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ORIGINAL ARTICLE

Five-year mortality of heart failure with preserved, mildly reduced, and reduced ejection fraction in a 4880 Chinese cohort

Shiqun Chen[1*], Zhidong Huang[1], Yan Liang[2], Xiaoli Zhao[3], Xiemuxikaimaier Aobuliksimu[4], Bo Wang[1], Yibo He[1], Yu Kang[1], Haozhang Huang[1], Qiang Li[1], Younan Yao[1], Xiaozhao Lu[1], Xiaoxian Qian[3], Xujing Xie[3], Jin Liu[1*] and Yong Liu[1*]

[1]*Department of Cardiology, Guangdong Provincial Key Laboratory of Coronary Heart Disease Prevention, Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, 510080, China;* [2]*Maoming People's Hospital, Maoming, China;* [3]*The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China; and* [4]*The First People's Hospital of Kashgar, Kashi, China*

Abstract

Aims Available evidence is incomplete and inconsistent in the outcomes of heart failure (HF) patients with preserved ejection fraction (HFpEF), mildly reduced ejection fraction (HFmrEF), and reduced ejection fraction (HFrEF). There are also limited data on the proportions and long-term prognosis among the three HF phenotypes in China. We aimed to characterize the 5 year prognosis in three HF phenotypes according to EF in a cohort of hospitalized HF patients undergoing coronary angiography in southern China.

Methods and results Hospitalized patients with HF were enrolled from the Cardiorenal ImprovemeNt registry (CIN; ClinicalTrials.gov NCT04407936) between January 2007 and December 2014. HF phenotypes were defined as HFpEF (EF $\geq$ 50%), HFmrEF (EF 41–49%), and HFrEF (EF $\leq$ 40%). Kaplan–Meier and Cox proportional hazards models were constructed to examine differences in 5 year outcomes in HF patients with different phenotypes. A total of 4880 HF patients [mean age: 61.8 ± 10.3, male: 3156 (64.7%)] were included: 2768 (57%) had HFpEF, 1015 (21%) had HFmrEF, and 1097 (22%) had HFrEF. Patients with HFrEF were older than those with HFpEF (62.5 ± 10.6 vs. 61.3 ± 10.1, $P < 0.001$) and more likely to be male (78.0% vs. 55.9%, $P < 0.001$). With 5 year follow-up through the end of December 2019, 1624 (27.6%) patients died. Controlling confounding variables, declined EF category was independently associated with increased 5 year mortality {HFrEF 25.2% vs. HFpEF 13.4%, adjusted hazard ratio [aHR]: 1.85 [95% confidence interval (CI): 1.45 to 2.35]; HFmrEF 18.1% vs. HFpEF 13.4%, aHR: 1.40 [95% CI: 1.08 to 1.81]; HFrEF 25.2% vs. HFmrEF 18.1%, aHR: 1.32 [95% CI: 1.02 to 1.71]}.

Conclusions In this Chinese cohort, patients with HFrEF account for less than a fourth of HF patients. One-sixth individuals with HF died in 5 years. HFrEF was associated with a nearly two-fold increased risk of 5 year mortality than HFpEF. Further studies are needed to prospectively evaluate the efficacy of improving treatment on outcomes in all three HF phenotypes.

Keywords Five-year mortality; EF—ejection fraction; HFmrEF—heart failure with mildly reduced ejection fraction; HFpEF—heart failure with preserved ejection fraction; HFrEF—heart failure with reduced ejection fraction

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**Correspondence to: Yong Liu, Jin Liu and Shiqun Chen, Department of Cardiology, Guangdong Provincial Key Laboratory of Coronary Heart Disease Prevention, Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou 510080, China. Tel: (+86) 02083827812-10528; Fax: (+86) 02083851483. Email: liuyong@gdph.org.cn; ljaw397017568@163.com; shiqunchen@126.com*
Shiqun Chen, Zhidong Huang, and Yan Liang have contributed equally to this work and share first authorship.

Introduction

Heart failure (HF) is a global epidemic affecting close to 40 million people worldwide and putting constant pressure on clinical and public health systems with its significant mortality, morbidity, and need for hospitalization.[1–3] Detailed data on global burden and distribution by causes of HF was illustrated in the supporting information. The 2021 ESC Guidelines classify patients with HF as reduced ejection fraction (HFrEF), mildly reduced ejection fraction (HFmrEF), and

preserved ejection fraction (HFpEF), with the efficacy of evidence-based therapies varied by EF grouping.[4] Still, previous data from different countries and regions have reported that the long-term prognosis of these three HF phenotypes is heterogeneous. Indeed, several cohort studies have shown that HFpEF and HFmrEF patients have a substantially better prognosis than HFrEF patients,[5] whereas an American HF registry study and a Korean HF registry study have indicated similar mortality in HF patients across the EF spectrum.[6,7] A Finland cohort study and a Spanish cohort study have even observed a significantly worse outcome in HFpEF.[8,9] In addition, there are few data on proportions and 5 year mortality of HFpEF, HFmrEF, and HFrEF in China.

Accordingly, this study aimed to investigate the proportions and the differences in 5 year mortality prognosis of HFpEF, HFmrEF, and HFrEF in a large cohort of patients with HF across the whole EF spectrum in southern China.

