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Dynamic trajectories of left ventricular ejection fraction in heart failure with improved ejection fraction

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Abstract

Background Heart failure with improved ejection fraction (HFimpEF) has been regarded as a new heart failure (HF) type in 2022. However, studies on the impact of left ventricular ejection fraction (LVEF) trajectories on the prognosis of patients with HFimpEF are scarce. In this study, we investigated dynamic trajectories of LVEF and different clinical outcomes in HFimpEF.

Methods and results This was a multi-center study included patients diagnosed with HF with reduced ejection fraction (HFrEF) between January 1, 2015, and October 31, 2022. Enrolled patients were divided into HFimpEF and persistent HFrEF groups. To further investigate different LVEF trajectories in HFimpEF patients, they were classified into persistent HFimpEF and transient HFimpEF subgroups. Adverse clinical outcomes encompassed all-cause death, cardiovascular death, and HF-related rehospitalization. A total of 734 patients were included (HFimpEF: $n=162$; persistent HFrEF: $n=572$). Cox regression analysis revealed that compared with persistent HFrEF, patients with HFimpEF experienced a lower risk of all-cause and cardiovascular death. Subgroup analysis determined that only 113 (69.75%) patients maintained an LVEF exceeding 40%. Cox regression analysis revealed that persistent HFimpEF patients had a lower risk of all-cause and cardiovascular death compared to those with transient HFimpEF. Finally, multivariate logistic analysis showed that gender and high-density lipoprotein cholesterol levels were independent predictors of persistent HFimpEF.

Conclusions HFimpEF does not accurately represent HF recovery, given that there are different trajectories of LVEF in HFimpEF. Patients with persistent HFimpEF experience better clinical outcomes, highlighting clinicians should identify clinical modifiable factors to maintain a stable HF stage for better prognosis.

Trial registration ChiCTR2400086622, 08/07/2024.

Keywords Heart failure with improved ejection fraction, Dynamic trajectories, Left ventricular ejection fraction, Prognosis

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Introduction

Left ventricular ejection fraction (LVEF) is a key imageological parameter used for the classification of heart failure (HF). Previous guidelines [1] have classified HF into three categories according to LVEF, namely HF with reduced ejection fraction (HFrEF), HF with mildly reduced ejection fraction, and HF with preserved ejection fraction (HFpEF). However, LVEF is not static and can be decreased by acute cardiac injury or increased by guideline-directed medical therapy (GDMT) during the disease course [2]. The variation trends of LVEF, which defined as LVEF trajectories, was considered as an important characteristic of HF [3]. The 2022 American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA) HF Guideline [3] introduced a new type of HF, referred to as HF with improved ejection fraction (HFimpEF), with previous LVEF≤40% and a follow-up measurement of LVEF>40% as criteria. Several studies [4–6] have established that patients with HFimpEF experience better clinical outcomes than those with persistent HFrEF. Therefore, relying on a single measurement of LVEF is not adequate to evaluate the prognosis, emphasizing the need for regular monitoring of LVEF trajectories in the management of HF. Notably, HFimpEF does not imply complete HF recovery. It is not simply a mirror image of LVEF deterioration during disease progression but rather a less pathological steady state that reveals left ventricular (LV) pump function and structure reverse remodeling, and better clinical outcomes [2, 7]. However, this steady state can be disrupted, and patients with HFimpEF are still at risk of deterioration of LV systolic function, cardiovascular rehospitalization, and death [8]. Moreover, current studies predominantly focus on distinguishing clinical outcomes between HFimpEF and other HF types, with limited attention paid to the impact of fluctuations in LVEF trajectories on the prognosis in HFimpEF patients. Thus, the current study aimed to investigate the association between different LVEF trajectories and clinical outcomes in HFimpEF patients.

Methods

All clinical data and research materials in this study are available upon reasonable request from the Department of Cardiology, First Affiliated Hospital of Dalian Medical University, and the Department of Cardiology, Central Hospital of Dalian University of Technology.

Study population and grouping

This study was approved by both the institutional review board of First Affiliated Hospital of Dalian Medical University (PJ-KS-KY-2024-375) and the institutional review board of Central Hospital of Dalian University of Technology (YN2024-018-01). All procedures were performed in accordance with the Declaration of Helsinki and its subsequent amendments. Informed consent was obtained from all subjects prior to study initiation. The Clinical Trial Number is ChiCTR2400086622.

