

# Characteristics and outcomes of transitions among heart failure categories: a prospective observational cohort study

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## Abstract

**Aims** Patients with heart failure (HF) are typically designated as having reduced, mid-range, or preserved ejection fraction (EF) (HF<sub>r</sub>EF, HF<sub>m</sub>rEF, or HF<sub>p</sub>EF, respectively) because of the importance of left ventricular EF (LVEF) on therapeutic decisions and prognosis. However, such designations are not necessarily static, as there are many transitions among the three HF phenotypes during follow-up. This prospective longitudinal cohort study sought to examine the HF transitions over time and their clinical characteristics, prognosis, and response to medical therapy.

**Methods and results** We identified 1920 patients from a prospective cohort with a primary diagnosis of HF between 1 January 2007 and 31 December 2012. The enrolled HF patients were re-classified into three groups on the basis of baseline and 1 year follow-up echocardiography: HF with improved EF (HF<sub>i</sub>EF), HF with deteriorated EF (HF<sub>d</sub>EF), and HF with unchanged EF (HF<sub>u</sub>EF). The primary outcome was 5 year all-cause mortality. According to 1 year follow-up echocardiography, 490 (25.5%) were diagnosed as HF<sub>i</sub>EF, 179 (9.3%) as HF<sub>d</sub>EF, and 1251 (65.2%) as HF<sub>u</sub>EF. Ischaemic heart disease was an independent predictor of HF<sub>d</sub>EF, and beta-blocker prescription was an independent predictor of HF<sub>i</sub>EF. During the 5 year follow-up, patients with HF<sub>d</sub>EF had higher mortality, whereas patients with HF<sub>i</sub>EF had lower mortality. After adjustment, HF<sub>i</sub>EF, compared with HF<sub>u</sub>EF, was associated with a 62.1% decreased risk for mortality. Finally, the use of beta-blockers was associated with improved prognosis of patients with HF<sub>i</sub>EF and HF<sub>u</sub>EF.

**Conclusions** In this cohort of patients with HF, LVEF is a dynamic factor related to coexisting conditions and drug therapy. HF<sub>i</sub>EF and HF<sub>d</sub>EF are distinct HF phenotypes with different clinical outcomes than other phenotypes.

**Keywords** Heart failure; Left ventricular ejection fraction; Transition; Prognosis

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## Introduction

Patients are typically classified into heart failure (HF) with preserved EF (HF<sub>p</sub>EF), with mid-range EF (HF<sub>m</sub>rEF), or with reduced EF (HF<sub>r</sub>EF) on the basis of left ventricular EF (LVEF) at HF diagnosis.<sup>1</sup> However, LVEF is not necessarily static, as LVEF can worsen over time owing to progressive heart disease, or it can improve in response to HF treatment or reversal of the underlying pathogenesis.<sup>2,3</sup> Recent studies suggest that the changes of LVEF during follow-up might be associated with clinical prognosis.<sup>4,5</sup> To date, little is known about

the transitions among the three HF categories in the same cohort that occur over time and their clinical characteristics, prognosis, and response to medical therapy.

The objectives of this prospective longitudinal cohort study were to examine the natural history of LVEF in a cohort of patients with HF and to identify the factors associated with the transitions among different HF phenotypes and death. An understanding of the pattern of HF transitions over time in a representative cohort and the relationship of clinical factors and treatment to these patterns would help guide decisions

about the follow-up frequency, need for repeat cardiac imaging, prognostic evaluation, and treatment strategy.

## Methods

### Study design and population

We conducted a prospective longitudinal cohort study of adults with HF from Shanghai Ninth People's Hospital. Patients were those over age 18 years with a clinical diagnosis of HF, according to the attending physician. Recruitment occurred where the patient was either in the hospital for a primary diagnosis of HF (the assessment was performed following stabilization of the acute HF) or in the outpatient setting within 3 months of an episode of decompensated HF (requiring hospitalization or treatment in an outpatient setting). Exclusion criteria included severe valve disease, transient acute pulmonary oedema in the context of primary acute coronary syndrome, end-stage renal failure [estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m<sup>2</sup>], specific HF subgroups (including constrictive pericarditis, congenital heart disease, hypertrophic cardiomyopathy, cardiac amyloid, and chemotherapy-associated cardiomyopathy), isolated right HF, and life-threatening co-morbidity with life expectancy < 1 year. According to a baseline echocardiographic assessment, patients with HF were classified into those with HFrEF (LVEF < 40%), HFmrEF (40% ≤ LVEF < 50%), and HFpEF (LVEF ≥ 50%).<sup>1</sup> All participants were encouraged to undergo follow-up echocardiography after 1 year from initial recruitment. After 1 year follow-up, these patients shifted to higher HF category from baseline (including from HFrEF to HFmrEF/HFpEF, or from HFmrEF to HFpEF), referred to as 'HF with improved LVEF' (HFIEF). These patients transitioned to lower HF phenotype from baseline (including from HFpEF to HFmrEF/HFrEF, or from HFmrEF to HFrEF), referred to as 'HF with deteriorated LVEF' (HFDEEF). And the rest of enrolled patients were referred to as 'HF with unchanged LVEF' (HFUEF). In terms of medication, the use of beta-blockers, renin-angiotensin system (RAS) inhibitors, and mineralocorticoid receptor antagonist (MRA) in HF patients was up to the attending physician on the basis of clinical guidelines. The study protocol was approved by the local ethics committee, and informed consent was obtained from all patients.