Methods

Study population

Hospitalized patients undergoing coronary angiography (CAG) were enrolled from the Cardiorenal ImprovemeNt registry (CIN; ClinicalTrials.gov NCT04407936) in Guangdong Provincial People's Hospital, Guangdong, China, from January 2007 to December 2014, with a 5 year follow-up until the end of December 2019. The diagnosis of HF was determined by physical examination signs, symptoms, and biomarkers of the patient. Only patients aged ≥18 years were included; those with cancer, missing left ventricular ejection fraction (LVEF) data at baseline, or missing follow-up data were excluded. Detailed information is presented in *Figure 1*. All patients received a complete baseline clinical, bio-humoral, and echocardiographic evaluation in hospitalization. The study protocol was approved by the institution's human research committee. The investigation conforms with the principles outlined in the Declaration of Helsinki.

Data collection

The baseline information included demographics, laboratory test results, mortality, and other clinical variables. Blood samples were collected in the early morning after overnight fasting.[10] N-terminal pro-brain natriuretic peptide (NT-proBNP) was measured with the electro chemo luminescent immunoassay (ECLIA) monoclonal method using the Cobas e411 platform (Roche Diagnostics). The LVEF measurements were performed with the same standard by senior echocardiography physicians, who were responsible for data quality control and periodical data verification. The reading was standardized and consistent across years.

Endpoint and definition

The primary endpoint of this study was 5 year all-cause mortality. Part of the follow-up data was obtained from

Figure 1 Study flow diagram. LVEF, left ventricular ejection fraction.

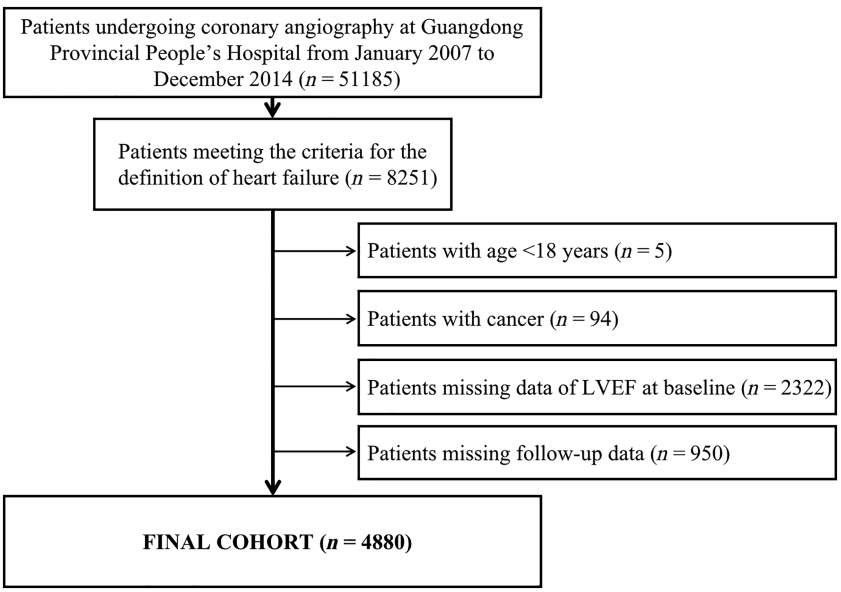

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Table 1 Baseline characteristics of the patients hospitalized with heart failure with preserved, mildly reduced, and reduced ejection fraction

