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

Shiqun Chen1*, Zhidong Huang1, Yan Liang2, Xiaoli Zhao3, Xiemuxikaimaier Aobuliksimu4, Bo Wang1, Yibo He1, Yu Kang1, Haozhang Huang1, Qiang Li1, Younan Yao1, Xiaozhao Lu1, Xiaoxian Qian3, Xujing Xie3, Jin Liu1* and Yong Liu1*

1Department 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; 2Maoming People’s Hospital, Maoming, China; 3The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China; and 4The 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 ≥ 50%), HFmrEF (EF 41 – 49%), and HFrEF (EF ≤ 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; HFrEF—heart failure with reduced ejection fraction

Received: 21 July 2021; Revised: 18 February 2022; Accepted: 27 March 2022

*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; jinniu09397017568@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 (HFrEF), 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 HFrEF 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 \(\geq 18\) 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.
| Characteristics                  | Overall N = 4880 | HFrEF n = 1015 | HfmrEF n = 1097 | HFpEF n = 2768 | P values | % Std. Diff. |
|---------------------------------|-----------------|----------------|-----------------|----------------|----------|--------------|
| **Age, years**                  |                 |                |                 |                | <0.001   |              |
| **Male**                        | 3156 (64.67)    | 1546 (55.85)   | 754 (74.29)     | 856 (78.03)    | <0.001   |              |
| **Medical history**             |                 |                |                 |                | <0.001   |              |
| **AMI**                         | 1115 (22.85)    | 562 (20.30)    | 360 (35.47)     | 193 (17.59)    | <0.001   |              |
| **CHF**                         | 1056 (21.64)    | 513 (18.53)    | 227 (22.36)     | 316 (28.81)    | <0.001   |              |
| **Anaemia**                     | 1962 (40.84)    | 1093 (40.31)   | 448 (45.12)     | 421 (38.73)    | 0.006    |              |
| **Hypertension**                | 1986 (40.70)    | 1047 (37.83)   | 504 (49.66)     | 435 (39.65)    | <0.001   |              |
| **DM**                          | 1071 (21.95)    | 480 (17.34)    | 273 (26.90)     | 318 (28.99)    | <0.001   |              |
| **CKD**                         | 1483 (30.39)    | 748 (27.02)    | 333 (32.81)     | 402 (36.65)    | <0.001   |              |
| **Stroke**                      | 284 (5.82)      | 172 (6.21)     | 53 (5.22)       | 59 (5.38)      | 0.399    |              |
| **Arrhythmia**                  | 1054 (21.60)    | 852 (30.78)    | 105 (10.34)     | 97 (8.84)      | <0.001   |              |
| **COPD**                        | 41 (0.84)       | 14 (0.51)      | 15 (1.48)       | 12 (1.09)      | <0.001   |              |
| **VHD**                         | 1753 (35.92)    | 1264 (45.66)   | 204 (20.10)     | 285 (25.98)    | <0.001   |              |
| **Pre-AMI**                     | 3164 (64.84)    | 1488 (53.76)   | 204 (20.10)     | 285 (25.98)    | <0.001   |              |
| **Pre-PCI**                     | 266 (5.45)      | 111 (4.01)     | 78 (7.68)       | 77 (7.02)      | <0.001   |              |
| **Pre-CABG**                    | 24 (0.49)       | 11 (0.40)      | 4 (0.39)        | 9 (0.82)       | 0.210    |              |
| **Dialysis history**            | 43 (0.88)       | 21 (0.76)      | 11 (1.08)       | 11 (1.00)      | 0.566    |              |
| **In-hospital dialysis**        | 118 (2.42)      | 62 (2.24)      | 30 (2.96)       | 26 (2.37)      | 0.443    |              |
| **Heart function**              | 122 (3.96)      | 50 (2.97)      | 32 (5.41)       | 40 (4.95)      | 0.001    | 12.2         |
| **NYHA class I**                | 884 (28.68)     | 515 (30.60)    | 176 (29.78)     | 193 (23.89)    | <0.001   |              |
| **NYHA class II**               | 1379 (44.74)    | 755 (44.86)    | 259 (43.82)     | 365 (45.17)    | <0.001   |              |
| **NYHA class III**              | 697 (22.62)     | 363 (21.57)    | 124 (20.98)     | 210 (25.99)    | <0.001   |              |
| **NYHA class IV**               | 122 (3.96)      | 50 (2.97)      | 32 (5.41)       | 40 (4.95)      | 0.001    | 12.2         |
| **Laboratory findings**         |                 |                |                 |                | <0.001   |              |
| **LDL-C, mmol/L**               | 2.78 ± 0.99     | 2.68 ± 0.96    | 2.68 ± 0.93     | 2.85 ± 1.12    | 0.041    | 0.8          |
| **HDL-C, mmol/L**               | 1.00 ± 0.29     | 1.01 ± 0.30    | 0.97 ± 0.28     | 0.97 ± 0.28    | <0.001   | 22.4         |
| **ALB, g/L**                    | 33.82 ± 4.80    | 34.40 ± 4.82   | 32.96 ± 4.69    | 33.16 ± 4.63   | <0.001   | 30.1         |
| **ProBNP, pg/mL**               | 2114.5          | 2143           | 2352            | 3426           | <0.001   | 26.4         |
| **eGFR, mL/min/1.73 m²**        | 69.40 ± 25.11   | 71.43 ± 25.01  | 68.50 ± 26.45   | 65.28 ± 23.52  | <0.001   | 11.4         |
| **CHOL, mmol/L**                | 4.53 ± 1.19     | 4.54 ± 1.16    | 4.48 ± 1.18     | 4.53 ± 1.29    | 0.042    | 4.9          |
| **Potassium, mEq/L**            | 3.82 ± 0.49     | 3.82 ± 0.49    | 3.81 ± 0.50     | 3.82 ± 0.50    | 0.819    | 1.5          |
| **ACEI or ARB**                 | 2057 (43.78)    | 972 (36.26)    | 504 (51.53)     | 581 (55.87)    | <0.001   | 31.2         |
| **Beta-blocker**                | 3088 (65.72)    | 1543 (57.55)   | 754 (77.10)     | 791 (76.06)    | <0.001   | 42.6         |
| **Spirolactone**                | 2471 (52.59)    | 1335 (49.79)   | 422 (43.15)     | 714 (68.65)    | <0.001   | 13.4         |
| **Furosemide**                  | 2505 (53.31)    | 1380 (51.47)   | 431 (44.07)     | 694 (66.73)    | <0.001   | 14.9         |
| **Thiazide**                    | 172 (3.66)      | 91 (3.29)      | 27 (2.76)       | 54 (6.19)      | 0.008    | 3.7          |
| **CCB**                         | 677 (14.41)     | 435 (16.23)    | 125 (12.78)     | 117 (11.25)    | <0.001   | 9.8          |