### Echocardiography

Transthoracic echocardiography was performed using the Cardiovascular Ultrasound System (GE VIVIDT, GE Healthcare, LaMarque, TX, USA) as we previously described.<sup>6-8</sup> Briefly, the frequency of the ultrasonic probe was 2.5 MHz. Standard techniques were adopted to obtain M-mode, two-

dimensional, and Doppler measurements, in accordance with the American Society of Echocardiography's guidelines.<sup>9</sup> LV volumes were measured using the biplane method of disks, and LVEF was determined using biplane modified Simpson's measurements. All our enrolled patients have undergone echocardiography at index admission and 1 year thereafter. And all echocardiography tests were performed at a single echocardiography laboratory, which had followed strict standards of practice such that an LVEF assessment likely had high internal validity. According to our internal statistics, the variation in measurements between the two investigators was 3.5%.

### Endpoints and follow-up

The primary outcome of this study was defined as 5 year all-cause mortality from the time of 1 year follow-up echocardiography. Most of the patients visited our outpatient clinic at least every 3 months. However, if the patients did not appear at their scheduled clinic, they were interviewed by telephone annually. Information regarding the primary outcomes was documented in chart records and via telephone interviews. For each patient, the time to death was calculated from the time of 1 year follow-up echocardiography to the date that the primary outcome occurred.

### Statistical analysis

Statistical analysis was performed using SPSS Statistical Software, Version 22.0 (SPSS Inc., Chicago, IL, USA). Arithmetic means ± standard deviations were calculated for quantitative variables, while qualitative variables were given as frequency and percentage (%). For a quantitative variable analysis, the *t*-test was used. A two-sided  $\chi^2$  test was used to compare qualitative variables. Differences in clinical endpoints between HF phenotype were tested with  $\chi^2$  test. Univariate and multivariate logistic regression analyses of relevant variables were performed to identify predictors for the transitions among three HF categories. Univariate and multivariate Cox proportional hazards regression model was used to explore the association between risk factors and all-cause mortality. All predictors with a significance of  $P \leq 0.10$  in the univariate analysis were entered into the multivariable model. Odds ratios (ORs)/hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were reported. Freedom from occurrence of all-cause mortality at 5 years was analysed with Kaplan-Meier statistics, with difference assessed using the log rank test. All values were two-tailed, and a *P* value < 0.05 was considered statistically significant.