This was a multi-center, retrospective study, which included patients diagnosed with HFrEF at First Affiliated Hospitalization of Dalian Medical University and Central Hospital of Dalian University of Technology between January 1, 2015, and October 31, 2022. All participants in this study underwent at least two echocardiography examinations to determine LVEF and assess changes in LV systolic function. LVEF was calculated by Simpson Biplane method. All echocardiography examinations in this study were conducted by experienced echocardiographic doctors in the dedicated Echocardiogram Room, and all reports were reviewed by director of Echocardiogram Room to reduce error of results. In order to avoid acute changes in LVEF due to heart rate or loading conditions, the time interval between two echocardiography examinations was at least 3 months. Participants lost to follow-up, missing echocardiography data, or time interval between two echocardiography examinations less than 3 months were excluded from this study. Afterward, enrolled subjects were divided into two groups: patients who met the criteria for HFimpEF were assigned to the HFimpEF group, whereas the remaining participants were included in the persistent HFrEF group. Patients in the HFimpEF group were further subdivided into two subgroups according to LVEF trajectories between the second and third echocardiography examinations. HFimpEF patients with LVEF maintained over 40% at the third echocardiography examination were in the persistent HFimpEF group. Otherwise, they were assigned to the transient HFimpEF group.

All clinical data in this study, including baseline demographics, laboratory examination, imaging results, and therapeutic regimen, were collected from the Electronic Medical Record System at First Affiliated Hospital of Dalian Medical University and Central Hospital of Dalian University of Technology.

Definitions of different HF types

In the present study, HFrEF and HFimpEF were diagnosed according to the 2022 ACC/AHA/HFSA HF Guideline [3]. Patients diagnosed with HFimpEF fulfilled the following criteria: (1) previous LVEF≤40%, (2) a follow-up measurement of LVEF>40%.

Study endpoints and follow-up

Adverse clinical outcomes comprised all-cause death, cardiovascular death, and HF-related rehospitalization. Participants were followed up until June 30, 2023, or the occurrence of the aforementioned end-points, whichever came first. All enrolled participants were encouraged to

regularly monitor their physical condition through outpatient follow-up. Those who did not attend follow-up visits were followed up by phone.

Statistical analysis

Statistical analysis was performed using SPSS Statistical Software, Version 26.0 (SPSS Inc, Chicago, IL, USA). Categorical variables were expressed as percentage. Continuous variables following a normal distribution were presented as mean ± SD, while non-normally distributed continuous variables were expressed as median and interquartile range. The independent-sample t-test, Kruskal-Wallis test, and chi-square test were used to compare normally distributed variables, non-normally distributed variables, and categorical variables, respectively. Kaplan-Meier analysis was carried out to calculate the incidence of adverse clinical outcomes, and the log-rank test was used to assess differences. Cox regression analysis was employed to compare the hazard risk for different clinical adverse events. Covariates included in the multivariate model were those with statistical significance in the univariate analysis, and clinically relevant variables including age, gender, pacemaker, ICD, and CRT. Logistic regression analysis was used to identify independent factors predicting persistent HFimpEF. Covariates showed statistical significance in the univariate analysis and other clinically relevant variables (gender and age) were adjusted in the multivariable model. A two-sided P value < 0.05 was considered statistically significant.

Results

Demographics and clinical characteristics

A total of 859 patients diagnosed with HFrEF between January 1, 2015, and October 31, 2022, at the First Affiliated Hospitalization of Dalian Medical University and Central Hospital of Dalian University of Technology were initially included. Among them, 125 subjects were excluded for meeting exclusion criteria, and 734 patients were finally enrolled in our cohort (Fig. 1). According to the definition of HFimpEF, 162 (22.1%) patients were included in the HFimpEF group, with 572 (77.9%) patients assigned to the persistent HFrEF group. Detailed