(Continues)
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 ≤ 40%), HFmrEF (EF 41–49%), or HfPEF (EF ≥ 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^ 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 ≤ 39% (male) or ≤36% (female). Hypertension and diabetes mellitus (DM) were defined using ICD-10 codes.

---

**Table 1 (continued)**

| Characteristics | EF category | Overall | HFpEF | HFmrEF | HFrEF | P values | % Std. Diff. |
|-----------------|-------------|---------|-------|--------|--------|----------|-------------|
| Echocardiography | Overall | n = 4880 | n = 2768 | n = 1015 | n = 1097 | 83.7 | 81.1 |
| | N = 4880 | 48.27 ± 7.43 | 31.11 ± 6.48 | 40.40 ± 7.58 | 50.44 ± 10.20 | < 0.001 | 13 |
| Follow-up death, 5 years | 832 (17.05) | 371 (13.40) | 184 (18.13) | 277 (25.25) | < 0.001 | 13 |

Values are mean ± standard deviation, number (%), or median (inter-quartile range). Standardized differences (Std. Diff.) of 10% or higher indicate relevant differences.

---

The **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 years 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. 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, while HFmrEF accounted for the largest proportion in a 3580 Spanish cohort study, a 5414 Korean registry study, and another 10 312 European cohort study. HFrEF 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. 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%). In the Spanish cohort study and Finland cohort study, patients with HfPEF even had higher mortality than those with HFrEF and HFmrEF. 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. But in our study, no similar results were observed. These heterogeneities may be attributable to differences 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...
all studied regions except North Africa, where HFmrEF patients outnumbered HFrEF patients. 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%). 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.

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

| Characteristics          | Model 1   |          | Model 2   |          | Model 3   |          |
|--------------------------|-----------|----------|-----------|----------|-----------|----------|
|                          | 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), 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).