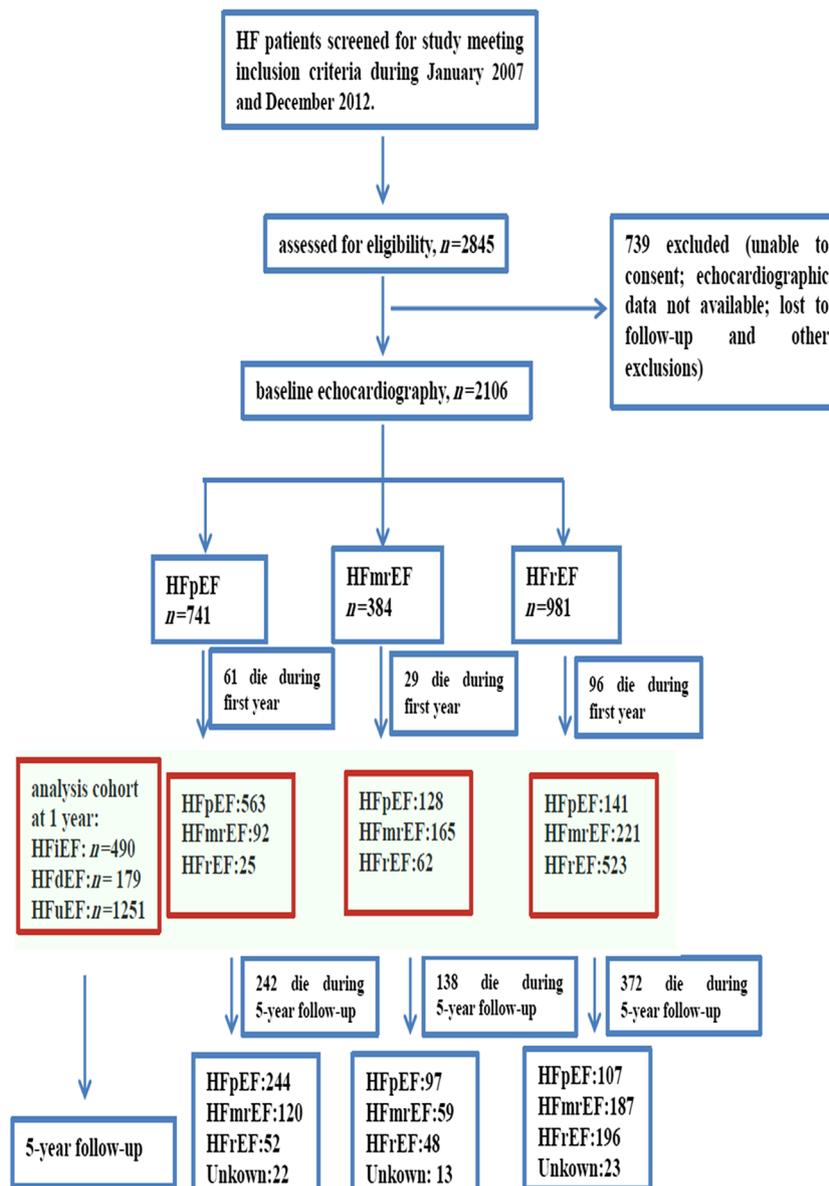
## Results

### Demographic and clinical characteristics

There were 2845 patients with a diagnosis of HF enrolled in this prospective longitudinal cohort from January 2007 to December 2012, and 739 patients were excluded because of missing echocardiographic data (baseline and 1 year follow-up), lost to follow-up, or other exclusion criteria. Of the 2106 remaining patients, 46.6% ( $n = 981$ ) had HFrEF, 18.2% ( $n = 384$ ) had HFmrEF, and 35.2% ( $n = 741$ ) had HFpEF. And 186 patients died during the first year, leaving 1920 patients included in the study (Figure 1). Compared with patients with

HFrEF, those with HFpEF were older (mean age 70.6 vs. 67.8 years); more often female (41.9% vs. 29.5%); more likely to have a history of hypertension (73.4% vs. 66.0%), type 2 diabetes mellitus (T2DM) (34.0% vs. 28.0%), and atrial fibrillation (39.4% vs. 33.0%); and less often have ischaemic heart disease (IHD) (39.0% vs. 52.7%). Not surprisingly, patients with HFrEF were more likely to be on guideline-directed medical therapy for their diagnosis, including angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB), beta-blocker, and spironolactone. Additionally, HFpEF patients were also have higher systolic blood pressure and diastolic blood pressure. In regard to the echocardiographic findings, HFpEF patients had a lower E/e' ratio and smaller

Figure 1 Flowchart of the study protocol.



left atrium diameter. And B-type natriuretic peptide (BNP) in HFrEF was higher than in HFpEF or HFmrEF (Table 1).

### Left ventricular ejection fraction change and heart failure transition

Based on 1 year follow-up echocardiography, 1920 HF patients were re-classified as HFief (*n* = 490, 25.5%), HFdef (*n* = 179, 9.3%), and HFuef (*n* = 1251, 65.2%). HFief patients were younger, whereas HFdef patients had higher functional status (New York Heart Association functional class) and more likely to have a history of IHD, hypertension, and

T2DM (not significantly). And more HFief patients received ACEI/ARB, beta-blocker, or spironolactone therapy. Besides, HFief patients had a lower E/e' ratio and BNP level than had HFdef or HFuef (Table 2).

Among these enrolled patients, 25.0% (*n* = 221) and 15.9% (*n* = 141) who previously had HFrEF improved to HFmrEF and HFpEF, respectively; 36.1% (*n* = 128) and 17.5% (*n* = 62) who had HFmrEF previously improved to HFpEF and progressed to HFrEF, respectively; 13.5% (*n* = 92) and 3.7% (*n* = 25) who previously had HFpEF progressed to HFmrEF and HFrEF, respectively. Additionally, 82.8% (*n* = 563) HFpEF, 46.5% (*n* = 165) HFmrEF, and 59.1% (*n* = 523) HFrEF remained in the same HF category as initial enrolment stage. It appeared that

**Table 1** Baseline characteristics of heart failure with preserved ejection fraction, heart failure with mid-range ejection fraction, and heart failure with reduced ejection fraction