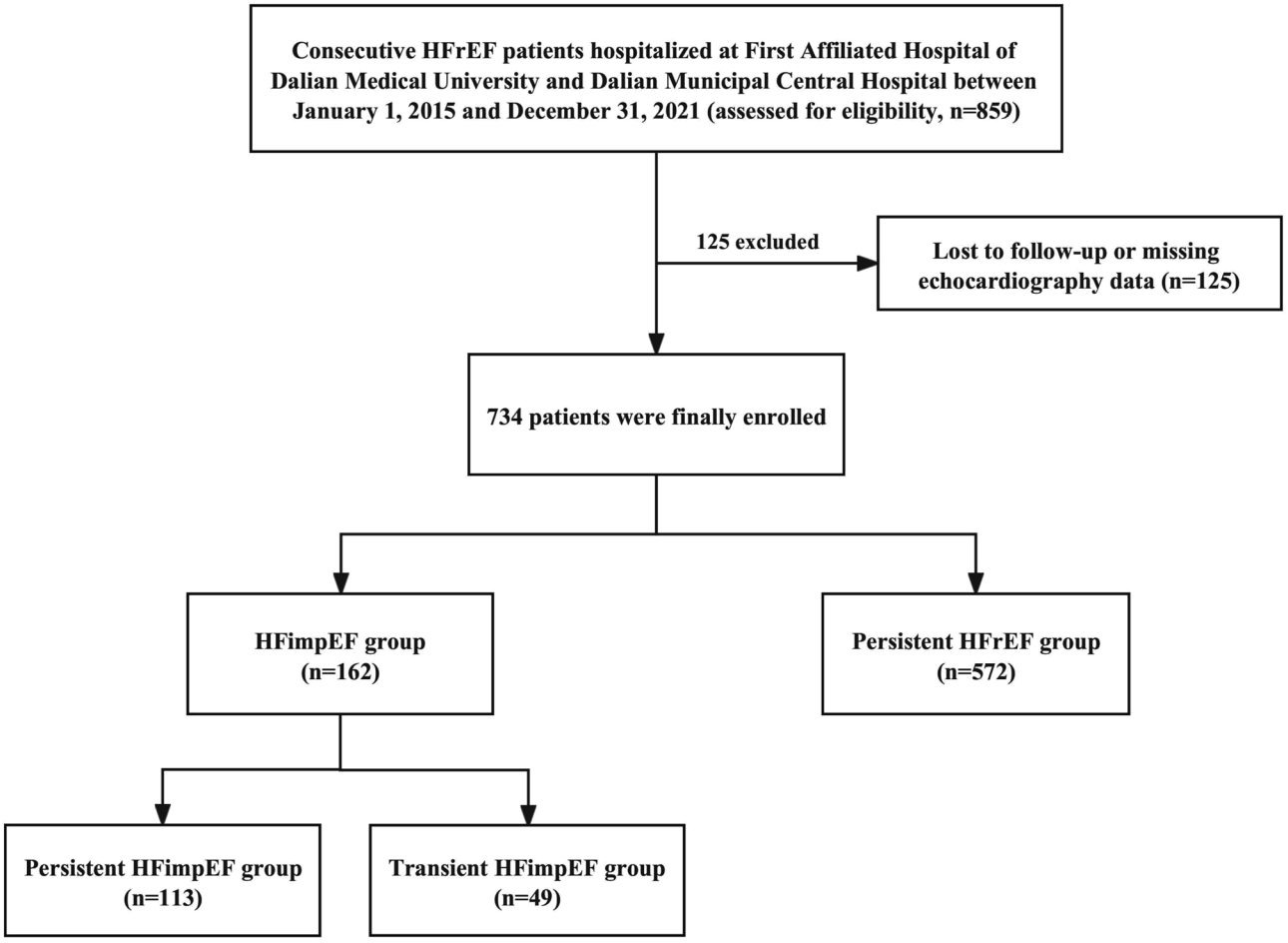

Fig. 1 Flow diagram of inclusion and exclusion of study subjects. HFrEF indicates heart failure with reduced ejection fraction; HFimpEF, heart failure with improved ejection fraction

clinical characteristics are listed in Table 1. Compared to the persistent HFrEF group, patients with HFimpEF had higher systolic and diastolic blood pressure and were more likely to be non-smokers. Moreover, patients in the HFimpEF group had higher LVEF values and thicker interventricular septal, lower levels of LV end-diastolic diameter, and were unlikely to receive pacemaker therapy. Additionally, the time interval between two echocardiography examinations was shorter in the HFimpEF group.

Clinical outcomes on follow-up

All patients were followed up for average 44.95±21.83 months, 368 (50.1%) patients developed adverse clinical events [HFimpEF group: $n=57$, (35.1%) vs. persistent HFrEF group: $n=311$, (54.4%)], including 147 patients experienced all-cause death [HFimpEF group: $n=17$, (10.5%) vs. persistent HFrEF group: $n=130$, (22.7%)], among whom 119 died from cardiovascular causes [HFimpEF group: $n=15$, (9.3%) vs. persistent HFrEF group: $n=104$, (18.2%)], and 292 patients were rehospitalized for heart failure exacerbation [HFimpEF group: $n=44$, (27.2%) vs. persistent HFrEF group: $n=248$, (43.4%)].

