF group (254 cases) or IHF+DM group (176 cases) according to whether they had DM. The prevalence of hypertension in the IHF + DM group was higher than that in the IHF group (68.8% vs. 54.3%, $\chi^2 = 9.024$, $P = 0.003$); and there was difference in BMI distribution (normal / overweight / obese) between the IHF + DM group and the IHF group ($\chi^2 = 11.486$, $P = 0.003$). No significant differences were observed between the two groups in age, gender, education, residence place, medical history other than hypertension history, as shown in Table 1.

Table 1. Baseline characteristics and comparison between the IHF and the IHF+DM groups

Clinical characteristics

The SBP, DBP, hemoglobin, TC, LDL-C and HDL-C of the IHF patients were in the normal range. The level of NT-proBNP increased, which was consistent with the featrues of heart failure. The UA and creatinine values were close to the high limit within the reference range. The proportion of CHD patients with multi-vessel lesions was 80.7% (347 / 430), and the proportion of patients in NYHA class III - IV patients was 76.3% (328 / 430). The FPG level of the IHF+DM group was higher than that of the IHF group [(8.85±3.49) mmol/L vs. (5.66±0.79) mmol/L, $P< 0.001$]. The average value of HbA1c of the IHF+DM group was higher than that of the IHF group [(7.10±1.07) % vs. (5.79±0.39) %, $P< 0.001$]. The proportion of NYHA patients in the IHF+DM group was higher than that in the IHF group (82.9% vs.71.6%, $P=0.007$). The average distance of 6 minute-walk-test (6-MWT) of the IHF+DM group was shorter than that of IHF group [(290.4±86.8) m vs. (313.5±113.8) m, $P= 0.024$]. The average left ventricle end-diastolic diameter (LVEDD) of the male patients in the IHF+DM group was longer than that in the IHF group [(58.1±3.8) mm vs.

	Total	IHF Group	IHF+DM Group	$t/\chi^2/Z$	*P*
	n=430	(n=254)	(n=176)		
Age (years) (n, %)	64.5±13.0	64.4±13.5	64.9±12.3	-0.391	0.725
< 60 years	160(37.21)	96（37.8）	64（36.4）	0.226	0.893
≥60, <75 years	158(36.74)	91（35.8）	67（38.1）		
≥75 years	112(26.05)	67（26.4）	45（25.6）		
Male (n, %)	312(72.6)	189(74.4)	123(69.9)	1.068	0.301
Qualification (n, %)				2.74	0.254
High school or below	71(16.5)	38(14.9)	33(18.8）		
(Professional) High school / Technical school / Junior College	284(66.4)	166(65.4)	118(67.0）		
Bachelor degree or above	75(17.4)	50(19.7)	25(14.2)		
Residence (n, %)				1.654	0.196
the eight regions of Beijing or other urban areas	127 (29.5)	81(31.9)	46(26.1)		
suburbs or other counties or towns	303 (70.5)	173(68.1)	130(73.9)		
BMI (n, %)	25.07±3.85	24.50±3.90	25.94±3.61	-3.880	<0.001
≤23.9 kg/m^2	162(37.7)	109(42.9)	53(30.11)	11.486	0.003
24-27.9 kg/m^2	172(40.0)	101(39.8)	71(40.34)		
≥28 kg/m^2	96(22.3)	44(17.3)	52(29.55)		
Smoke history (n, %)				2.355	0.308
Never smoke	238(55.3)	133(52.4)	105(59.7)		
Used to smoke	70(16.3)	43(16.9)	27(15.3)		
Now smoking	122(28.4)	78(30.7)	44(25.0)		
Medical history					
Hypertension (n, %)	259(60.2)	138(54.3)	121(68.8）	9.024	0.003
Dyslipidemia (n, %)	106(24.7)	67(26.4)	39(22.1)	0.996	0.318
Peripheral arterial disease (n, %)	35(8.1)	18(7.1)	17(9.7)	0.920	0.337
Stroke (n, %)	45(10.5)	24(9.4)	21(11.9)	0.684	0.408
Atrial fibrillation (n, %)	103(24.0)	62(24.4)	41(23.3)	0.071	0.790
Cardiovascular drugs					
ACEI/ARB	267(62.1)	163(64.2)	104(59.1)	1.141	0.286

β-blocker	342(79.5)	203(79.9)	139(79.0)	0.057	0.811
MRA	183(42.5)	114(44.9)	69(39.2)	1.371	0.242
statins	390(91.0)	232(91.3)	158(89.8)	0.302	0.583

(57.2±3.6) mm, *P*=0.013]. The Gensini score of the IHF+DM group was higher than that of the IHF group [(91.1±30.9) vs. (83.0±34.0), *P*= 0.012]. See table 2.

Table 2. Baseline characteristics and comparison between the IHF and the IHF+DM groups

Clinical outcomes

A total of 156 (36.3%) clinical endpoint events occurred after a median follow-up of 3.3 years (39 months). The IHF+DM group compared with the IHF group had higher all-cause mortality rate [25.6% (45/176) vs. 16.5% (42/254), χ2=5.256, *P*=0.022] as well as higher cardiovascular mortality rate [21.6% (38/176) vs. 12.6% (32/254), χ2=6.168, *P*=0.013]. See table 3.

Table 3. Major adverse clinical endpoints during the follow-up period

	Total n=430	IHF+DM Group n=176	IHF Group n=254	χ^2	*P*
All-cause death (n, %)	87（20.2）	45（25.6）	42（16.5）	5.256	0.022
Cardiovascular Death (n, %)	70（16.3）	38（21.6）	32（12.6）	6.168	0.013
Non-fatal MI (n, %)	15（3.5）	8（4.5）	7 （2.8）	0.989	0.320
Non-fatal stroke (n, %)	20（4.7）	7（4.0）	13（5.1）	0.305	0.581
Decompensation of HF (n, %)	34（7.9）	11（6.3）	23（9.1）	1.123	0.289
Composite clinical events (n, %)	156（36.3）	71（40.3）	85（33.5）	2.126	0.145

Correlation between DM history and the prognosis of IHF

Kaplan-Meier analysis demonstrated that the cumulative survival rates of IHF+DM group without all-cause death, cardiovascular death or composite clinical endpoints during follow-up period were lower than those of IHF group (log-rank $\chi 2$ values was 14.22，15.17 and 36.05 respectively, $P < 0.001$, see picture 1). Cox regression survival analysis demonstrated that compared with the IHF group, the IHF+DM group had greater risk of all-cause death [hazard ratio (HR): 3.64, 95% confidence interval (CI): 2.28-5.70, ($P < 0.001$)], greater risk of cardiovascular death (HR: 3.37, 95% CI: 2.08-5.46, $P < 0.001$), and greater risk of composite clinical endpoints (HR: 2.86, 95% CI: 2.07-3.94, $P < 0.001$). After balancing for age, gender, medical history, laboratory parameters and other clinical variables step by step, the above hazard ratio decreased, but were still of statistical significance ($P < 0.05$). See table 4.