	HFpEF (LVEF ≥ 50%)	HFmrEF (LVEF 40–49%)	HFrEF (LVEF < 40%)	P value
<i>n</i>	680 (35.4)	355 (18.5)	885 (46.1)	
Age (years)	70.6 ± 6.7	68.4 ± 6.4	67.8 ± 7.8	<0.001
Women (gender)	285 (41.9)	127 (35.8)	261 (29.5)	<0.001
BMI (kg/m <sup>2</sup> )	24.6 ± 2.2	24.6 ± 2.1	24.7 ± 2.2	0.283
Medical history				
IHD	265 (39.0)	174 (49.0)	466 (52.7)	<0.001
Prior PCI	148 (21.8)	88 (24.8)	217 (24.5)	0.375
Prior CABG	38 (5.6)	23 (6.5)	60 (6.8)	0.623
Hypertension	499 (73.4)	253 (71.3)	584 (66.0)	0.005
T2DM	231 (34.0)	106 (29.9)	248 (28.0)	0.039
Atrial fibrillation	268 (39.4)	137 (38.6)	292 (33.0)	0.020
Stroke	73 (10.7)	40 (11.3)	104 (11.8)	0.820
COPD	73 (10.7)	36 (10.1)	97 (11.0)	0.915
Smoking	190 (27.9)	101 (28.5)	281 (31.8)	0.260
Dyslipidaemia	197 (29.0)	105 (29.6)	256 (28.9)	0.972
HF device therapies				
ICD	11 (1.6)	3 (0.8)	13 (1.5)	0.150
CRT-P	0	0	10 (1.1)	0.097
CRT-D	0	0	9 (1.0)	0.121
Medications				
ACEI/ARB	482 (70.9)	293 (82.5)	740 (83.6)	<0.001
Beta-blocker	457 (67.2)	254 (71.5)	691 (78.1)	<0.001
Spironolactone	178 (26.2)	90 (25.4)	300 (33.9)	0.001
Anticoagulant	66 (9.7)	34 (9.6)	73 (8.2)	0.558
Antiplatelet	338 (49.7)	162 (45.6)	467 (52.8)	0.070
Statin	260 (38.2)	130 (36.6)	337 (38.1)	0.865
Clinical status				
NYHA class, in Classes I–IV	90/241/274/75	55/95/151/54	133/302/352/98	0.072
heart rate (b.p.m.)	80.6 ± 8.8	79.4 ± 8.0	80.3 ± 9.5	0.107
Systolic BP (mmHg)	132.6 ± 12.0	129.6 ± 13.9	128.8 ± 14.9	<0.001
Diastolic BP (mmHg)	78.7 ± 9.0	76.8 ± 7.4	77.1 ± 8.4	<0.001
Laboratory variables				
eGFR (mL/min/1.73 m <sup>2</sup> )	61.3 ± 9.6	60.5 ± 8.8	60.3 ± 8.4	0.094
Haemoglobin (g/dL)	12.0 ± 1.3	12.1 ± 1.1	12.1 ± 1.1	0.121
BNP (pg/mL)	802.4 ± 352.9	837.3 ± 382.0	860.5 ± 414.2	0.013
Echo data				
LVEF(%)	59.5 ± 4.8	44.5 ± 1.8	34.6 ± 2.5	<0.001
LAD (mm)	41.8 ± 4.0	41.8 ± 4.5	42.5 ± 4.5	0.003
E/e'	13.1 ± 2.0	14.0 ± 2.6	14.1 ± 2.9	<0.001

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; E/e', mitral Doppler early velocity/mitral annular early velocity; eGFR, estimated glomerular filtration rate; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; IHD, ischaemic heart disease; LAD, left atrium diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class; PCI, percutaneous coronary intervention; T2DM, type 2 diabetes mellitus.

Data are presented as mean ± SD or number (%) of subjects.

**Table 2** Baseline characteristics of heart failure with improved ejection fraction, heart failure with deteriorated ejection fraction, and heart failure with unchanged ejection fraction at index admission

	HFIEF	HFdEF	HFuEF	P value
<i>n</i>	490 (25.5)	179 (9.3)	1251 (65.2)	
Age (years)	67.5 ± 7.2	70.7 ± 6.6	69.2 ± 7.3	<0.001
Women (gender)	187 (38.2)	59 (33.0)	427 (34.1)	0.236
BMI (kg/m <sup>2</sup> )	24.6 ± 2.3	24.6 ± 2.1	24.6 ± 2.2	0.966
Medical history				
IHD	215 (43.9)	101 (56.4)	589 (47.1)	0.016
Prior PCI	124 (25.3)	30 (16.8)	299 (23.9)	0.064
Prior CABG	29 (5.9)	6 (3.4)	86 (9.7)	0.178
Hypertension	323 (65.9)	136 (76.0)	877 (70.1)	0.035
T2DM	128 (26.1)	59 (33.0)	398 (31.8)	0.051
Atrial fibrillation	164 (33.5)	71 (39.7)	462 (36.9)	0.248
Stroke	62 (12.7)	23 (12.8)	132 (10.6)	0.364
COPD	60 (12.2)	16 (8.9)	130 (10.4)	0.382
Smoking	144 (29.4)	49 (27.4)	383 (30.6)	0.637
Dyslipidaemia	160 (31.8)	54 (30.2)	348 (27.8)	0.128
HF device-therapies				
ICD	4 (0.8)	2 (1.1)	21 (1.7)	0.383
CRT-P	4 (0.8)	0	6 (0.5)	0.526
CRT-D	3 (0.6)	0	5 (0.4)	0.740
Medications				
ACEI/ARB	414 (84.5)	128 (71.5)	973 (77.8)	<0.001
Beta-blocker	390 (79.6)	113 (63.1)	899 (71.9)	<0.001
Spirolactone	161 (32.9)	46 (25.7)	361 (28.9)	<0.001
Anticoagulant	41 (8.4)	15 (8.4)	117 (9.4)	0.774
Antiplatelet	251 (51.2)	112 (62.6)	604 (48.3)	0.072
Statin	188 (38.4)	64 (35.8)	475 (38.0)	0.820
Clinical status				
NYHA class, in Classes I–IV	95/171/175/49	35/45/61/38	233/402/452/164	0.010
Heart rate (b.p.m.)	80.3 ± 9.0	80.2 ± 9.2	80.2 ± 8.9	0.998
Systolic BP (mmHg)	129.2 ± 14.9	131.6 ± 13.1	130.5 ± 13.5	0.072
Diastolic BP (mmHg)	77.6 ± 7.9	78.0 ± 7.5	77.5 ± 8.82	0.826
Laboratory variables				
eGFR (mL/min/1.73 m <sup>2</sup> )	59.9 ± 8.6	61.4 ± 9.1	60.9 ± 9.2	0.067
Haemoglobin (g/dL)	12.2 ± 1.0	12.1 ± 1.3	12.0 ± 1.2	0.072
BNP (pg/mL)	803.6 ± 323.2	896.4 ± 441.6	839.5 ± 402.2	0.020
Echo data				
LVEF at admission	37.3 ± 4.9	54.0 ± 7.9	47.1 ± 12.3	<0.001
LVEF 1 year	48.2 ± 5.7	41.8 ± 6.3	46.3 ± 11.6	<0.001
LAD (mm)	42.1 ± 4.4	42.2 ± 4.1	42.1 ± 4.1	0.963
E/e'	13.5 ± 2.5	14.0 ± 2.7	13.7 ± 2.6	0.044