Characteristics	Overall $N = 4880$	EF category HFpEF $n = 2768$	HFmrEF $n = 1015$	HFrEF $n = 1097$	*P* values	% Std. Diff. HFpEF vs. HFmrEF	% Std. Diff. HFmrEF vs. HFrEF
Age, years	61.8 ± 10.3	61.3 ± 10.1	62.4 ± 10.4	62.5 ± 10.6	<0.001	11.4	1.2
Male	3156 (64.67)	1546 (55.85)	754 (74.29)	856 (78.03)	<0.001	39.4	8.8
Medical history							
AMI	1115 (22.85)	562 (20.30)	360 (35.47)	193 (17.59)	<0.001	34.3	41.3
CHF	1056 (21.64)	513 (18.53)	227 (22.36)	316 (28.81)	<0.001	9.5	14.8
Anaemia	1962 (40.84)	1093 (40.12)	448 (45.12)	421 (38.73)	0.006	10.1	13
Hypertension	1986 (40.70)	1047 (37.83)	504 (49.66)	435 (39.65)	<0.001	24	20.2
DM	1071 (21.95)	480 (17.34)	273 (26.90)	318 (28.99)	<0.001	23.2	4.7
CKD	1483 (30.39)	748 (27.02)	333 (32.81)	402 (36.65)	<0.001	12.7	8.1
Stroke	284 (5.82)	172 (6.21)	53 (5.22)	59 (5.38)	0.399	4.3	0.7
Atrial fibrillation	1054 (21.60)	852 (30.78)	105 (10.34)	97 (8.84)	<0.001	52.3	5.1
COPD	41 (0.84)	14 (0.51)	15 (1.48)	12 (1.09)	0.009	9.8	3.4
VHD	1753 (35.92)	1264 (45.66)	204 (20.10)	285 (25.98)	<0.001	56.6	14
CAD	3164 (64.84)	1488 (53.76)	840 (82.76)	836 (76.21)	<0.001	65.6	16.3
Pre-AMI	291 (5.96)	71 (2.57)	87 (8.57)	133 (12.12)	<0.001	26.4	11.7
Pre-PCI	266 (5.45)	111 (4.01)	78 (7.68)	77 (7.02)	<0.001	15.7	2.6
Pre-CABG	24 (0.49)	11 (0.40)	4 (0.39)	9 (0.82)	0.210	0.1	5.5
Dialysis history	43 (0.88)	21 (0.76)	11 (1.08)	11 (1.00)	0.566	3.4	0.8
In-hospital dialysis	118 (2.42)	62 (2.24)	30 (2.96)	26 (2.37)	0.443	4.5	3.6
Heart function					0.001	12.2	15.7
NYHA class I	884 (28.68)	515 (30.60)	176 (29.78)	193 (23.89)			
NYHA class II	1379 (44.74)	755 (44.86)	259 (43.82)	365 (45.17)			
NYHA class III	697 (22.62)	363 (21.57)	124 (20.98)	210 (25.99)			
NYHA class IV	122 (3.96)	50 (2.97)	32 (5.41)	40 (4.95)			
Laboratory findings							
LDL-C, mmol/L	2.78 ± 0.99	2.76 ± 0.96	2.76 ± 0.93	2.85 ± 1.12	0.041	0.8	8
HDL-C, mmol/L	1.00 ± 0.29	1.03 ± 0.30	0.97 ± 0.28	0.97 ± 0.28	<0.001	22.4	1.1
ALB, g/L	33.82 ± 4.80	34.40 ± 4.82	32.96 ± 4.69	33.16 ± 4.63	<0.001	30.1	4.2
ProBNP, pg/mL	2114.5 [1308.50–3905.50]	1743 [1190.00–2883.50]	2352 [1458.50–4446.50]	3426 [1862.00–6823.00]	<0.001	26.4	25.3
eGFR, mL/min/1.73 m^2	69.40 ± 25.11	71.43 ± 25.01	68.50 ± 26.45	65.28 ± 23.52	<0.001	11.4	12.9
CHOL, mmol/L	4.53 ± 1.19	4.54 ± 1.16	4.48 ± 1.18	4.53 ± 1.29	0.422	4.9	4.2
Potassium, mEq/L	3.82 ± 0.49	3.82 ± 0.49	3.81 ± 0.50	3.82 ± 0.50	0.819	1.5	2.7
Treatment							
ACEI or ARB	2057 (43.78)	972 (36.26)	504 (51.53)	581 (55.87)	<0.001	31.2	8.7
Beta-blocker	3088 (65.72)	1543 (57.55)	754 (77.10)	791 (76.06)	<0.001	42.6	2.5
Spirolactone	2471 (52.59)	1335 (49.79)	422 (43.15)	714 (68.65)	<0.001	13.4	53.2
Furosemide	2505 (53.31)	1380 (51.47)	431 (44.07)	694 (66.73)	<0.001	14.9	46.8
Thiazide	172 (3.66)	91 (3.39)	27 (2.76)	54 (5.19)	0.008	3.7	12.5
CCB	677 (14.41)	435 (16.23)	125 (12.78)	117 (11.25)	<0.001	9.8	4.7

(*Continues*)

Table 1 (continued)

Characteristics	Overall $N = 4880$	EF category HFpEF $n = 2768$	HFmrEF $n = 1015$	HFrEF $n = 1097$	*P* values	% Std. Diff. HFpEF vs. HFmrEF	HFmrEF vs. HFrEF
Echocardiography							
LVEDD, mm	52.42 ± 9.42	48.27 ± 7.43	54.28 ± 7.38	61.18 ± 9.03	<0.001	81.1	83.7
LVESD, mm	37.39 ± 11.03	31.11 ± 6.48	40.40 ± 7.58	50.44 ± 10.20	<0.001	131.7	111.8
Follow-up death, 5 years	832 (17.05)	371 (13.40)	184 (18.13)	277 (25.25)	<0.001	13	17.3

ACEI or ARB, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; ALB, albumin; AMI, acute myocardial infarction; BNP, B-type natriuretic peptide; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCB, calcium-channel blocker; CHF, congestive heart failure; CHOL, cholesterol; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LDL-C, low-density lipoprotein cholesterol; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; VHD, valvular heart disease.
Values are mean ± standard deviation, number (%), or median [inter-quartile range]. Standardized differences (Std. Diff.) of 10% or higher indicate relevant differences.

the Public Security and matched with the records in the electronic Clinical Management System of the Guangdong Provincial People's Hospital according to ID numbers, while the rest was monitored and recorded by trained nurses and research assistants through outpatient interviews and telephones. Patients were then classified into HFrEF (EF $\leq$ 40%), HFmrEF (EF 41–49%), or HFpEF (EF $\geq$ 50%).[4] HF was defined as NT-proBNP $>$ 450 pg/mL (age $<$ 50 years); $>$900 pg/mL (age 50–75 years); and $>$1800 pg/mL (age $>$ 75 years).[11,12] Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) $<$ 60 mL/min/1.73 m^2. eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) equation.[13] Acute myocardial infarction (AMI) was defined if the diagnosis was present in the medical history. Anaemia was defined as a haematocrit $\leq$ 39% (male) or $\leq$36% (female). Hypertension and diabetes mellitus (DM) were defined using ICD-10 codes.