Table 4. Multivariate cox regression analysis of diabetes mellitus on clinical end point events

	Total (n=430)	Groups		t/χ^2/Z	*P*
		IHF group (n=254)	IHF+DM group (n=176)		
SBP (mmHg)	129.1±21.1	126.6±19.6	133.0±22.7	-1.626	0.105
DBP (mmHg)	73.7±12.7	72.8±13.1	74.5±12.1	-0.581	0.562
Hemoglobin (g/L)	129.2±16.5	130.1±13.6	128.6±18.6	0.966	0.338
TG (mmol/L)	1.44±0.75	1.39±0.71	1.49±0.82	-1.339	0.181
TC (mmol/L)	3.94±1.11	3.96±1.07	3.90±1.16	0.606	0.545
LDL-C (mmol/L)	2.36±0.93	2.40±0.92	2.31±0.94	0.916	0.360
HDL-C(mmol/L)	1.02±0.33	1.04±0.34	1.00±0.31	1.376	0.170
FPG（mmol/L）	7.19±2.93	5.66±0.79	8.85±3.49	-14.063	< 0.001
HbA1（%）	6.25±0.94	5.79±0.39	7.10±1.07	-17.881	< 0.001
UA(μmol/L)	381.1±264.3	388.1±329.1	371.1±120.4	0.653	0.514
	358.8(290.2,439.0)	355.5(292.2，438.0)	369.1(285.6，443.1)	-0.211	0.833
Creatinine (μmol/L)	106.5±97.7	101.3±102.3	114.0±90.3	-1.361	0.174
	81.4(69.2,108.6)	81.0(71.2，105.8)	81.9(68.6，124.0)	-0.485	0.628
NT-proBNP (pg/ml)	1592.0(513.7,4367.3)	1592.0(442.7,4167.5)	1563.0(573.2,5442.8)	-1.154	0.249
Multi-vessel disease	347（80.7）	199（78.4）	148（84.1）	2.202	0.138
2-vessel disease	152（35.3）	86（33.9）	66（37.5）	0.603	0.437
3-vessel disease	195（45.3）	113（44.5）	82（46.6）	0.185	0.667
NYHA class				7.860	0.020
Class II	102(23.7)	72(28.3)	30(17.0)	7.338	0.007
Class III	218(50.7)	124(48.8)	94(53.4)	0.876	0.349
Class IV	110(25.6)	58(22.8)	52(29.5)	2.459	0.117
6-MWT	300±97	313.5±113.8	290.4±86.8	2.273	0.024
LVEF (%)	34.5±3.7	34.7±3.7	34.2±3.6	1.393	0.164
LVEDD(mm)male	57.5±3.7	57.2±3.6	58.1±3.8	-2.492	0.013
female	52.7±2.1	52.5±2.1	52.9±2.1	-1.942	0.053
ACEF score	1.95±0.63	1.90±0.66	2.02±0.58	-1.947	0.052

Gensini score	86.6±32.0	83.0±34.0	91.1±30.9	-2.520	0.012

		95%CI		
	HR	Low	High	P
Composite endpoints				
DM	2.86	2.07	3.94	<0.001
DM, age, sex	3.00	2.17	4.14	<0.001
DM, age, sex, medical history	2.83	2.03	3.94	<0.001
DM, age, sex, medical history, laboratory parameters, other clinical variables	2.50	1.60	3.91	<0.001
All- cause death				
DM	3.64	2.28	5.70	<0.001
DM, age, sex	3.80	2.34	5.96	<0.001
DM, age, sex, medical history	3.52	2.21	5.38	<0.001
DM, age, sex, medical history, laboratory parameters, other clinical variables	2.61	1.37	4.96	0.003
Cardiovascular death				
DM	3.37	2.08	5.46	<0.001
DM, age, sex	3.60	2.22	5.83	<0.001
DM, age, sex, medical history	3.17	1.93	5.22	<0.001
DM, age, sex, medical history, laboratory parameters, other clinical variables	2.17	1.07	4.42	0.033

"HR" listed in the above table is the Hazard Ratio of clinical endpoints caused by "diabetes" after adjustment for confounding factors. The "medical history" variables in the table include hypertension, hyperlipidemia, stroke, PAD, history of atrial fibrillation and smoking history, the "laboratory parameters" include hemoglobin, UA, creatinine, NT-proBNP (logarithmic form) and levels of blood lipids, and the "Clinical variables" included pulse pressure, LVEF, LVEDD, Gensini score, NYHA grade and 6-MWT. All included variables met the equal proportional risk assumption.

Correlation between FPG levels and prognosis of IHF

Kaplan-Meier survival analysis demonstrated that differences existed in the cumulative survival rates of all-cause death, cardiovascular death and composite clinical endpoints during the follow-up period among different FPG groups [the normal group (< 6.1mmol/L), the higher group (≥ 6.1, < 7.0 mmol/L) and the highest group (≥ 7.0mmol/L)] (Log rank $\chi 2$ values were 44.52, 26.72 and 34.26 respectively, $P < 0.001$). See figure 2. Cox regression survival analysis demonstrated that after adjusting for 19 variables including age, gender, BMI, medical history, laboratory parameters, LVEF, NYHA grade, Gensini score and 6-MWT, the HR of all-cause death, cardiovascular death and composite clinical endpoints of the highest-FPG-level group were 2.92 (95% CI: 1.35, 5.35), 3.23 (95% CI: 1.99, 5.50) and 2.20 (95% CI: 1.51, 3.22) times of those of the normal-FPG-level group ($P < 0.05$). See table 5.