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; E/e', mitral Doppler early velocity/mitral annular early velocity; eGFR, estimated glomerular filtration rate; HF, heart failure; HFdEF, heart failure with deteriorated left ventricular ejection fraction; HFIEF, heart failure with improved left ventricular ejection fraction; HFuEF, heart failure with unchanged left ventricular ejection fraction; ICD, implantable cardioverter defibrillator; IHD, ischaemic heart disease; LAD, left atrium diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class; PCI, percutaneous coronary intervention; T2DM, type 2 diabetes mellitus. Data are presented as mean ± SD or number (%) of subjects.

more patients transitioned from HFpEF to HFmrEF and transitioned from HFrEF to HFmrEF, suggesting a downward trend and upward trend of LVEF in HFpEF and HFrEF, respectively. *Table 2* presents clinical characteristics of patients with HFIEF, HFdEF, and HFuEF at the index admission. For those with an echocardiography performed from 6 years after first enrolment (*n* = 1110), 27.6% had an EF < 40%, 40.3% had an EF ≥ 50%, and 32.1% had EF ≥ 40 and <50% (*Figure 1*). The patients with HFdEF had a decrease in LVEF of 12.2% from index admission to 1 year follow-up, whereas those with HFIEF had an increase in LVEF of 11.0%.

For patients with HFmrEF and HFrEF at baseline, the results of univariate and multivariate logistic regression indicated

that E/e' (OR 0.892, 95% CI 0.853–0.932, *P* < 0.001) as well as IHD (OR 0.606, 95% CI 0.479–0.768, *P* < 0.001) was associated with a reduced possibility of improved HF transition, whereas the use of beta-blockers (OR 1.386, 95% CI 1.044–1.840, *P* = 0.024) or female gender (OR 1.758, 95% CI 1.368–2.261, *P* < 0.001) was associated with an increased possibility of improved HF transition during the first year (*Table 3*). For patients with HFpEF and HFmrEF at baseline, the results of univariate and multivariate logistic regression indicated that E/e' (OR 1.147, 95% CI 1.067–1.233, *P* < 0.001) as well as IHD (OR 1.449, 95% CI 1.041–2.017, *P* = 0.028) was associated with an increased possibility of deteriorated HF transition during the first year (*Table 4*).

**Table 3** Multivariable logistic analysis for improved heart failure transition in heart failure with mid-range ejection fraction/heart failure with reduced ejection fraction

	OR	95% CI	P value
Age	0.990	1.292–1.987	0.225
Female	1.758	1.368–2.261	<0.001
IHD	0.606	0.479–0.768	<0.001
ACEI/ARB	1.342	0.970–1.858	0.076
Beta-blocker	1.386	1.044–1.840	0.024
BNP	0.876	0.758–1.011	0.071
E/e'	0.892	0.853–0.93	<0.001

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; BNP, B-type natriuretic peptide; E/e', mitral Doppler early velocity/mitral annular early velocity; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFrfEF, heart failure with reduced ejection fraction; IHD, ischaemic heart disease.

**Table 4** Multivariable logistic analysis for deteriorated heart failure transition in heart failure with preserved ejection fraction/heart failure with mid-range ejection fraction