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).
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; 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.\textsuperscript{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 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{5} 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.\textsuperscript{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.\textsuperscript{23} HFpEF was more common in women, and the higher prevalence of AF was in line with previous studies.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.
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 HFrEF, extracardiac co-morbidities and renal insufficiency can cause left ventricular...
remodelling and dysfunction via systemic inflammation and coronary microvascular endothelial dysfunction.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\%.\textsuperscript{32} Meanwhile, two new drugs, vericiguat and omecamtiv mearcil, were proved effective in patients with HFrEF in the VICTORIA\textsuperscript{31} and the COSMIC-HF trial.\textsuperscript{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.\textsuperscript{19,34} Screening, diagnosis, and treatment of sleep apnoea were also shown to be beneficial to the prognosis of HFrEF.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.

**Funding**

This research was funded and supported by the National Key Research and Development Program of China (Grant 2016YFC1301202), Multi-center study on key techniques for prevention, diagnosis and treatment of high risk coronary artery disease (DFJH2020026), Study on the function and mechanism of the potential target for early warning of cardiorenal syndrome after acute myocardial infarction based on transformism (DFJH201919), Natural Science Foundation of Guangdong Province General Project (2020A1515010940), and Science and Technology Planning Project of Guangdong Province (2017B030314041). The funders had no role in the study design, data collection, and analysis, decision to publish, or preparation of the manuscript; the work was not funded by any industry sponsors.
Five-year mortality of HfPEF, HfMR EF, and HfREF

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.

References

1. Ziaeian B, Fonarow GC. Epidemiology and aetiology of heart failure. *Nat Rev Cardiol.* 2016;13:36–378.

2. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, Aboyans V, Abraham J, Ackerman I, Aggarwal R, Ahn SY, Ali MK, AlMazroa MA, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Bahalim AN, Barker-Collo SL, Barrero LH, Bartels DH, Basuáñez MG, Baxter A, Bell ML, Benjamin EJ, Bennett D, Bernabe E, Bhalla K, Bhandari B, Bikbov B, Abdulkhal AB, Birbeck G, Black JA, Blencowe H, Blore JD, Blyth F, Bollinger I, Bonaventure A, Bouroua S, Bourne SR, Boussiasq M, Braithwaite T, Brayne C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-Hancock C, Bucello C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-Hancock C, Bucello C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-Hancock C, Bucello C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-Hancock C, Bucello C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-Hancock C, Bucello C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-Hancock C, Bucello C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-Hancock C, Bucello C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-H Hancock C, Bucello C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-H Hancock C, Bucello C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-H Hancock C, Bucello C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-H Hancock C, Bucello C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-H Hancock C, Bucello C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-H Hancock C, Bucello C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-H Hancock C, Bucello C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-H Hancock C, Bucello C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-H Hancock C, Bucello C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-H Hancock C, Bucello C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-H Hancock C, Bucello C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-H Hancock C, Bucello C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-H Hancock C, Bucello C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-H Hancock C, Bucello C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-H Hancock C, Bucello C, Bridgett L, Brooker S, Broo...
10. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, Gong Y, Liu PP. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med*. 2006; 355: 260–269.

11. Bodkurt B, Coats AJS, Tsutsui S, Abdelhamid CM, Adamopoulos S, Albert N, Anker SD, Atherton J, BöhM M, Butler J, Dzarnaz MH, Michael Felker G, Filipatos G, Fiuzaet M, Fonarow GC, Gomez-Mesa JE, Heidenreich P, Imamura T, Jankowska EA, Januzzi JL, Khazanie P, Kinugawa K, Lam CSP, Matsue Y, Metra M, Ohtani T, Francesco Piepoli M, Ponikowski P, Rosano GMC, Sakata Y, Sferovic P, Starling RC, Teerlink JR, Vardeny O, Yamamoto K, Yancy C, Zhang J, Zieroth S. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. *Eur J Heart Fail*. 2021; 23: 352–380.

12. Ibrahim NE, Burnett JC Jr, Butler J, Camacho A, Felker GM, Fiuzaet M, O’Connor C, Solomon SD, Vaduganathan M, Zile MR, Januzzi JL Jr. Natriuretic peptides as inclusion criteria in clinical trials: a JACC Heart Failure position paper. *JACC Heart Fail*. 2020; 8: 347–358.