Table 5. Multivariate cox regression analysis of the relationship between FPG levels and clinical endpoints of the IHF patients

	Model I		Model II		Model III	
	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
Composite endpoints						
FPG (mmol/L)	1.14(1.09, 1.19)	<0.001	1.14(1.08, 1.20)	<0.001	1.14(1.08,1.20)	<0.001
FPG Normal	Reference		Reference		Reference	
Higher	2.15(1.40, 3.29)	0.002	1.91(1.22, 3.01)	0.005	1.86(1.18,2.93)	0.008
Highest	2.91(2.05, 4.15)	<0.001	2.47(1.70, 3.58)	<0.001	2.20(1.51,3.22)	<0.001
All-cause death						
FPG (mmol/L)	1.19(1.13, 1,26)	<0.001	1.19(1.12, 1.27)	<0.001	1.19(1.12, 1.27)	<0.001
FPG Normal	Reference		Reference		Reference	
Higher	2.03(1.09, 3.77)	0.025	1.81(0.92, 3.56)	0.086	1.76(0.89,3.49)	0.103
Highest	3.64(1.91, 5.39)	<0.001	3.31(1.60, 5.33)	<0.001	2.92(1.35,5.35)	<0.001
Cardiovascular death						
FPG (mmol/L)	1.17(1.10, 1.25)	<0.001	1.16(1.08,1.25)	<0.001	1.17(1.08,1.26)	<0.001
FPG Normal	Reference		Reference		Reference	
Higher	1.73(0.86, 3.46)	0.124	1.48(0.68, 3.24)	0.322	1.41(0.64, 3.12)	0.393
Highest	3.77(2.26, 6.29)	<0.001	3.41(2.05,5.67)	<0.001	3.23(1.99,5.50)	<0.001

The above table shows the results of multivariate Cox regression analysis by dividing FPG into normal (< 6.1 mmol / L, n = 232), high (≥ 6.1, < 7.0 mmol / L, n = 89) and highest (≥ 7.0 mmol / L, n = 109) groups, and taking FPG as continuous variable and categorical variable respectively. Model I adjusted age and gender. Model II adjusted age, gender, BMI, medical history (except DM history), laboratory parameters (UA, creatinine, NT-proBNP and blood lipids), and model III adjusted LVEF, NYHA grade, Gensini score and 6-MWT on the basis of the model II, with a total of 19 variables.

Correlation between HbA1c and prognosis of IHF

Kaplan-Meier survival analysis demonstrated that the cumulative survival rates free of composite clinical endpoints, all-cause death or cardiovascular death during follow-up period of the higher-HbA1c-level group (HbA1c ≥ 6.5%) were lower than those of the lower-HbA1c-level group (HbA1c < 6.5%) (log rank $\chi 2$ = 22.28, 32.88 and 19.19 respectively, P < 0.001). See figure 3. The Cox's regression analysis demonstrated that after adjusting for 19 variables including gender, age, BMI, medical history, laboratory parameters, LVEF, NYHA grade, Gensini score and 6-MWT, the risks of all-cause death, cardiovascular death and composite clinical endpoints in the higher-HbA1c-level

group were 1.75 (HR: 1.75, 95% CI: 1.05-2.94), 1.87 (HR: 1.87, 95% CI: 1.01-3.48) and 1.62 (HR: 1.62, 95% CI: 1.14-2.28) times of those of the lower-HbA1c-level group ($P < 0.05$). See table 6.

Table 6. Multivariate cox regression analysis of the relationship between HbA1c levels and clinical endpoints of the IHF patients

	Model I		Model II		Model	
	HR (95%CI)	*P*	**HR (95%CI)**	*P*	**HR (95%CI)**	*P*
Composite endpoints						
HbA1c	1.24(1.10, 1.40)	0.001	1.22(1.07, 1.39)	0.002	1.13(0.98,1.30)	0.083
HbA1c≥6.5%	1.95(1.41,2.69)	<0.001	1.85(1.32, 2.59)	<0.001	1.62(1.14,2.28)	0.006
All-cause death						
HbA1c	1.35(1.18,1.55)	<0.001	1.32(1.14, 1.52)	<0.001	1.31(1.12, 1.54)	0.001
HbA1c≥6.5%	2.28(1.83,4.21)	<0.001	1.80(1.09, 3.00)	0.023	1.75(1.05,2.94)	0.034
Cardiovascular death						
HbA1c	1.33(1.14.1.56)	<0.001	1.34(1.13,1.59)	0.001	1.27(1.05, 1.52)	0.012
HbA1c≥6.5%	2.67(1.67,4.29)	<0.001	2.05(1.14, 3.68)	0.016	1.87(1.01, 3.48)	0.048

The above table shows the results of multivariate Cox regression analysis by dividing HbA1c into higher (< 6.1 mmol / L, HbA1c≥6.5%) and lower (HbA1c< 6.5%) groups, and taking HbA1c as continuous variable and categorical variable respectively. Model I adjusted age and gender. Model II adjusted age, gender, BMI, medical history (except DM history), laboratory parameters (UA, creatinine, NT-proBNP and blood lipids), and model III adjusted LVEF, NYHA grade, Gensini score and 6-MWT on the basis of the model II, with a total of 19 variables.

DM factors and the IHF risk model

When the diabetes related factors (diabetes history, FPG, HbA1c) were incorporated into the risk model made by the basic risk factors, the area under the receiver operating characteristic (ROC) curve for predicting IHF composite outcomes significantly increased (0.803 vs. 0.775, $P = 0.039$). See figure 4. Univariate Cox regression analysis showed that male, hypertension, stroke, diabetes, pulse pressure > 60mmhg, FPG ≥ 7.0mmol/l, HbA1c ≥6.5%, uric acid ≥ 400 μ mol / L, creatinine ≥ 100 μ mol / L, 6-MWT > 300m, blood pressure > 60mmhg, Gensini score > 80, and the increase of age, Lg (NT- proBNP) and ACEF Score increased the risk of composite endpoints in IHF patients ($P < 0.05$), while 6-MWT > 300m and LVEF > 36% were protective factors for the bad prognosis of IHF patients. See table 7. Multivariate Cox regression analysis demonstrated that diabetes mellitus, male, uric acid ≥ 400 μmol / L, creatinine ≥ 100 μmol / L, Gensini score > 80 and ACEF score were independent risk factors for the occurrence of composite clinical endpoints among IHF patients. See table 8.