Multivariate Cox regression analysis (Table 2) revealed that age (HR 1.020, 95% CI 1.003–1.038, $P=0.021$), systolic blood pressure (HR 0.990, 95% CI 0.980–0.999, $P=0.033$), New York Heart Association class III or IV (HR 0.439, 95% CI 0.269–0.715, $P=0.001$), hemoglobin level (HR 0.987, 95% CI 0.977–0.996, $P=0.006$), and urea level (HR 1.054, 95% CI 1.014–1.096, $P=0.008$) were correlated with cardiovascular death. Additionally, patients with HFimpEF experienced a lower risk of cardiovascular death not only before (HR 0.482, 95% CI 0.280–0.828, $P=0.008$) but also after (HR 0.518, 95% CI 0.281–0.957, $P=0.036$) multivariate adjustment. Likewise, the Kaplan-Meier survival curve illustrated that HFimpEF patients exhibited a lower incidence of cardiovascular death (Fig. 2). However, HFimpEF was not significantly correlated with a lower risk of HF-related hospitalization in our study (Univariate Cox regression analysis: HR 0.800, 95% CI 0.577–1.108, $P=0.179$). The Cox regression model and Kaplan-Meier survival curve for all-cause death are presented in Supplementary Materials.

Trajectories change in HFimpEF

Furthermore, the association between trajectory change and clinical outcomes was explored in the HFimpEF subgroup. 113 patients (69.75%) from the HFimpEF group who maintained an LVEF of over 40% were included in the persistent HFimpEF subgroup. Multivariate Cox regression model (Table 3) determined that systolic blood pressure (HR 0.956, 95% CI 0.929–0.985, $P=0.003$), presence of diabetes mellitus (HR 4.084, 95% CI 1.160-14.377, $P=0.028$), and hemoglobin levels (HR 0.974, 95% CI 0.949-1.000, $P=0.046$) were associated with cardiovascular death in the HFimpEF subgroup. What's more, the univariate (HR 0.202, 95% CI 0.069–0.595, $P=0.004$) and multivariate (HR 0.212, 95% CI 0.063–0.716, $P=0.013$) analysis displayed that persistent HFimpEF was a protective factor that lowered the risk of cardiovascular death. Kaplan-Meier survival curve presented a similar result, that is, the incidence of cardiovascular death was lower in patients with persistent HFimpEF (Fig. 3). Nevertheless, no significant correlation was noted between persistent HFimpEF and HF-related hospitalization in the HFimpEF subgroup (Univariate Cox regression analysis: HR 1.223, 95% CI 0.654–2.287, $P=0.528$). The Cox regression model and Kaplan-Meier survival curve for all-cause death in the HFimpEF subgroup are depicted in Supplementary Materials.

Predictors of HFimpEF

Additionally, predictive factors of persistent HFimpEF were identified in our study. Multivariate logistic regression analysis (Table 4) exposed that male gender (OR 2.983, 95% CI 1.241–7.172, $P=0.015$) and high-density lipoprotein cholesterol levels (HDL-C) (OR 6.910, 95% CI 1.358–35.155, $P=0.020$) were positive predictors of persistent HFimpEF. On the other hand, urea level (OR 0.892, 95% CI 0.805–0.989, $P=0.031$) was a negative predictor of persistent HFimpEF.

Discussion

The major findings of this study can be summarized as follows: (1) patients with HFimpEF exhibited different LVEF trajectories, and (2) patients with persistent HFimpEF experienced a lower risk of adverse outcomes.

LVEF is a significant imageological parameter in the diagnosis and treatment of HF, which can be enhanced with GDMT, LV assist devices, and invasive/surgical approaches in the clinical setting [2]. The 2022 ACC/AHA/HFSA HF Guidelines described that different LVEF trajectories might lead to different clinical outcomes and consequently defined a new HF category termed HFimpEF. Previous studies have found that patients with HFimpEF experienced better clinical outcomes, including a lower risk of rehospitalization and mortality. As anticipated, the findings in our research were consistent with those of previous studies [4, 5, 9], demonstrating that patients with HFimpEF had a lower risk of all-cause and cardiovascular death than those with persistent HFrEF. HFimpEF represents not only an improvement in LV systolic function but also a reversal of LV structural remodeling. Studies have shown that during LV reverse remodeling, normalization of gene expression related to myocardial contraction occurs before changes in the expression of genes related to the extracellular