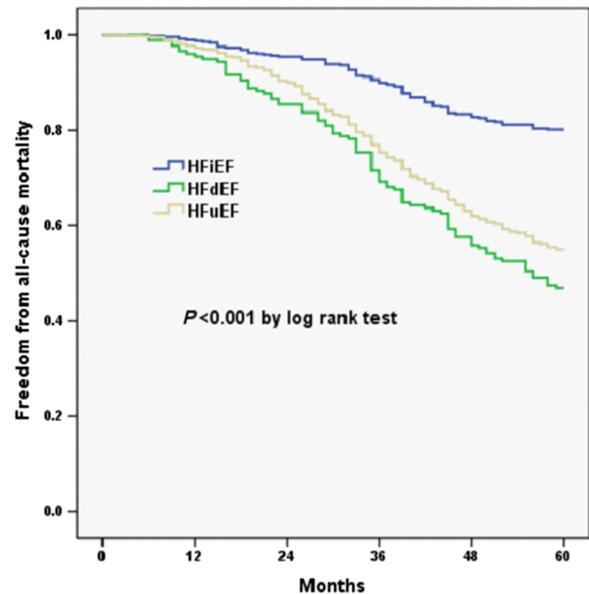
	OR	95% CI	P value
Age	1.022	0.997–1.048	0.083
Female	1.719	0.508–1.019	0.064
IHD	1.449	1.041–2.017	0.028
ACEI/ARB	0.729	0.508–1.047	0.087
beta-blocker	0.768	0.544–1.083	0.132
BNP	1.919	0.972–1.459	0.092
E/e'	1.147	1.067–1.233	<0.001

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; BNP, B-type natriuretic peptide; E/e', mitral Doppler early velocity/mitral annular early velocity; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; IHD, ischaemic heart disease.

### Clinical outcomes of heart failure with improved ejection fraction, heart failure with deteriorated ejection fraction, and heart failure with unchanged ejection fraction

When compared with patients with other HF phenotypes, patients with HFief had the lowest all-cause mortality (mortality rate: 19.8% with HFief, 53.1% with HFdEF, and 45.0% with persistent HFuEF,  $P < 0.001$ ) after 5 year follow-up. Patients with HFief also showed higher survival rate than did those with HFdEF and HFuEF in Kaplan–Meier plot (log rank test,  $P < 0.001$ , Figure 2). In the univariate and multivariate Cox models, compared with HFuEF, HFief was associated with 62.1% decreased risk of 5 year mortality (HR 0.379, 95% CI 0.305–0.472,  $P < 0.001$ ), and HFdEF was accompanied with an increased trend of 5 year mortality (HR 1.211, 95% CI 0.972–1.158,  $P = 0.089$ ), along with other significant factors: eGFR, body mass index (BMI), IHD, BNP, and E/e' (Table 5). As for the medical therapy, the use of beta-blockers, RAS inhibitors, or spironolactone was not associated with better survival among the total enrolled HF patients. Multivariate Cox analyse for 5 year mortality was also performed in HFief,

**Figure 2** Kaplan–Meier curves of freedom from all-cause mortality in HFief, HFdEF, and HFuEF patients. The numbers at the bottom of the figure are 'number at risk'. HFdEF, heart failure with deteriorated ejection fraction; HFief, heart failure with improved ejection fraction; HFuEF, heart failure with unchanged ejection fraction.



<b>HFief</b>	490	484	468	441	406	393
<b>HFdEF</b>	179	171	153	124	100	84
<b>HFuEF</b>	1251	1217	1126	943	776	688

**Table 5** Multivariable Cox analysis for all-cause mortality in the whole cohort

	HR	95% CI	P value
Age	1.005	0.995–1.015	0.318
eGFR	0.990	0.982–0.998	0.018
BMI	1.033	1.001–1.067	0.046
IHD	1.257	1.088–1.452	0.002
ACEI/ARB	0.903	0.760–1.072	0.243
Beta-blocker	0.872	0.747–1.020	0.086
BNP	1.168	1.067–1.279	0.001
E/e'	1.049	1.022–1.078	<0.001
HF transition	1.494	1.356–1.647	<0.001

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; E/e', mitral Doppler early velocity/mitral annular early velocity; eGFR, estimated glomerular filtration rate; HF, heart failure; IHD, ischaemic heart disease.

HFdEF, and HFuEF group (Tables S1–S3), which indicated that beta-blocker prescription as well as RAS inhibitors use was associated with better survival in HFief and beta-blocker therapy was associated with better survival in HFuEF. And all-cause mortality was lower in HFpEF (40.9%) than HFmrEF (43.5%) and HFrfEF (47.7%) on the basis of initial diagnosis ( $P = 0.017$ ). In addition, we performed an analysis looking at baseline LVEF as a continuous variable, defining LVEF change

of 5 percentage point on the basis of 1 year follow-up echocardiography as increased (LVEF increased  $\geq 5\%$ ), decreased (LVEF decreased  $\geq 5\%$ ), or unchanged (LVEF change no more than 5%). And our result indicated that the LVEF decreased group was associated with markedly higher mortality rate (21.9% with increased group, 48.2% with decreased group, and 45.2% with unchanged group,  $P < 0.001$ ).

## Discussion

The present study clearly demonstrates that (i) there were important LVEF transitions among HFpEF, HFmrEF, and HFrfEF, especially during the first year. (ii) Compared with HFuEF patients during 5 year follow-up, HFief patients showed lower mortality, whereas HFdef patients manifested higher mortality. (iii) Beta-blockers, but not RAS inhibitors or MRAs, were associated with an improved HF transition. (iv) Beta-blockers were associated with lower all-cause mortality in both HFief and HFuEF. (v) All-cause mortality was lower in HFpEF than HFrfEF on the basis of initial diagnosis.