The black curve is the ROC curve of the predictive model of the outcome of IHF patients established by basic factors, including the traditional risk factors and the significant factors in Cox univariate analysis ($P < 0.05$), including age, gender, BMI, hypertension, hyperlipidemia, smoking, UA, creatinine, NT-proBNP, Gensini score, PP, LVEF 6-MWT and ACEF score. The red curve is the ROC curve of the predictive model that after incorporating the DM-related factors (DM history, FPG and HbA1c) into the above basic model. All the continuous variables were not converted to categorical variables.

Table 7. Univariate cox regression analysis of IHF patients' composite clinical endpoints risk

Variables	*B*	*SE*	*Wald*	95%CI	*P*
Age (years)	0.035	0.006	30.586	1.036(1.023,1.048)	<0.001*
<60, n=161				Reference	
≥60, <75, n=157	0.438	0.206	4.534	1.549(1.035,2.318)	0.033*
≥75, n=112	1.016	0.203	24.975	2.761(1.854,4,112)	<0.001*
Male	0.423	0.172	6.046	1.527(1.090, 2.139)	0.014*
Qualification (junior college and above)	-0.162	0.160	1.017	0.851(0.621,1.165)	0.313
Residence (urban areas)	-0.013	0.078	0.029	0.987(0.846,1.150)	0.864
BMI (kg/m^2) <24				Reference	
≥24 <28	-0.010	0.179	0.003	0.990(0.697,1.406)	0.955
≥28	-0.025	0.212	0.014	0.976(0.644,1.478)	0.907
Used to smoke or now smoking	-0.162	0.160	1.017	0.851(0.621,1.165)	0.313
Hypertension	0.704	0.162	18.945	2.022(1.472, 2.775)	<0.001*
Dyslipidemia	-0.391	0.187	4.388	0.676(0.469, 0.975)	0.036
Stroke	0.577	0.159	13.161	1.781(1.304, 2.432)	<0.001*
Peripheral arterial disease	0.330	0.301	1.204	1.391(0.772, 2.506)	0.272
Atrial fibrillation	0.265	0.180	2.181	1.304(0.917, 1.854)	0.140
DM	1.049	0.164	34.940	2.855(2.070, 3.937)	<0.001*
ACEI/ARB	-0.104	0.162	0.415	0.901(0.656, 1.238)	0.519
B-blocker	0.274	0.208	1.735	1.315(0.875, 1.978)	0.188
MRA	-0.265	0.166	2.548	0.767(0.554, 1.062)	0.110
Statins	0.201	0.280	0.515	1.223(0.706,2.117)	0.473
SBP≥140mmHg n=108	0.246	0.173	2.005	1.278(0.910, 1.796)	0.157
DBP≥80mmHg n=113	-0.355	0.193	3.363	0.701(0.480, 1.025)	0.067
PP≥60mmHg n=137	0.443	0.161	7.539	1.557(1.135, 2.136)	0.006*
Hemoglobin ≥120g/L n=313	-0.180	0.175	1.061	0.835(0.593, 1.176)	0.303
LDL-C (mmol/L)	-0.139	0.080	3.004	0.870(0.744, 1.018)	0.083
TC mmol/L	-0.080	0.066	1.492	0.923(0.811, 1.050)	0.222
TG mmol/L	-0.093	0.101	0.850	0.911(0.747, 1.111)	0.356
HDL-C mmol/L	0.127	0.239	0.281	1.135(0.710, 1.814)	0.596
FPG≥7.0mmol/L n=109	0.861	0.158	29.764	2.365(1.736, 3.222)	<0.001*
HbA1c ≥ 6.5% n=127	0.551	0.164	11.318	1.735(1.259, 2.392)	0.001*

HbA1c（%）	0.191	0.063	9.313	1.211(1.071, 1.369)	0.002*
UA≥400μmol/L（n=153）	0.875	0.215	16.525	2.400(1.573, 3.660)	<0.001*
Creatinine ≥100μmol/L（n=140）	0.880	0.159	30.793	2.410(1.766, 3.288)	<0.001*
Lg（NT-pro BNP）	0.318	0.059	29.592	2.082 (1.599, 2.712)	<0.001*
NYHA class					
Class II（n=102）				Reference	
Class III（n=218）	0.183	0.189	0.937	1.201(0.829, 1.740)	0.333
Class IV（n=110）	0.118	0.209	0.319	1.125(0.747, 1.695)	0.572
6-MWT>300m（n=211）	-0.429	0.160	7.205	0.651(0.476, 0.891)	0.007*
LVEF>36%（n=209）	-0.650	0.165	15.505	0.522(0.377, 0.721)	<0.001*
LVEDD（mm）	0.022	0.018	1.569	1.022(0.988,1.058)	0.210
ACEF score	1.191	0.136	76.520	3.291(2.520, 4.298)	<0.001*
Gensini score > 80（n=205）	0.353	0.158	5.011	1.424(1.045, 1.940)	0.025*

**P*< 0.05, *B*（coefficient of regression, *SE*（standard error, *Wald*（wald statistic.

Table 8. Results of multivariate cox proportional hazards model analysis

Variables	*B*	*SE*	*Wald*	HR(95%CI)	*P*
Male	0.389	0.197	3.876	1.475(1.002, 2.171)	0.049
DM	0.719	0.161	19.857	2.051(1.496, 2.814)	<0.001
UA≥400μmol/L	0.724	0.219	10.925	2.063(1.343, 3.168)	0.001
Creatinine≥100μmol/L	0.514	0.175	8.584	1.672(1.185, 2.358)	0.003
Gensini score >80	0.340	0.161	4.457	1.405(1.025, 1.927)	0.035
ACEF score	0.946	0.149	40.147	2.574(1.921, 3.449)	<0.001

This regression model took into account the basic confounders (age, gender), traditional risk factors associated with the prognosis of CHD or HF (smoking, hypertension, diabetes, hyperlipidemia, NT-proBNP), and factors significantly associated with the risk of composite clinical endpoint events in the univariate Cox regression analysis (PP, FPG, HbA1c, UA, creatinine, ACEF score, Gensini score, LVEF, 6-MWT). Among them, age, FPG, HbA1c, ACEF score, and Lg (NT-proBNP) were included in the model as a continuous variable. UA, creatinine, and PP were included in the model as classification variables, with the cutoff points of 6.5%, 600 μmol/L,100μmol/L and 60mmHg; according to their clinical significance. LVEF（6-MWT and Gensini score were also converted into classification variables according to their medians of 36%, 300m and 80. *B*（coefficient of regression, *SE*（standard error, *Wald*（wald statistic.