Table 1 Baseline demographics and clinical characteristics at the time of first echocardiography

Variables	HFimpEF, *n* = 162	persistent HFrEF, *n* = 572	*P* value
Age, y	64.00 (55.00–75.00)	66.00 (58.25-74.00)	0.223
Men, n (%)	117 (72.2)	410 (71.7)	0.892
Height, cm	170.00 (163.00-175.00)	170.00 (162.00-175.00)	0.830
Weight, kg	74.00 (63.75-85.00)	72.00 (63.00–80.00)	0.156
Heart rate, bpm	83.00 (70.00-100.75)	80.00 (70.00-95.75)	0.080
SBP, mmHg	130.00 (119.50–148.00)	128.00 (112.00-140.00)	0.011
DBP, mmHg	80.00 (70.00–92.00)	80.00 (70.00–90.00)	0.024
Smoking, n (%)	51 (31.5)	234 (40.9)	0.030
Alcohol consumption, n (%)	34 (21.0)	140 (24.5)	0.357
DM, n (%)	56 (34.6)	208 (36.4)	0.674
Hypertension, n (%)	110 (67.9)	347 (60.7)	0.093
IHD, n (%)	78 (48.1)	282 (49.3)	0.796
NYHA class III/IV, n (%)	72 (44.4)	217 (37.9)	0.135
AF, n (%)	45 (27.8)	148 (25.9)	0.627
Laboratory values			
FBG, mmol/L	5.49 (4.86–6.98)	5.44 (4.80–7.10)	0.511
BNP, pg/ml	800.74 (328.84-1689.87)	906.16 (451.61-1709.85)	0.139
White blood cell, 10^9/L	6.84 (5.56–8.19)	6.70 (5.40–8.38)	0.837
Hemoglobin, g/dL	136.39 ± 21.475	135.42 ± 20.846	0.606
Creatinine, μmol/L	87.00 (70.00-106.00)	88.00 (74.00-112.00)	0.171
Urea, mmol/L	7.71 (5.80-10.12)	8.09 (6.39–10.48)	0.228
Cholesterol, mmol/L	4.09 (3.33–5.19)	4.20 (3.46–5.01)	0.547
Triglyceride, mmol/L	1.15 (0.83–1.61)	1.11 (0.87–1.50)	0.527
HDL-C, mmol/L	0.99 ± 0.272	1.02 ± 0.310	0.416
LDL-C, mmol/L	2.42 (1.89–3.08)	2.44 (1.88–3.04)	0.942
Echocardiography parameters			
LVEF	32.05 ± 6.244	30.65 ± 6.043	0.012
LAD, mm	45.73 ± 6.500	45.25 ± 6.804	0.434
LVEDD, mm	60.38 ± 6.818	62.58 ± 8.849	0.001
E/e'	15.43 ± 11.519	15.65 ± 7.057	0.800
IVS, mm	10.54 ± 1.760	9.98 ± 1.978	0.001
LVPWT, mm	9.83 ± 1.602	9.70 ± 4.521	0.718
Time interval, mo	11.00 (6.00-20.25)	15.00 (7.00–30.00)	< 0.001
Treatment			
β-Blockers, n (%)	154 (95.1)	525 (91.8)	0.162
RAAS blockers, n (%)	130 (80.2)	440 (76.9)	0.370
Spironolactone, n (%)	105 (64.8)	414 (72.4)	0.062
Digoxin, n (%)	44 (27.2)	155 (27.1)	0.987
Loop diuretic, n (%)	90 (55.6)	328 (57.3)	0.685
Aspirin, n (%)	73 (45.1)	286 (50.0)	0.267
Statins, n (%)	95 (58.6)	353 (61.7)	0.479
Warfarin, n (%)	39 (24.1)	151 (26.4)	0.551
ICD, n (%)	1 (0.6)	14 (2.4)	0.146
Pacemaker, n (%)	14 (8.6)	19 (3.3)	0.004
CRT, n (%)	4 (2.5)	29 (5.1)	0.158

Abbreviations: HFimpEF, heart failure with improved ejection fraction; HFrEF, heart failure with reduced ejection fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; IHD, ischemic heart disease; NYHA, New York Heart Association; AF, atrial fibrillation; FBG, fasting blood glucose; BNP, B-type natriuretic peptide; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; E/e', mitral Doppler early velocity/mitral annular early velocity; IVS, interventricular septal; LVPWT, left ventricular posterior wall thickness; RAAS, renin-angiotensin-aldosterone system; ICD, implantable cardioverter-defibrillator; CRT, cardiac resynchronization therapy