Statistical analysis

Descriptive statistics are reported as the mean ± standard deviation (SD), median [inter-quartile range (IQR)], or number (percentages), as appropriate. The demographic characteristics, medical history, admission data, and hospital characteristics of three groups of HF phenotypes were described. Differences between three groups were examined with one-way analysis of variance (ANOVA). Per cent standardized differences (standardized differences ×100) are also provided. Time-to-event data are presented graphically using Kaplan–Meier curves, and log-rank tests were used to compare survival among three groups. Hazard ratios (HRs) for 5 year all-cause mortality were calculated using Cox regression models to compare the difference in prognosis between the three HF phenotypes. Additionally, we constructed a model adjusted only for sex and age, and a multivariable-adjusted model adjusted for demographics (age and sex), complications [AMI, congestive heart failure (CHF), anaemia, hypertension, diabetes, CKD, stroke, atrial fibrillation (AF), chronic obstructive pulmonary disease (COPD), valvular heart disease (VHD), and New York Heart Association (NYHA) classification], medical history [pre-AMI, pre-percutaneous coronary intervention (PCI), and pre-CABG], examination [low-density lipoprotein cholesterol (LDL-C), potassium, and albumin (ALB)], and discharge medication [angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (ACEI or ARB), beta-blockers, spironolactone, furosemide, and thiazide]. All *P* values presented are based on two-tailed tests, and values $<$ 0.05 were considered statistically significant. All statistical analyses were performed using R (ver. 4.0.3).

Results

Characteristics of patients

Among the 4880 patients enrolled (mean age: 61.8 ± 10.3 years, male: 64.7%), 2768 (57%) had HFpEF, 1015 (21%) had HFmrEF, and 1097 (22%) had HFrEF (*Table 1*). Patients with HFrEF were older than those with HFpEF; more likely to be male (78.0% vs. 55.9%); and more often complicated with hypertension, DM, COPD, CKD, prior myocardial infarction, and NYHA class III/IV status. Conversely, patients with HFpEF were more likely to have comorbidities such as AF and VHD. On laboratory findings, patients with HFpEF had higher ALB and lower NT-proBNP. Compared with patients with HFrEF, those with HFpEF were less likely to receive ACEI or ARB, beta-blockers, spironolactone, and diuretic agents at discharge. There was no indication that general characteristics of patients with HFmrEF were intermediate between that of the other two groups. Patients with HFmrEF were most likely to have coronary artery disease (CAD), hypertension, and anaemia, but had the lowest prevalence of VHD.

Study outcomes

Overall, 832 (17%) patients died. Kaplan–Meier analysis for mortality by EF groups were shown in *Figure 2*. After controlling confounding variables, declined EF category was significantly associated with an increased risk of 5 year mortality. HFrEF patients had an 85% increased risk of 5 year mortality compared with HFpEF patients {HFrEF [25.2%] vs. HFpEF [13.4%], adjusted hazard ratio [aHR]: 1.85 [95% confidence interval (CI): 1.45 to 2.35]}. Similarly, patients with HFmrEF had a 40% increased risk for death compared with HFpEF patients [HFmrEF (18.1%) vs. HFpEF (13.4%), aHR: 1.40 (95% CI: 1.08 to 1.81)]. In addition, patients with HFrEF had a 32% increased risk of 5 year mortality compared with HFmrEF patients [HFrEF (25.2%) vs. HFmrEF (18.1%), aHR: 1.32 (95% CI: 1.02 to 1.71)] (*Table 2*). In the current study, the proportion of HFrEF was smaller when compared with studies in other countries and regions; notably, the mortality of all three HF phenotypes rose as EF declined (*Figure 3*). On subgroup analysis by gender, the relationship between HFmrEF and 5 year mortality is inconsistent. In men, the association between HFmrEF and 5 year mortality was closer to that in HFpEF, while in women, the association between HFmrEF and 5 year mortality was closer to that in HFrEF (*Figure 4*).

Discussion

To our knowledge, this study is the first to report the proportions and the differences in 5 year prognosis in a large cohort of patients with HF across the whole EF spectrum in southern China. Findings from our study indicated that HFpEF accounted for half of all HF patients, and one out of six individuals with HF died within 5 years. HFrEF was associated with a nearly two-fold increased risk of 5 year mortality compared with HFpEF. Declined EF category was independently associated with an increased risk of 5 year mortality. The three HF phenotypes classified by EF can be used for risk stratification, which is a good compass for clinical intervention and management (*Figure 5*).

At present, these three HF types stratified by EF are distributed differently around the world. In our study, 57% of the patients had HFpEF, 21% had HFmrEF, and 22% had HFrEF. In general, the proportion of HFpEF was relatively high, while that of HFrEF was low, which was similar to the results reported by Vergaro *et al*. (HFrEF, HFmrEF, and HFpEF accounted for 55%, 22%, and 23%, respectively), in a 2791 cohort of stable HF patients in a single centre in Italy.[5] Other studies have observed inconsistent distribution among three HF types. In a 39 982 elderly American HF registry and a 4042 Finland HF cohort study, proportions of HFpEF and HFrEF were similar,[6,8] while HFrEF accounted for the largest proportion in a 3580 Spanish cohort study, a 5414 Korean registry study, and another 10 312 European cohort study.[7,9,14] HFmrEF had the lowest proportion in all of the aforementioned studies. Furthermore, the 5 year all-cause mortality of HFrEF, HFmrEF, and HFpEF were significantly inconsistent among studies in other regions. In our study, the 5 year mortality in HFrEF was the highest, followed by that in HFmrEF and then HFpEF. Consistent with our findings, the Italian cohort reported similar results in a stable HF population.[5] However, the 5 year mortality of HFrEF, HFmrEF, and HFpEF had no significant difference in the Korean (the mortality of three groups were approximately 50%) and American cohort (the mortality of three groups were approximately 75%).[6,7] In the Spanish cohort study and Finland cohort study, patients with HFpEF even had higher mortality than those with HFrEF and HFmrEF.[8,9] In terms of clinical baseline characteristics from the aforementioned studies, patients with HFrEF were more likely to have ischaemic aetiology, higher NT-proBNP, higher rate of NYHA class III/IV status and diuretic agent usage, and lower eGFR. On the other hand, patients with HFpEF tended to be older, female, better in heart function, and higher in prevalence of diabetes, hypertension, and AF than the other two types of HF. Clinical characteristics of patients with HFmrEF were in general intermediate between HFrEF and HFpEF, in accordance with the results of previous studies.[15,16] But in our study, no similar results were observed. These heterogeneities may be attributable to difference in study design, geography, health care, and social systems. Geographic differences may be a potential factor leading to inconsistent distribution of HF phenotypes in different studies. In the ESC Heart Failure Long-Term Registry, the proportion of participants with HFpEF in the south was higher than in the rest of Europe; HFrEF was the dominant type in