Discussion

HF and diabetes often occur together in patients. It has been shown that diabetes predicts the occurrence of HF independently of risk factors such as hypertension, dyslipidemia, and CHD (HR:1.56, 95%CI:1.45-1.69) [10]. The pathophysiology of diabetic cardiomyopathy makes diabetes a key risk factor for HF. IHF is an important part of HF: data from Framingham Heart Study showed that after adjusting for age and gender, the hazard ratio of occurring HFrEF in CHD patients was 1.73 (95% CI, 1.27-2.34), and that in myocardial infarction patients was 3.49 (95% CI, 2.48-4.9). Data from the CHARM study showed that 66% of the diabetes-HF patients were attributed to ischemic heart disease[11]. IHF, a major component of HF with severe myocardial ischemia, heart enlargement and reduced ejection fraction, has been rarely studied about its comorbidity with diabetes in China or abroad. In our study, 40.9% (176 / 430) of the IHF patients were with diabetes, the proportion of which was similar to that in HFrEF population mentioned in other studies[6, 8], even 10.2% (44 / 430) impaired fasting glucose and impaired glucose tolerance cases were not included.

Clinical characteristics of IHF population

It is unquestionable that links exist between cardiovascular disease and diabetes. Our study showed the following baseline features of the IHF-DM patients. 1) The prevalence of hypertension in DM-IHF patients reached 68.8%, which may be due to the high incidence of hypertension in diabetic patients. What's more, hypertension and diabetes are also risk factors for ischemic heart disease and coronary multivessel disease, the synergistic effect of which will further increase the risk of coronary artery disease. 2) The overweight proportion in IHF-DM patients reached 69.89% (123/176). Obesity, especially visceral obesity, is closely related not only to cardiovascular diseases and metabolic syndrome, but also to type 2 diabetes. China's cardiovascular health and disease report points out that among Chinese overweight patients (BMI≥24 kg/m2), 36% of type 2 diabetes were caused by overweight or obesity[12]. Moreover, recent studies have shown that the high BMI is closely related to the accumulation of epicardial adipocytes, which can lead to the increase of local inflammatory mediators, microvascular injury, myocardial fibrosis and cardiac dysfunction[13]. 3) 44.7% (192 / 430) of IHF patients now or used to smoke, the proportion is much higher than the standardized smoking rate of Chinese people (25% - 26%)[14]. A cohort study of about 270 thousand diabetes patients in Sweden showed that the risk of hospitalization for heart failure in diabetics was significantly higher than that in non-diabetic groups, and smoking was the strongest predictor of mortality in diabetics[15]. Smoking can increase the risk of almost all subtypes of cardiovascular diseases in the general population, including heart failure, myocardial infarction and cerebrovascular diseases. Quitting smoking can greatly reduce this risk[16]. So smoking cessation may be of great practical significance for patients with IHF.

And there were other findings about the IHF-DM patients in our study. 1) The symptoms of HF were more serious in IHF-DM people. The proportion of patients in NYHA class III – IV in the IHF+DM group was higher than that in the IHF group. And the average distance of 6-MWT in the IHF+DM group was shorter than that in the IHF group. 2) The structure of the heart of the IHF-DM patients changed more significantly that the average LVEDD of the male people in the IHF+DM group was longer than that of the IHF group. 3) The degree of ischemia was higher in IHF-DM patients that the score of Gensini in the IHF+DM group was higher than that in the IHF group. These changes may be closely related to the pathophysiological mechanisms of heart failure-diabetes comorbidity. 4) The blood pressure, hemoglobin, HDL-C, LDL-C, TC and TG of IHF population were basically at normal levels, the level of NT-pro BNP was consistent with the characteristics of HF, and the average levels of UA and creatinine were relatively high although within the normal range. There were not a few patients with hypertension in the IHF population, but the overall blood pressure levels were properly controlled, with an average SBP of 129 mmHg and an average DBP

of 74 mmHg. The normal level of blood lipid and blood pressure could be due to the secondary prevention of CHD, such as the using of angiotensin converting enzyme inhibitor / angiotensin II receptor blocker (ACEI / ARB), β Receptor blockers, statins and the low-fat diet.

Pathological mechanism of HF complicated with DM

Severe symptoms and poor long-term prognosis of the IHF-DM people may be caused by the following pathological mechanisms. First of all, the long-term hyperglycemia in diabetics may lead to endothelial dysfunction, which would promote thrombosis and coronary plaque ulcers and vascular smooth muscle cell proliferation[17]. Secondly, insulin resistance in diabetic patients is related to cardiac parasympathetic degeneration and the activation of sympathetic nervous system which may produce electrical instability, affecting the systolic and diastolic function of the heart. Thirdly, the common complications of diabetes such as hypertension and renal impairment would accelerate the progression of cardiac insufficiency. And in addition, the activated renin angiotensin aldosterone system (RAAS) in diabetic patients promotes myocardial fibrosis and aggravates HF by increasing collagen synthesis, vascular inflammation and oxidative damage.