Table 2 Cox regression analysis for cardiovascular death in patients with HFimpEF and persistent HFrEF

	Univariate analysis			*Multivariate analysis		
	HR	95 CI	P-Value	HR	95 CI	P-Value
HFimpEF	0.482	0.280–0.828	0.008	0.518	0.281–0.957	0.036
Weight	0.985	0.971–0.998	0.030	0.991	0.974–1.009	0.331
Male	0.981	0.659–1.460	0.923	1.240	0.774–1.987	0.371
Age	1.029	1.014–1.045	< 0.001	1.020	1.003–1.038	0.021
SBP	0.991	0.983–0.999	0.034	0.990	0.980–0.999	0.033
DBP	0.979	0.967–0.992	0.002	0.994	0.974–1.014	0.549
NYHA class III/IV	0.567	0.379–0.847	0.006	0.439	0.269–0.715	0.001
Hemoglobin	0.985	0.978–0.992	< 0.001	0.987	0.977–0.996	0.006
Creatinine	1.003	1.002–1.005	< 0.001	1.001	0.998–1.004	0.648
Urea	1.065	1.037–1.093	< 0.001	1.054	1.014–1.096	0.008
Statins	0.690	0.481–0.989	0.044	0.842	0.562–1.261	0.403
Pacemaker	0.949	0.387–2.323	0.908	0.877	0.316–2.434	0.800
ICD	0.395	0.055–2.829	0.355	0.362	0.050–2.603	0.312
CRT	0.520	0.165–1.637	0.264	0.393	0.120–1.288	0.123

Abbreviations: HFimpEF, heart failure with improved ejection fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure; NYHA, New York Heart Association; ICD, implantable cardioverter-defibrillator; CRT, cardiac resynchronization therapy; HR, hazard ratio; CI, confidence interval

*Adjusted for covariates that were statistically significant in the univariate Cox regression model. Additional covariates were adjusted for clinically relevant characteristics, including gender, pacemaker, ICD, and CRT

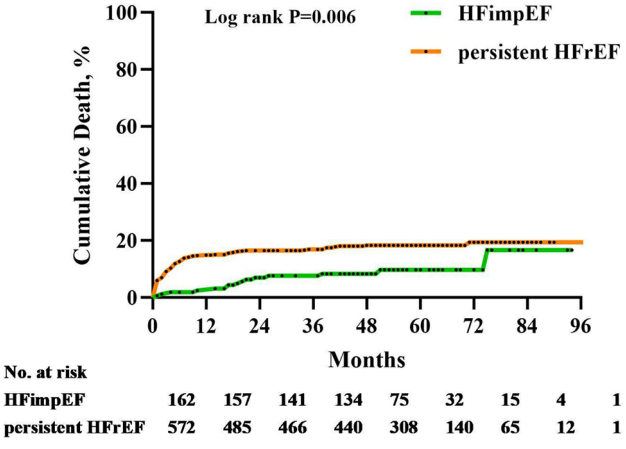

Fig. 2 Kaplan-meier survival curve for cardiovascular death between the HFimpEF and persistent HFrEF Groups. HFrEF indicates heart failure with reduced ejection fraction; HFimpEF, heart failure with improved ejection fraction

matrix [10]. This suggests that recovery of cardiac systolic function may be necessary for changes in LV geometry to occur, ultimately promoting structural reverse remodeling. Moreover, clinical studies [11] have identified specific characteristics in patients with HFimpEF, demonstrating that a higher proportion of these patients undergo LV structural reverse remodeling. Notably, LV structural reverse remodeling is associated with a better clinical prognosis, and there is a direct correlation between this remodeling and improved cardiovascular outcomes [12]. The improvement in cardiac function and the subsequent structural reverse remodeling may help explain why patients with HFimpEF tend to experience a more favorable cardiovascular prognosis. Additionally, fewer patients with HFimpEF had a history of smoking in this study, which might have contributed to improved clinical outcomes. Indeed, several studies have highlighted the association between smoking and clinical prognosis. A Korean study [13] undertaken by Ki YJ et al. revealed that the incidence of major adverse cardiovascular and cerebrovascular events was 19.8% higher in smokers than in non-smokers, and that smoking was related to a higher risk of adverse outcomes (HR 1.198, 95% CI 1.137–1.263) in patients undergoing PCI. At the same time, a meta-analysis conducted by Pan A et al. [14] validated that smoking was associated with an increased risk of cardiovascular death (Relative Risk 1.49, 95% CI 1.29–1.71) in diabetic patients. What's more, smokers were at a 1.15-fold higher risk of cardiovascular death compared to non-smokers.