Over the years, the clinical outcomes for patients with HFpEF, compared with HFrfEF, are uncertain and controversial.<sup>10,11</sup> More than 10 years ago, two epidemiological studies reported similar outcomes for the two HF phenotypes.<sup>10,11</sup> However, the subsequent meta-analyses reported that patients with HFpEF had lower risk of death from any cause than had those with HFrfEF.<sup>12,13</sup> And a recent prospective multi-centre longitudinal study in New Zealand and Singapore further showed that the prevalence and mortality were lower in HFpEF than HFrfEF.<sup>14</sup> Our recent cohort study in patients with HF and T2DM indicated that the all-cause mortality and HF hospitalization were lower in HFpEF than HFrfEF.<sup>6</sup> In the present study, all-cause mortality was also lower in HFpEF than HFrfEF on the basis of initial diagnosis.

However, the classification of preserved and reduced LVEF was not static in a substantial proportion of HF patients. It was estimated that the probability was  $>1$  in 3 that patients with HFpEF would experience a transition to HFrfEF, and conversely, the estimated probability was  $>1$  in 8 that patients with HFrfEF would experience a transition to HFpEF during a 5 year period.<sup>2</sup> Among 1233 HF patients in a community cohort study, LVEF increased in HFrfEF patients by an average 6.9% over 5 years, while it decreased in HFpEF patients by an average 5.8% over 5 years.<sup>15</sup> Because most transitions occurred in the first year,<sup>2,3</sup> we chose 1 year as HF transition point to observe the clinical characteristics, outcome, and prognosis of HF transition. The CHART-2 Study indicated that HFmrEF and HFrfEF, but not HFpEF, dynamically transitioned to other categories, HFrfEF transitioned to HFpEF and HFmrEF by 18% and 22%, respectively, and HFmrEF transitioned to HFpEF and HFrfEF by 44% and 16%, respectively. However, HFpEF patients transitioned to HFmrEF and HFrfEF by only

8% and 2%, respectively.<sup>16</sup> Consistent with previous studies, our results indicated that the most transitions were 'HFrfEF to HFmrEF' and 'HFmrEF to HFpEF'. And HFmrEF might represent a transitional status between HFpEF and HFrfEF and an overlap zone of HFpEF with lower-end LVEF and HFrfEF with higher-end LVEF.<sup>16</sup> One recent study<sup>17</sup> also indicated that categorical HF classification based solely on LVEF might be arbitrary. This might be related with the variability of LVEF measurement and HF transitions during follow-up. And patients with HF also share many epidemiological, clinical, and pathophysiological characteristics regardless of LVEF. It is suggested that LVEF will likely remain temporarily part of the assessment of HF, as a rough evaluation of a patient's sensitivity to neurohormonal inhibitors, and during a transition phase to incorporate current evidence-based medicine into a more personalized evidence-based HF management regimen.

Previous studies showed that IHD aetiology, higher BNP level, and history of myocardial infarction were positively associated with decreased LVEF, whereas younger age, female sex, and hypertension were positively associated with increased LVEF.<sup>2,4,5,15-18</sup> And HFpEF patients with IHD and  $50\% \leq \text{LVEF} < 55\%$  were more likely to progress to HFmrEF in the future.<sup>19</sup> Furthermore, those patients who transitioned from HFpEF to HFmrEF had considerably more complex profiles and were less aggressively managed than were those who remained with HFmrEF.<sup>20</sup> Our present study also indicated that LVEF was a dynamic factor related to sex and IHD aetiology in HF patients. IHD has been suggested to be associated with a decline of LVEF; Dunlay *et al.* previously reported that HFpEF with advanced age and coronary artery disease had greater reduction in LVEF.<sup>15</sup> In addition, ischaemic cardiomyopathy was associated with less viable myocardium, extensive scarring, and LV dysfunction and remodelling.<sup>21,22</sup> Besides, our data also suggested that beta-blocker therapy was linked with improved HF transition and higher E/e' was associated with deteriorated HF transition. It was showed that patients who were adherent to beta-blockers were more likely to transition from HFrfEF to HFpEF.<sup>2</sup> E/e', an important index for LV diastolic function, is useful in predicting cardiac events in the general population<sup>23</sup> and is a reliable predictor of 1 year mortality patients with hypertension and acute HF,<sup>24</sup> which suggest that the evaluation of diastolic function provides additional prognostic information.<sup>25</sup> Our results further indicated that higher E/e' might be related to the deterioration of LVEF.