13. Aguiar-Souto P, Ferrante G, Del Furia F, Barlis P, Khurana R, Di Mario C. Frequency and predictors of contrast-induced nephropathy after angiography for chronic total occlusions. *Int J Cardiol*. 2010; 139: 68–74.

14. Fröhlich H, Rosenfeld N, Täger T, Goode JS, Zannad F, Hole T, Katus HA, Atar D, Cleland JGF, Agewall S, Clark AL, Francofilo, Frankenstein L, Grundtvig M. Epidemiology and long-term outcome in outpatients with chronic heart failure in Northwestern Europe. *Heart*. 2019; 105: 1252–1259.

15. Toma M, Ezekowitz JA, Bakal JA, O’Connor CM, Hernandez AF, Sardar MR, Zolyt R, Massie BM, Swedberg K, Armstrong PW, Starling RC. The relationship between left ventricular ejection fraction and mortality in patients with acute heart failure: insights from the ASCEND-HF Trial. *Eur J Heart Fail*. 2014; 16: 334–341.

16. Rickenbacher P, Kaufmann BA, Maeder MT, Bernheim A, Goetschalckx K, Pfister O, Pfisterer M, Brunner-la Rocca HP, TIME-CHF Investigators. Heart failure with mid-range ejection fraction: a distinct clinical entity? Insights from the Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF). *Eur J Heart Fail*. 2017; 19: 1586–1596.

17. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, Parissis J, Laroche C, Piepoli MF, Fonseca C, Mebazaa A, Lund L, Ambrosio GA, Coats AJ, Ferrari R, Ruschitzka F, Maggioni AP, Filippatos G. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2017; 19: 1574–1585.

18. Li L, Liu R, Jiang C, du X, Huffman MF, Lam CSP, Patel A, Hillsis GS, Anderson CS, Ma C, Zhao X, Wang X, Li L, Dong J. Assessing the evidence-practice gap for heart failure in China: the Heart Failure Registry of Patient Outcomes (HERO) study design and baseline characteristics. *Eur J Heart Fail*. 2020; 22: 646–660.

19. Zhang Y, Zhang J, Butler J, Yang X, Xie P, Guo D, Wei T, Yu J, Wu Z, Gao Y, Han X, Zhang X, Wen S, Anker SD, Filipatos G, Fonarow GC, Gan T, Zhang R, China-HF Investigator Group. Characteristics of community epidemiology, management, and outcomes of patients hospitalized for heart failure in China: results from the China Heart Failure (China-HF) Registry. *J Card Fail*. 2017; 23: 868–875.

20. Amanal JS, Gupta P. Anemia and iron deficiency in heart failure: current concepts and emerging therapies. *Circulation*. 2018; 138: 80–98.

21. Grote Beverborg N, van Veldhuisen DJ, de Camacho A, Felker GM, Fiuzat M, B, Gafeer MM, Lima BB, Kim JH, Ward NK, Bernheim A, Goeschalck K, Pfister O, Pfisterer M, Brunner-la Rocca HP, TIME-CHF Investigators. Heart failure with mid-range ejection fraction: a distinct clinical entity? Insights from the Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF). *Eur J Heart Fail*. 2017; 19: 1586–1596.

22. Lown L, Grundtvig M, Zile MR, Januzzi J, Jr. Natriuretic peptides as inclusion criteria in clinical trials: a JACC: Heart Failure position paper. *JACC Heart Fail*. 2020; 8: 347–358.

23. Aguiar-Souto P, Ferrante G, Del Furia F, Barlis P, Khurana R, Di Mario C. Frequency and predictors of contrast-induced nephropathy after angiography for chronic total occlusions. *Int J Cardiol*. 2010; 139: 68–74.

24. Fröhlich H, Rosenfeld N, Täger T, Goode JS, Zannad F, Hole T, Katus HA, Atar D, Cleland JGF, Agewall S, Clark AL, Frankenstein L, Grundtvig M. Epidemiology and long-term outcome in outpatients with chronic heart failure in Northwestern Europe. *Heart*. 2019; 105: 1252–1259.

25. Toma M, Ezekowitz JA, Bakal JA, O’Connor CM, Hernandez AF, Sardar MR, Zolyt R, Massie BM, Swedberg K, Armstrong PW, Starling RC. The relationship between left ventricular ejection fraction and mortality in patients with acute heart failure: insights from the ASCEND-HF Trial. *Eur J Heart Fail*. 2014; 16: 334–341.