Notably, HFimpEF does not reflect completely HF recovery. Our research demonstrated that patients with HFimpEF still display different dynamic trajectories. In HFimpEF subgroup, some patients can maintain LVEF at 40% or higher, defined as persistent HFimpEF, while others may exhibit a decrease in LVEF to below 40% again. Additionally, the Cox regression model constructed in our study unveiled that patients with persistent HFimpEF had a lower risk of all-cause and cardiovascular death, indicating that persistent HFimpEF is associated with better clinical outcomes. As previously mentioned, LV reverse remodeling promotes normalization of cardiac structure and function, which subsequently improves the clinical prognosis of HF patients. The myocardial cells and extracellular matrix undergo numerous significant changes during LV reverse remodeling [15]. However, some morphological and molecular determinants are still

Table 3 Cox regression analysis for cardiovascular death among HFimpEF Subtype

	Univariate analysis			*Multivariate analysis		
	HR	95 CI	P-Value	HR	95 CI	P-Value
Male	0.627	0.220–1.787	0.383	2.253	0.653–7.778	0.199
Age	1.049	1.005–1.095	0.030	1.029	0.971–1.090	0.340
SBP	0.972	0.948–0.996	0.023	0.956	0.929–0.985	0.003
DBP	0.950	0.917–0.985	0.005	1.019	0.957–1.085	0.560
DM	2.996	1.065–8.428	0.038	4.084	1.160-14.377	0.028
IHD	4.778	1.339–17.049	0.016	1.090	0.197–6.030	0.921
LVEDD	0.904	0.847–0.965	0.002	0.925	0.853–1.002	0.056
LVEF	1.142	1.010–1.290	0.034	1.047	0.934–1.174	0.434
Hemoglobin	0.960	0.939–0.982	0.001	0.974	0.949-1.000	0.046
Creatinine	1.005	1.002–1.008	0.001	1.004	0.997–1.011	0.315
Urea	1.107	1.045–1.174	0.001	0.974	0.895–1.060	0.537
persistent HFimpEF	0.202	0.069–0.595	0.004	0.212	0.063–0.716	0.013
Pacemaker	1.702	0.384–7.548	0.484	2.806	0.360-21.871	0.325

Abbreviations: SBP indicates systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; IHD, ischemic heart disease; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; HFimpEF, heart failure with improved ejection fraction; HR, hazard ratio; CI, confidence interval

*Adjusted for covariates that were statistically significant in the univariate Cox regression model. Additional covariates were adjusted for clinically relevant characteristics, including gender and pacemaker

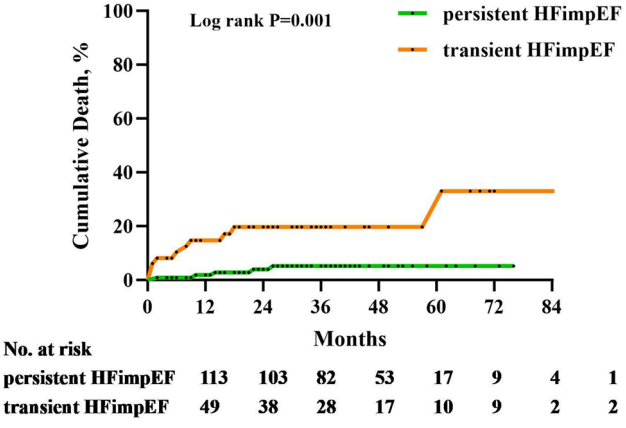

Fig. 3 Kaplan-meier survival curve for cardiovascular death between the persistent HFimpEF and transient HFimpEF subgroups. HFimpEF indicates heart failure with improved ejection fraction

dysregulated following the improvement in LV abnormal structure and function [16–18]. Previous study [19] has corroborated that transcription patterns varied between the general population and individuals with recovery of abnormal cardiac structure and function following heart failure, over 75% of patients with LV reverse remodeling still exhibited HF-related persistent abnormal gene transcription. Thus, LV reverse remodeling in HFimpEF patients does not necessarily represent myocardial recovery, and it should be regarded as a stable stage in the course of HF, which allows heart to maintain a less pathological state for better clinical outcomes. However, this adaption has limited biological reserve capacity, putting patients at risk of redeveloping LV dysfunction due to disturbed hemodynamics, neurohormonal factors, or environmental stress [2]. Therefore, HFrEF may recur in a proportion of HFimpEF patients. While, persistent HFimpEF may signifies a consistently stable stage during the course of HF, which is accompanied by milder