Figure 2 Kaplan–Meier curves for 5 year all-cause mortality in 4880 heart failure patients. Five-year mortality in patients hospitalized with heart failure with preserved ejection fraction (HFpEF), mildly reduced ejection fraction (HFmrEF), and reduced ejection fraction (HFrEF).

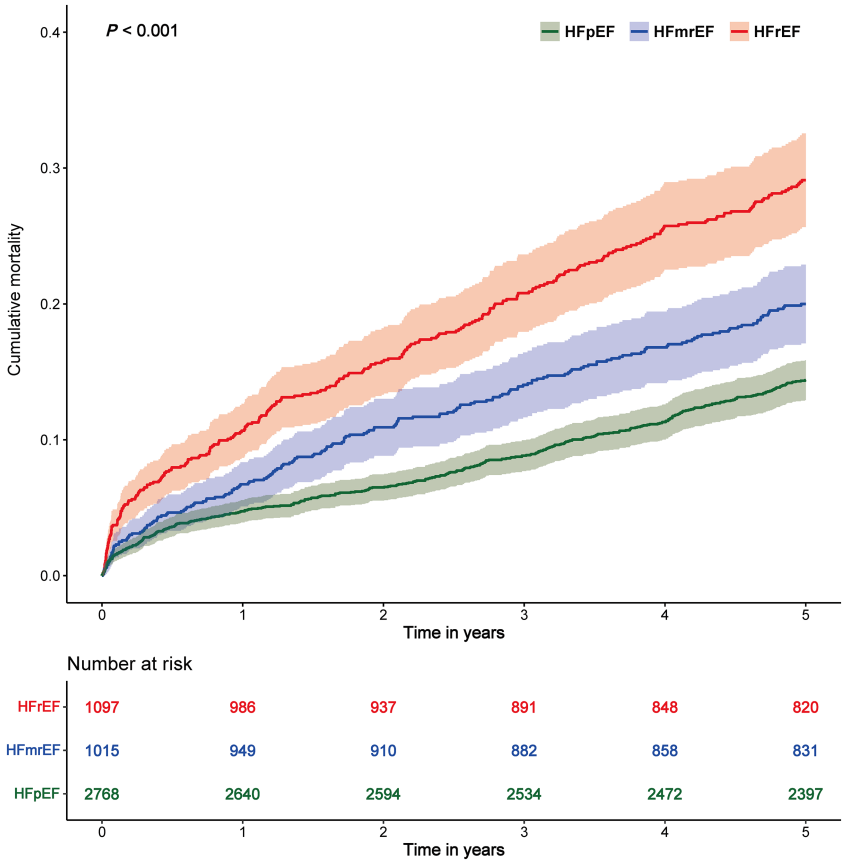


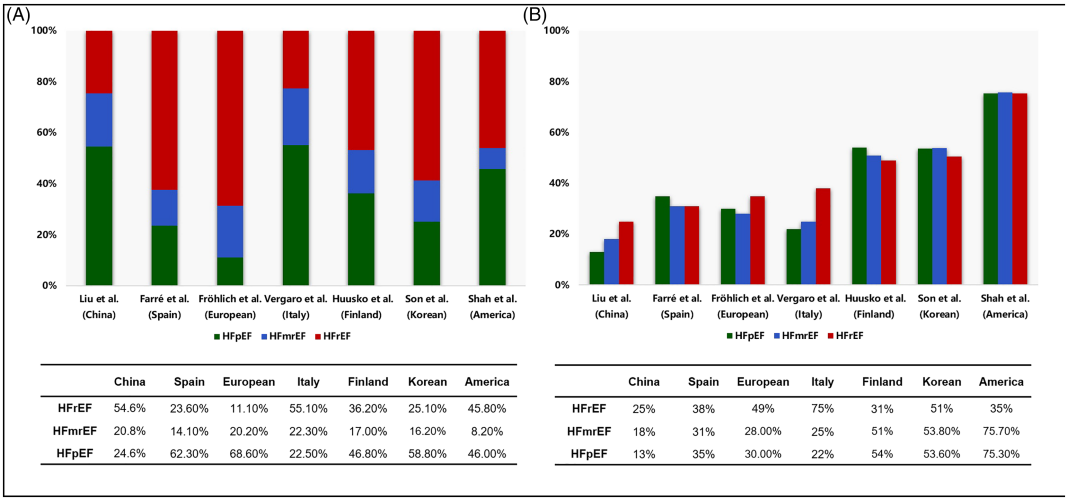
Table 2 Hazard ratios for 5 years of mortality in patients hospitalized with heart failure with preserved, mildly reduced, and reduced ejection fraction