The above is elucidated from the macro perspective. Meanwhile, the IHF-DM patients' having more severe symptoms, more significantly changed heart structure and higher degree of ischemia may be due to the following microscopic mechanism. Firstly, in the cardiomyocytes of diabetic patients, the glucose metabolism transferring to fatty acid metabolism will increase oxygen consumption and decrease myocardial efficiency. When the intake of free fatty acids exceeded myocytes' ability of utilization, the lipids will accumulate in cardiomyocytes and epicardial tissue, producing toxic metabolic intermediates, and accelerating the oxidation and apoptosis of cardiomyocytes[18]. However, when without insulin resistance, even if at risk of heart failure, the diabetic cardiomyocytes can enhance glucose uptake and activate enzymes involved in the glycolytic pathway, as well as activate the adaptive cardioprotective response by reducing free fatty acid oxidation[19]. In a word, the conversion of the utilization of free fatty acid to glucose oxidation increases ATP production and reduces oxygen consumption, so the myocardial contraction efficiency would be improved. On the other hand, when heart failure progresses to the later stage, which can induce compensatory adrenergic drive, the lipolysis would be enhanced and the concentration of free fatty acid would increase, leading to the cardiac metabolic curves shifting to insulin resistance / diabetes.

Secondly, the dysfunction of the contraction of cardiac fiber is common in IHF patients complicated with DM. Abnormal expression of myocardial contractile and regulatory proteins in diabetic patients will lead to the decrease of myofibril ATPase activity and contractility[20]. In addition, studies have shown that the Ca^{2+}-ATP of the sarcoplasmic reticulum of the high glucose medium is inactivated by oxidative stress, resulting in the Ca^{2+} overload and diastolic dysfunction [21], which is also a micro factor aggravating the remodeling of the myocardial structure and the cardiac dysfunction in patients with heart failure.

Thirdly, microvascular dysfunction occurred in IHF-DM patients. The expression of VEGF in diabetic patients was downregulated [22], and the production of advanced glycation end products and free radicals increased, resulting in the thickening of capillary basement membrane and microvascular remodeling, which affected the function of the coronary microcirculation. The insufficiency of coronary flow reserve and the myocardial ischemia would lead to the loss of contraction protein, the necrosis of myocardial cells, the deposition of collagen, the increment of focal perivascular and the interstitial fibrosis and the aggravation of heart failure, which are manifestations of the late diabetic cardiomyopathy.

Prognostic factors of IHF

The average age of the subjects involved in this study was 64.5 years old. The duration of diabetes in elderly patients is longer, and the function of organs such as large blood vessels, kidney and autonomic neuropathy has reduced. The design of this study innovatively found that after adjust gradually the age and gender, medical history (hypertension, hyperlipidemia, stroke, PAD, atrial fibrillation and smoking), laboratory indicators (hemoglobin, UA, creatinine, NT proBNP, LDL-C, HDL-C, TG and TC) and the clinical variables (blood pressure, LVEF, LVEDD, Gensini score, ACEF score, NYHA grade, 6-MWT) , the diabetes history was all along an independent risk factor for all-cause death, cardiovascular death and composite clinical end point in IHF patients (P< 0.05).

Then the authors conducted multivariate cox regression analysis to analyze the relationship between FPG levels and clinical endpoints of the IHF patients for the following reasons: (1) impaired fasting blood glucose (IFG), when FPG levels are elevated while the postprandial blood glucose levels are basically normal, is related to the insulin resistance and the early-phase insulin secretion defects. And there were 10.2% (44 / 430) patients with IFG in our study; (2) FPG represents the daily blood glucose level to a certain extent; (3) any form of glycometabolism disorder is strongly associated with the development of heart failure[23]. IFG as an important stage of pre diabetes, significantly increases the risk of cardiovascular disease. Kristensen et al. found that patients with diabetes or pre diabetes had significantly higher risk of hospitalization due to heart failure or death caused by cardiovascular diseases than those with normal plasma glucose [6]. In this study, we found that there were differences in the cumulative survival rate without all-cause death, cardiovascular death and composite adverse cardiovascular and cerebrovascular events among the low, medium and high FPG level groups (P≤0.001). The risk of composite clinical end points in the FPG ≥ 7.0mmol/l group was significantly higher than that in the normal FPG group (P < 0.001), Patients with FPG between 6.1mmol/l and 7.0mmol/l also had an increased risk of composite clinical endpoints (*P* = 0.008), as shown in Table 5. It suggests that clinicians may need to strengthen fasting blood glucose control for IHF-DM patients.

Glycosylated hemoglobin can accurately reflect the average blood glucose level of individuals in recent 2-3 months. The results of a large sample prospective study by Paul et al. showed that delayed treatment and poor blood glucose control (HbA1c ≥ 7.0%) significantly increased the risk of myocardial infarction, stroke, HF or cardiovascular and cerebrovascular events[24]. The results of this study also found that the high level of HbA1c was not conducive to the outcome of IHF patients. The crude risk of adverse clinical endpoints in IHF population with HbA1c ≥ 6.5% was 1.735 times higher than that in HbA1c < 6.5% (HR: 1.735, 95% CI: 1.259-2.392).

Meanwhile, the univariate Cox regression analysis in our study showed that the elderly, male, lower education, history of hypertension or stroke, bigger pulse pressure difference, higher levels of UA, creatinine and NT-proBNP were unfavorable to the prognosis of IHF patients, while the 6-MWT distance greater than 300m and left ventricular ejection fraction (LVEF) greater than 36% were the protective factors for IHF patients, see Table 7. Age, Creatinine, and Ejection fraction (ACEF) score was included in the multivariate Cox's proportional hazard regression model. The ACEF score was developed and validated by Ranucci et al. in 2009 and was initially used for patients undergoing coronary artery bypass grafting[9]. Currently, the ACEF score has been incorporated into the guidelines of the European Heart Association as a risk stratification tool for surgical and percutaneous myocardial revascularization. The higher the ACEF score, the greater the risk of major adverse cardiovascular events[25, 26]. The heart failure of IHF patients is attributed to myocardial ischemia caused by coronary artery disease. The majority of IHF patients have received PCI or CABG treatment. In the univariate analysis of this study, age, creatinine and LVEF were all related to the prognosis of IHF patients. Therefore, the authors considered that ACEF score may also be related to the long-term prognosis of IHF patients. As expected, the final multivariate Cox regression analysis in this study showed that ACEF score, together with male gender, diabetes history, UA ≥ 400 μ mol / L, creatinine ≥ 100 μ mol / L

and Gensini score > 80, was an independent risk factor for composite adverse endpoints in patients with IHF (HR: 2.574, 95% CI: 1.921-3.449, P < 0.001), which suggested that clinical attention should be paid to these factors of the IHF patients.