26. Lam CSP, Arnott C, Beale AL, Chandramouli C, Hilfiker-Kleiner D, Kaye DM, Ky B, Santema BT, Sliwa K, Voors AA. Sex differences in heart failure. *Eur Heart J*. 2019; 40: 3859–3868C.

27. Aimo A, Gaggin HK, Barston A, Emdin M, Januzzi JL Jr. Imaging, biomarker, and clinical predictors of cardiac remodeling in heart failure with reduced ejection fraction. *JACC Heart Fail*. 2019; 7: 782–794.

28. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling—concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. *J Am Coll Cardiol*. 2000; 35: 569–582.

29. Shah SJ, Kritzman DW, Borlaug BA, van Heerebeek L, Zile MR, Kass DA, Paulus WJ. Phenotype-specific treatment of heart failure with preserved ejection fraction: a multigorgan roadmap. *Circulation*. 2016; 134: 73–90.

30. Heidenreich PA, Fonarow GC, Breathekk K, Jurgens CY, Pisani BA, Pozehl BJ, Specht JA, Taylor KC, Thibodeaux JT, Vempaty CW, Ziaeian B. 2020 ACC/AHA clinical performance and quality measures for adults with heart failure: a report of the American College of Cardiologys/American Heart Association Task Force on Performance Measures. *J Am Coll Cardiol*. 2020; 76: 2527–2564.

31. Vaduganathan M, Caggett BL, Hjund PS, Cunningham JW, Pedro Ferreira J, Zannad F, Packer M, Fonarow GC, McMurray JIV, Solomon SD. Estimating lifetime benefits of comprehensive disease-modifying pharmacological ther- apies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. *Lancet*. 2020; 396: 121–128.

32. Butler J, Packer M, Filipatos G, Ferreira JP, Zeller C, Schnee J, Brueckmann M, Pocock SJ, Zannad F, Anker SD. Effect of empagliflozin in patients with heart failure across the spectrum of left ventricular ejection fraction. *Eur Heart J*. 2022; 43: 416–426.

33. Biering-Sørensen T, Minamisawa M, Caggett B, Liu J, Felker GM, McMurray JJV, Malik FI, Abbasi S, Kurcz CE, Teerlink JR, Solomon SD. Cardiac myosin activator omecamtiv mcecarib improves left ventricular myocardial deformation in chronic heart failure: the COSMIC-HF trial. *Circ Heart Fail*. 2020; 13: e008007.

34. Mullens W, Aurichio A, Martens P, Witte K, Cowie MR, Delgado V, Dickstein K, Linde C, Verneyo K, Levy F, Bausersachs J, Israel CW, Lund LH, Donal E, Borian G, Jaarsma T, Berruzo A, Traykov V, Yousef Z, Kalarus Z, Coseduez Nielsen J, Cardoza A, Coats A, Seferovic P, Edvardsen T, Heidbuechel H, Ruschitzka F, Leclercq C. Optimized implementation of cardiac resynchronization therapy: a call for ac-
tion for referral and optimization of care: a joint position statement from the Heart Failure Association (HFA), European Heart Rhythm Association (EHRA), and European Association of Cardiovascular Imaging (EACVI) of the European Society of Cardiology. Eur J Heart Fail. 2020; 22: 2349–2369.

35. Yumino D, Kasai T, Kimmerly D, Amirthalingam V, Floras JS, Bradley TD. Differing effects of obstructive and central sleep apneas on stroke volume in patients with heart failure. Am J Respir Crit Care Med. 2013; 187: 433–438.

36. Ruiz-Ruiz F, Menéndez-Orenga M, Medrano FJ, Calderón EJ, Lora-Pablos D, Navarro-Puerto MA, Rodríguez-Torres P, Gómez de la Cámara A. The prognosis of patients hospitalized with a first episode of heart failure, validation of two scores: PREDICE and AHEAD. Clin Epidemiol. 2019; 11: 615–624.

37. Taylor RS, Davies EJ, Dalal HM, Davis R, Doherty P, Cooper C, Holland DJ, Jolly K, Smart NA. Effects of exercise training for heart failure with preserved ejection fraction: a systematic review and meta-analysis of comparative studies. Int J Cardiol. 2012; 162: 6–13.