	Model 1		Model 2		Model 3	
Characteristics	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
HFmrEF vs. HFpEF	1.40 (1.17–1.67)	<0.001	1.33 (1.11–1.59)	0.002	1.40 (1.08–1.81)	0.01
HFrEF vs. HFpEF	2.05 (1.75–2.39)	<0.001	1.92 (1.64–2.25)	<0.001	1.85 (1.45–2.35)	<0.001
HFrEF vs. HFmrEF	1.46 (1.22–1.76)	<0.001	1.45 (1.20–1.75)	<0.001	1.32 (1.02–1.71)	0.034

CI, confidence interval; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio.
Model 1: unadjusted. Model 2: adjustment for demographics (age and sex). Model 3: adjustment for demographics (age and sex), complication (acute myocardial infarction, congestive heart failure, anaemia, hypertension, diabetes, chronic kidney disease, stroke, atrial fibrillation, chronic obstructive pulmonary disease, valvular heart disease, and New York Heart Association classification), medical history (pre-acute myocardial infarction, pre-percutaneous coronary intervention, and pre-coronary artery bypass graft), examination (low-density lipoprotein cholesterol, potassium, and albumin), and discharge medication (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, beta-blocker, spironolactone, and diuretics).

all studied regions except North Africa, where HFmrEF patients outnumbered HFrEF patients.[17] In addition, race/ethnicity differences might be another potential factor. Shah *et al.* reported that among 39 982 American patients hospitalized with HF, HFrEF was more prevalent in Black (51.1%) and Hispanic (50.2%) patients compared with White (45.2%) and Asian (38.4%), while HFpEF was most common in Asian patients (52.2%), followed by White, Black, and Hispanic (46.5%, 41.7%, and 41.7%).[6] This finding may not be representative of HF patients in general, because it is a US cohort with the White race accounting for the majority of participants, but it still manages to reflect a racial disparity in the distribution of HF phenotypes of LVEF. Further studies and systemic reviews on how races contribute to HF phenotypes around the world

Figure 3 Geographic proportions of mortality of heart failure (HF) patients according to ejection fraction category. (A) Different proportions of HF with reduced ejection fraction (HFrEF), mildly reduced ejection fraction (HFmrEF), and preserved ejection fraction (HFpEF) in the China cohort and comparison with other cohorts. (B) Five-year all-cause mortality of HFrEF, HFmrEF, and HFpEF in China and comparison with other cohorts. Part of the data is extrapolated from the Kaplan–Meier curves of the self-corresponding research results, and the mortality may be overestimated. However, it does show some of the differences in mortality among the three HF types in these studies.



	China	Spain	European	Italy	Finland	Korean	America
HFrEF	54.6%	23.60%	11.10%	55.10%	36.20%	25.10%	45.80%
HFmrEF	20.8%	14.10%	20.20%	22.30%	17.00%	16.20%	8.20%
HFpEF	24.6%	62.30%	68.60%	22.50%	46.80%	58.80%	46.00%

	China	Spain	European	Italy	Finland	Korean	America
HFrEF	25%	38%	49%	75%	31%	51%	35%
HFmrEF	18%	31%	28.00%	25%	51%	53.80%	75.70%
HFpEF	13%	35%	30.00%	22%	54%	53.60%	75.30%

could be done to provide original evidence on contemporary epidemiology in this regard. Importantly, our study adds to existing scientific knowledge by providing real-world data on the distribution of three groups.

It is noteworthy that the category with lower EF was associated with an increased risk of 5 year all-cause mortality. HFrEF was associated with an 85% risk increase in 5 year mortality than HFpEF; HFmrEF was associated with a 40% increased risk of 5 year mortality compared with HFpEF; HFrEF was associated with a 32% risk increase in 5 year mortality than HFmrEF. Notably, patients with HFrEF had worse cardiac function and higher rate of AMI history, which were consistent with the previous report that cardiovascular (CV)-related causes of death were more prevalent in HFrEF patients than in the other groups.[5] In the current study, only 55.9% of HFrEF patients were prescribed with ACEI/ARBs at discharge. Similar to our result, in the Heart Failure of Registry of Patient Outcomes (HERO) study that included 5620 Chinese patients with acute HF from November 2017 to November 2018, of 668 patients with elevated B-type natriuretic peptide and EF $<$ 40%, only 52.2% received ACEIs, ARBs, or angiotensin receptor blocker-neprilysin inhibitor (ARNI) therapy on discharge.[18] However, percentage of ACEI/ARBs use at discharge in our study is lower compared with the China Heart Failure (China-HF) Registry, which reported that 67.5% HFrEF patients, defined as LVEF $<$ 45%, were prescribed with ACEI/ARBs at discharge.[19] The insufficiency of guideline-recommended treatment might be accountable for the higher risk of long-term mortality in HFrEF than in the other groups in our study. The higher prevalence of CKD and lower eGFR may affect the application of evidence-based medications in eligible patients. Patients with HFmrEF also had a higher prevalence of CAD, hypertension, and anaemia, which are important risk factors of mortality. Previous studies have reported that nearly one-third of all patients with HF have anaemia, and its presence is associated with various clinical symptoms, increased rates of hospitalization, and increased mortality.[20–22] CAD commonly causes left ventricular systolic dysfunction because of ischaemia and fibrosis, and hypertension is also a common cause of LV hypertrophy. ACEI/ARB proved to be effective in protecting the CV system from a further progression of atherosclerosis, LV hypertrophy, and thrombosis.[23] HFpEF was more common in women, and the higher prevalence of AF was in line with previous studies.[7,24] Son *et al*. reported that AF was associated with a 20% increased risk for all-cause and CV mortality only in patients with HFpEF and not in those with HFrEF and HFmrEF, but the reason remained unclear.[7] It should be noted by clinicians that the percentage of AF in HFpEF reached 30% in our cohort. VHD was more prevalent in HFpEF patients and could worsen the cardiac function for it is not often treated timely and effectively. In women, the risk of mortality of HFmrEF was closer to that of HFrEF, while in men, HFmrEF was closer to that of HFpEF. One possible explanation for this phenomenon is that impaired LVEF is mostly related to myocardial ischaemia due to atherosclerosis, which has a poorer prognosis in women.[25] Moreover, previous studies have shown that there are important sex differences in pharmacokinetics and pharmacodynamics, which may be one of the potential causes of this phenomenon.[26] Therefore, there is a critical need to develop effective therapeutic strategies and individualized treatment options. One possible mechanism accounting for the poor prognosis in HFrEF is that the declined EF may be an alternative indicator of myocardial remodelling.