Limitations of the study

There were certain limitations in our study. Firstly, this was a retrospective study, so that influence of other potential confounding factors could not be wholly excluded. Secondly, this was a single center study with small sample size, so that the conclusion might be slightly biased. Thirdly, for patients with pre diabetes, IFG was considered in this study. However, patients with impaired glucose tolerance were not taken into account. In addition, in 2020, JACC issued the latest consensus and put forward the concept of heart failure with recovered left ventricular ejection fraction (HFrecEF). The definition includes heart failure with an absolute LVEF improvement of more than 10% during the course of the disease and a LVEF of more than 40% when measured again[27]. It is speculated that HFrecEF may suggest a better prognosis. However, this study failed to obtain the data of cardiac ultrasound again.

Conclusion

1) There exists a high incidence rate of DM in the IHF population. IHF is often caused by severe myocardial ischemia and usually has a poor prognosis. IHF patients with diabetes have more severe clinical symptoms and worse prognosis than those without diabetes. 2) The diabetes related factors (diabetes history, FPG, HbA1c) significantly increased the predictive value of the risk model made by the basic risk factors in predicting the IHF outcomes. DM history, male, uric acid ≥ 400 μmol / L, creatinine ≥ 100 μmol / L, Gensini score > 80 and ACEF score were independent risk factors for the occurrence of composite clinical endpoints in IHF patients. The above findings are of great significance for clinical judgment of high-risk patients and targeted intensive treatment and management for IHF patients.

Abbreviations

ACEF Score: age, creatinine and ejection fraction score; ACEI: Angiotension converting enzyme inhibitors; ARB: angiotensin II receptor blocker; AUC: area under curve; BMI: body mass index; CI: confidence interval; DM: diabetes mellitus; DBP: diastolic blood pressure; FPG: fasting plasma glucose; HDL-C: high density lipoprotein cholesterol; HbA1c: glycosylated hemoglobin A1c; HFrEF: heart failure with reduced ejection fraction; HFrecEF: heart failure with recovered left ventricular ejection fraction; HR: Hazard Ratio; IFG: impaired fasting glucose; IHF: ischemic heart failure; LDL-C: low density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter left ventricular end-diastolic diameter; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association; NT-proBNP: N-terminal pro-brain natriuretic peptide; PAD: peripheral arterial disease; ROC: receiver operating characteristic; SBP: systolic blood pressure; 6-MWT: 6-minute walk test

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Board of the Chinese PLA General Hospital and written informed consent was obtained from each patient.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on the reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Yongyi Bai and Hongbin Liu designed the study and provided the methodological expertise. Huiying Li and Chunlin Li drafted the manuscript including the figures and tables. Man Li, Jianqiao Chen, Yulun Cai, Benchuan Hao and Zifan Zhu followed up the subjects and recorded the details of their clinical outcomes. Wei Wang and Huiying Li collected the baseline data and performed the statistical analysis.

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Figures

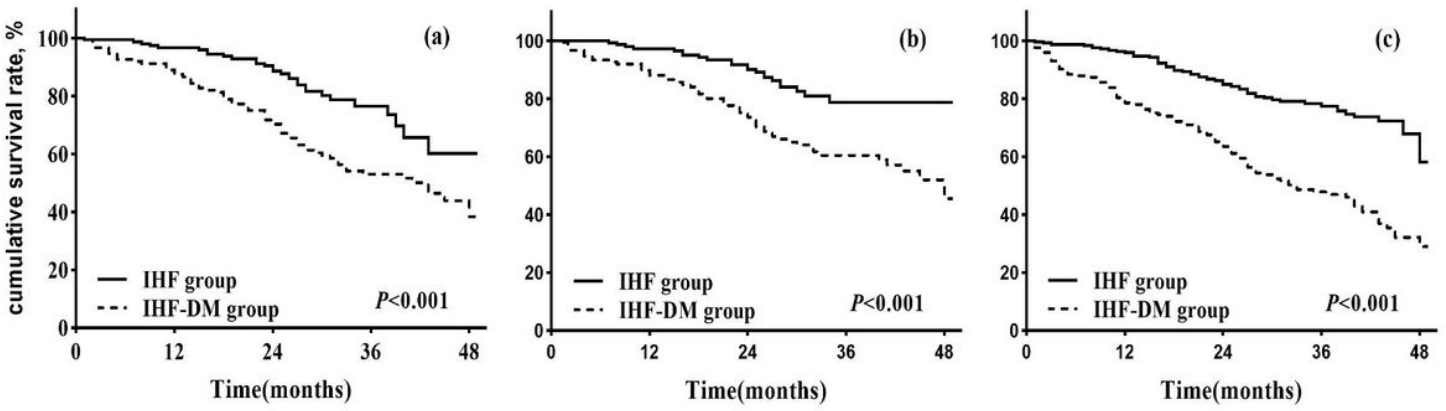


Figure 1

(a) is the Kaplan-Meier survival curves for the risk of all-cause death, (b) is the Kaplan-Meier survival curves for the risk of cardiovascular death, (c) is the Kaplan-Meier survival curves for the risk of composite endpoint events.