The changes in LVEF might be associated with subsequent clinical outcomes in patients with HF. Dunlay *et al.* reported that decreases in LVEF over time were associated with an increase in mortality, whereas increases were associated with an increase in survival, suggesting that progressive systolic contractile dysfunction might, at least in part, contribute to the HF outcomes.<sup>15,26</sup> A prospective cohort study from Zhang *et al.* showed that LVEF changes after implantable

cardioverter defibrillator implantation for primary prevention of sudden cardiac death were inversely associated with all-cause mortality.<sup>27</sup> The V-HeFT study reported that improvement in LVEF (>5%) from baseline at 6 months and 1 year was the strongest predictor of survival and was still significant after adjustment for therapy and baseline LVEF.<sup>27</sup> Basuray *et al.* also reported that patients with recovered LVEF, defined as those who had LVEF  $\geq$  50% but had a previous LVEF < 50%, had better event-free survival than persistent HFrEF patients (defined as HF with LVEF < 50%).<sup>28</sup> Furthermore, a recent review revealed that HF patients with recovered LVEF had a different clinical course than those with HFpEF or HFrEF, with lower mortality, less frequent hospitalizations, and fewer composite endpoints.<sup>29</sup> In HFrEF, short-term improvements in EF in response to therapy have been associated with improved survival.<sup>30,31</sup> CHART-2 Study also reported that HFmrEF patients at registration had increased mortality when transitioned to HFrEF at 1 year,<sup>16</sup> a finding consistent with the observation that subtle impairment in resting myocardial contractility was associated with increased mortality in HFpEF patients.<sup>32</sup> Consistent with previous studies, our present results indicated that transitions to higher HF category from baseline were associated with better prognosis, or transitions from lower HF category from baseline were associated with worse outcome, suggesting the importance in preventing a decrease in LVEF for better prognosis of HF patients.

Chronic activation of sympathetic nervous and neurohumoral system after the initial myocardial injury is associated with progression of HF and adverse outcomes.<sup>1</sup> However, beta-blockers, RAS inhibitors, and MRAs proved to be beneficial effects in patients with HFrEF, but not in those with HFpEF.<sup>1</sup> It is of clinical interest whether guideline-directed medical therapy could improve outcomes in HFief, HFdef, and HFuef patients. A recent study indicated that the use of beta-blockers, RAS inhibitor, and MRA in LVEF-declined patients (transitioned from LVEF  $\geq$  50% to LVEF < 50%) was not associated with the improved clinical outcomes.<sup>4</sup> However, this report is based on a post hoc analysis of a prospective cohort study, and further studies are originally designed to analyse the LVEF-declined patients would be necessary to determine the effectiveness of the medical therapies. Regarding the effect of guideline-directed medical therapy in LVEF improved patients, patients prescribed with beta-blockers had lower 4 year all-cause mortality.<sup>5</sup> In a multivariate analysis, only the use of beta-blockers was associated with a 41% reduced risk of mortality, whereas the effect of RAS inhibitor and MRA use on mortality appeared to be neutral.<sup>5</sup> It was also reported that patients who were adherent to beta-blockers were more likely to transition from HFrEF to HFpEF than were patients who were non-adherent to beta-blockers, whereas RAS inhibitor adherence was not associated with LVEF transitions.<sup>2,33</sup> In the present study, both beta-blockers and RAS inhibitors therapy were associated with significantly

lower mortality in HFief, supporting the importance of evidence-based HF therapies in this specific population. Besides, beta-blocker therapy was also associated with decreased risk of mortality in HFuef. We speculate that much of the improvement or lack of progressive impairment in EF over time might reflect appropriate HF medical therapy and favourable response to drug therapy. Taken together, beta-blockers might not only be conducive to improved transition in patients with HFrEF and HFmrEF during the first year but also increase the survival rate of HFief and HFuef patients thereafter, suggesting the need for beta-blocker prescription in this subset of HF patients.

## Limitation

First, the prospective cohort study was not designed to specifically evaluate the transition of HF phenotype, and the sample size was too small to provide definitive results. The use of beta-blockers, RAS inhibitors, and MRA may have been changed during follow-up. Therefore, a larger prospective cohort or a randomized-controlled study is necessary to understand the characteristics and evaluate the effects of drugs in HF population. Second, the variability of LVEF determination could not be entirely averted during our long-term follow-up. Third, we enrolled HF patients who first visited our centre, and echocardiography at index admission and 1 year thereafter was performed. Some patients might have a history of HF before visiting our centre, and not each patient's echocardiogram time relative to initial HF diagnosis can be clearly recorded. Therefore, some HF transitions in our enrolled patients might be missed. Fourth, the study participants were from a single centre in China, and it is uncertain whether these findings can be generalized to other ethnic groups. Last, as we enrolled and analysed patients who underwent a 1 year follow-up echocardiographic assessment after index admission, there might be selection biases, and patients who had died during the first-year follow-up were not included.

## Conclusions

Temporary changes in LVEF and transitions among HF phenotypes are common and associated with prognosis in patients with HF. These results suggest that in the modern era of HF therapeutics, the use of LVEF to categorize the pathophysiology of HF might be non-comprehensive, and we argue for establishing a new classification method for HF patients. And beta-blocker was associated with an improved transition of HF type as well as lowering all-cause mortality in HFief and HFuef. Further prospective observational studies or randomized clinical trials are needed to fully elucidate the

pathophysiology of LVEF recovery and deterioration to improve clinical outcomes of HF patients.

## Conflict of Interest

The authors confirm that there are no conflicts of interest.

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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.** Multivariable cox analysis for all-cause mortality in HFIEF.

**Table S2.** Multivariable cox analysis for all-cause mortality in HFdEF.

**Table S3.** Multivariable cox analysis for all-cause mortality in HFuEF.

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