Figure 4 Forest plots of hazard ratio and Kaplan–Meier curves for 5 year all-cause mortality in subgroup analysis by gender. Hazard ratio adjusted for demographics (age), complication (acute myocardial infarction, congestive heart failure, anaemia, hypertension, diabetes, chronic kidney disease, stroke, atrial fibrillation, chronic obstructive pulmonary disease, valvular heart disease, and New York Heart Association classification), medical history (pre-acute myocardial infarction, pre-percutaneous coronary intervention, and pre-coronary artery bypass graft), examination (low-density lipoprotein cholesterol, potassium, and albumin), and discharge medication (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, beta-blockers, spironolactone, and diuretics). CI, confidence interval; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

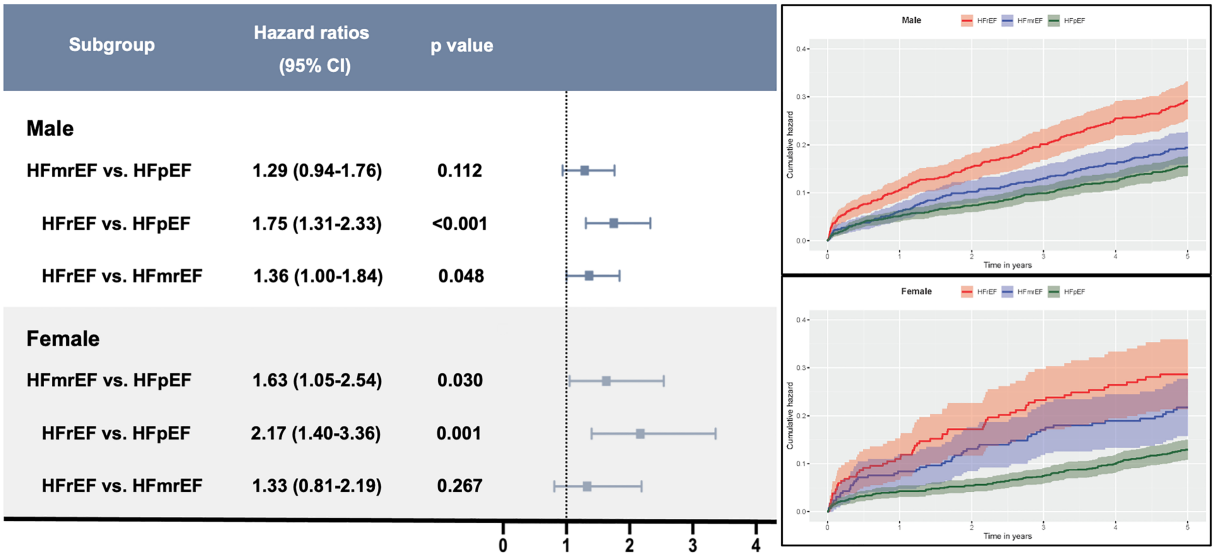
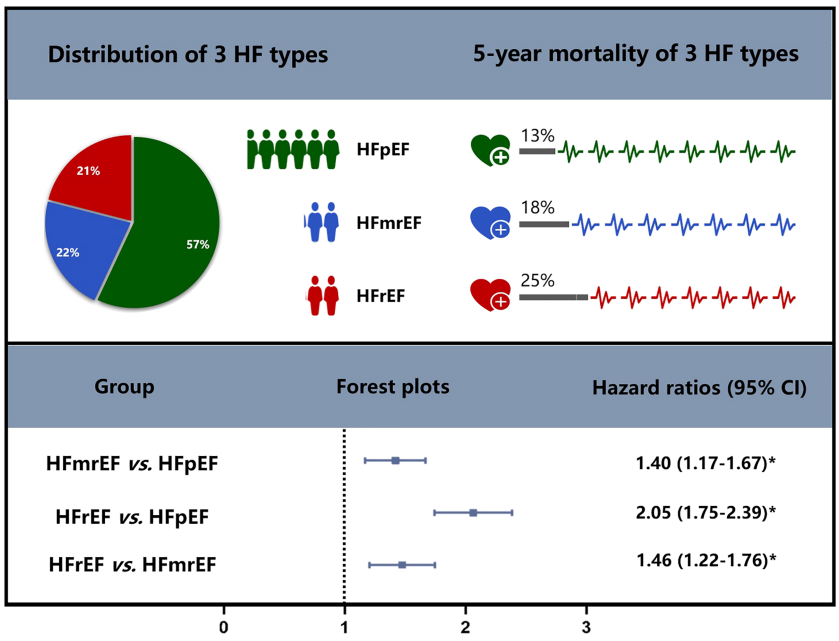