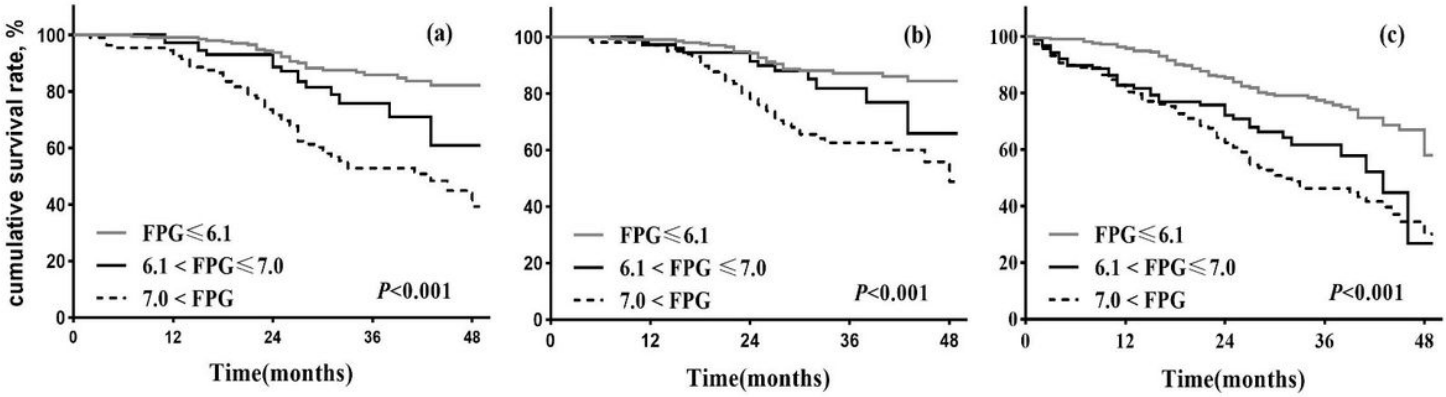


Figure 2

(a) is the Kaplan-Meier survival curves for the risk of all-cause death, (b) is the Kaplan-Meier survival curves for the risk of cardiovascular death, (c) is the Kaplan-Meier survival curves for the risk of composite endpoint events.

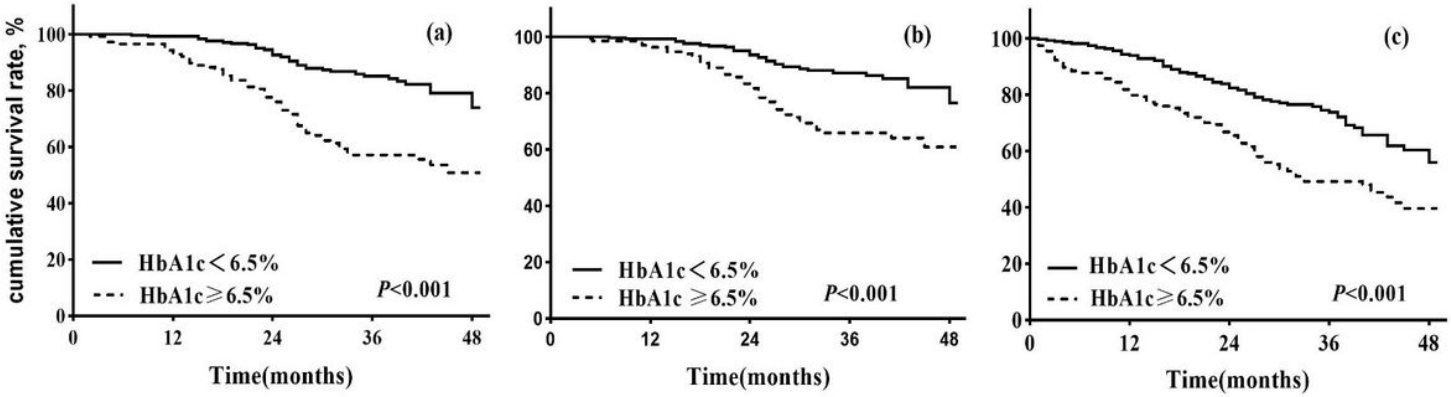
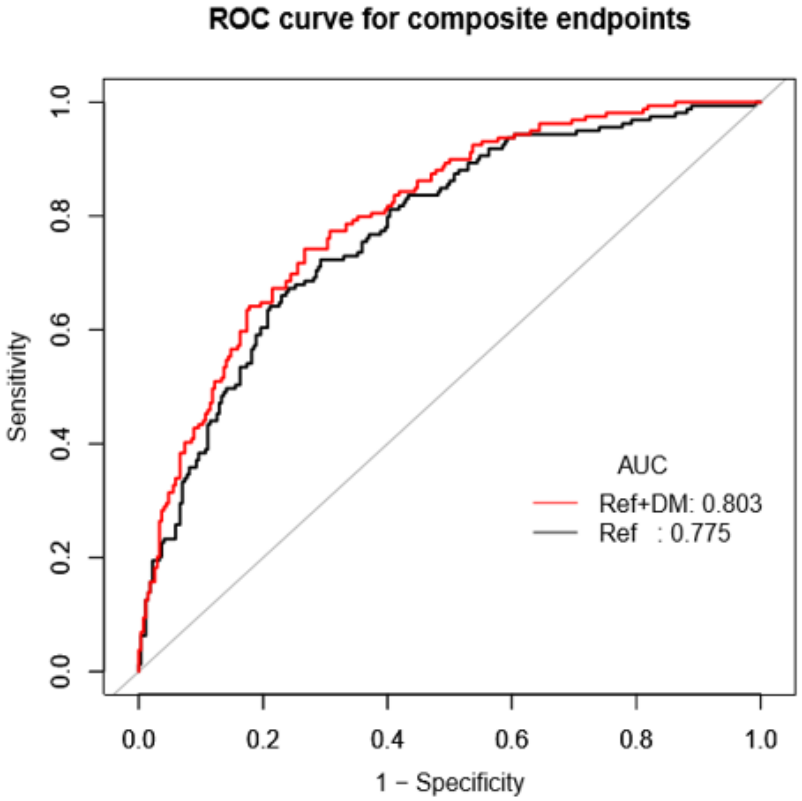


Figure 3

(a) is the Kaplan-Meier survival curves for the risk of all-cause death, (b) is the Kaplan-Meier survival curves for the risk of cardiovascular death, (c) is the Kaplan-Meier survival curves for the risk of composite endpoint events.



	Ref	Ref+DM
AUC	0.7749	0.8028
95%CI Low	0.7299	0.7610
95%CI High	0.8199	0.8446
特异度	0.7593	0.7333
敏感度	0.6730	0.7421
阳性预测值	0.6221	0.6211
阴性预测值	0.7977	0.8285
两曲线比较 $P = 0.0392$*		

Figure 4

ROC curves before and after incorporating DM-related factors into the model.