Figure 5 Graphical abstract of the current study. Different proportions of patients with heart failure with reduced ejection fraction (HFrEF), mildly reduced ejection fraction (HFmrEF), or preserved ejection fraction (HFpEF); 5 year mortality of patients with HFrEF, HFmrEF, or HFpEF; forest plots of hazard ratio among HFrEF, HFmrEF, and HFpEF. CI, confidence interval.



Although myocardial remodelling may compensate for abnormal haemodynamic parameters and function in the short term, subsequent haemodynamic load and neurohormonal activation may lead to deterioration of cardiac function, resulting in a poor prognosis.[27,28] In HFpEF, extracardiac comorbidities and renal insufficiency can cause left ventricular

remodelling and dysfunction via systemic inflammation and coronary microvascular endothelial dysfunction.[29] We can only suppose the mechanism is the same, due to the lack of studies on the prognosis of HFmrEF.

Findings from our study support the need for cardiologists to consciously distinguish HF in their daily practice, although such distinction is somewhat arbitrary. This may improve risk stratification and guide subsequent interventions of secondary prevention. EF can be easily assessed during routine clinical practice and may provide clinical decision support tools for improving long-term mortality in HF patients. Both current and previous findings suggest that classification of patients in three HF types is not static.[9] Screening HF patients with declined EF might identify patients at high risk of adverse 5 year outcomes and benefit them from tailored secondary prevention programmes with treatment options to improve their prognosis. In terms of treatment strategies, ARNI and the sodium-glucose cotransporter 2 inhibitor (SGLT2i) have been listed as first-line medications in guidelines and evidence-based medicine.[30,31] The SGLT2i empagliflozin has been proved to significantly improve clinical outcomes for HF patients with EF $<$ 25% to $<$65%, although the effect was attenuated in patients with EF $\geq$ 65%.[32] Meanwhile, two new drugs, vericiguat and omecamtiv mecarbil, were proved effective in patients with HFrEF in the VICTORIA[31] and the COSMIC-HF trial.[33] In addition, implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT) have been recommended to prevent sudden death or improve heart function for high-risk patients, but these devices have been underused in our country until now.[19,34] Screening, diagnosis, and treatment of sleep apnoea were also shown to be beneficial to the prognosis of HFrEF.[4,35] Cardiologists should keep abreast of new research evidence and recommendations on such topics to provide meaningful and effective guidance. The medical treatment has an obvious therapeutic effect on HFrEF and HFmrEF but has a limited effect on HFpEF. Although the prevalence of HFpEF has increased significantly in recent years,[36] the treatment for HFpEF remains a challenge for clinicians. It is also necessary to develop multidisciplinary interventions for HF patients to provide appropriate treatment for this population to improve their quality of life. Exercise training in HFpEF has shown benefits in improving exercise tolerance and managing obesity.[37] Clinicians should refer patients with HFpEF to exercise programmes when appropriate. Specific therapeutic evidence for HFmrEF is lacking, and current guidelines recommend that HFmrEF should be treated similarly to HFpEF.[4] The goal of multimodal and multidisciplinary care would be to optimize cardiologists' individualized treatment strategies for HF patients with different EF phenotypes.

This is a single-centre, observational study with the inherent disadvantage due to its nature, so our inferences did not reflect direct causality. However, because it is single centre, the standard of testing and diagnosis is relatively uniform and the results obtained are relatively reliable. Secondly, all patients in our study underwent CAG and had a high prevalence of CAD, which is the most common cause of HF. Although we adjusted variables including demographics, medical history, laboratory examinations, and medications, there may be additional potential confounders that were not accounted for in our study. Unfortunately, our data did not record the specific cause of death and other adverse events of the patients, so we were unable to evaluate the information from additional dimensions. Thirdly, because this study was conducted in a CAG population, it only illustrated a subpopulation of HF patients and could not represent the general population of HF patients. However, to a certain extent, it provides a more targeted guidance for cardiologists. In addition, because we performed a single baseline evaluation, we could not identify patients with recovered EF, whose outcomes may be different from other HF categories. In the future, larger prospective cohorts should be utilized to evaluate the effect of dynamic EF changes on prognosis.

In conclusion, patients with HFpEF are common in southern China, followed by those with HFrEF. HFrEF was associated with a nearly two-fold increased risk of 5 year mortality than HFpEF. Declined EF was associated with an elevated risk of 5 year all-cause mortality. These findings underscore the risk stratification across the EF spectrum and will be a crucial step in the development of strategies to reduce the burden of mortality. Further studies are needed to prospectively evaluate the efficacy of improving treatment on outcomes in all three HF phenotypes.

Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Characteristics of 6 studies in different countries or regions. *Data is not shown in the paper and is acquired through a calculation based on the baseline characteristics.

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