Table 4 Logistic regression analysis to identify predictors of persistent HFimpEF

	Univariate analysis			*Multivariate analysis		
	OR	95 CI	P-Value	OR	95 CI	P-Value
Male	2.428	1.179–4.999	0.016	2.983	1.241–7.172	0.015
Age	0.988	0.966–1.010	0.275	1.009	0.980–1.039	0.535
NYHA class III/IV	0.424	0.214–0.840	0.014	0.919	0.359–2.350	0.859
IHD	0.365	0.182–0.733	0.005	0.642	0.277–1.491	0.303
Hemoglobin	1.022	1.005–1.038	0.010	1.007	0.983–1.031	0.582
FBG	0.892	0.801–0.994	0.039	0.890	0.781–1.013	0.079
HDL-C	5.219	1.265–21.537	0.022	6.910	1.358–35.155	0.020
Urea	0.920	0.859–0.985	0.017	0.892	0.805–0.989	0.031

Abbreviations: NYHA indicates New York Heart Association; IHD, ischemic heart disease; FBG, fasting blood glucose; HDL, high-density lipoprotein cholesterol; OR, odds ratio; CI, confidence interval

*Adjusted for covariates that were statistically significant in the univariate logistic regression model. Additional covariates were adjusted for clinically relevant characteristics, including age

pathological conditions. That may account for the more favorable clinical prognosis of patients with persistent HFimpEF.

Identifying clinical factors associated with the maintenance of improved LVEF plays a critical role in clinical decision-making. Dyslipidemia is a major modifiable risk factor contributing to the development of cardiovascular disease. Aside from total cholesterol and low-density lipoprotein cholesterol, which are traditionally related to cardiovascular risk [20], HDL-C is currently considered a predictor of cardiovascular diseases. Numerous clinical studies [21, 22] have portrayed the U-shaped association between HDL-C levels and the risk of cardiovascular events. Specifically, low (<40 mg/dL) and very high (>80 mg/dL) levels of HDL-C are associated with higher incidence of adverse cardiovascular outcomes. Interestingly, recent studies [23–25] have demonstrated that HDL-C plays a significant cardioprotective role in HF patients by reducing oxidative stress, limiting abnormal release of inflammatory cytokines, and preventing cardiomyocyte injury. In our study, we found that HDL-C was identified as a positive independent factor related to persistent HFimpEF after multivariate adjustment. Although more large-scale basic and clinical studies need to be conducted to explore the association between HDL-C and HFimpEF, the former appears to be a predictor of changes in LVEF. Chen L et al. [26] conducted a clinical study involving 1,418 HFpEF patients and revealed that low baseline HDL-C levels (multivariate logistic regression analysis: OR 0.60, 95% CI 0.38–0.94) were associated with worse LVEF. Therefore, clinicians should pay more attention to dyslipidemia in HF patients in order to reduce or reverse adverse cardiovascular outcomes in the future.

Taken together, considering that unstable factors present in HFimpEF patients may exacerbate heart failure, it is vital to conduct regular follow-up examinations, including clinical, laboratory, and imageological examinations. The 2020 Journal of the American College of Cardiology [2] recommends that while HFimpEF patients have a low risk of HF recurrence, they should be followed up every six months for at least three years. Besides, it is recommended to continue GDMT in HFimpEF populations until additional predictors of relapse are identified in future studies [3]. However, to date, only one randomized controlled trial (TRED-HF) [27] examined and documented the detrimental effects of GDMT withdrawal in asymptomatic patients with HFimpEF. Thus, further clinical studies are warranted to assess the feasibility of GDMT withdrawal in distinct HF populations.

Limitations

This study has several limitations. To begin, due to the retrospective nature of our study, the possibility of selection bias cannot be excluded. Secondly, the clinical data of enrolled patients were retrospectively collected from the Electronic Medical Record System at the First Affiliated Hospital of Dalian Medical University and Central Hospital of Dalian University of Technology. However, some patients might have sought medical treatment in other hospitals, and these clinical data were not available, which may have compromised rehospitalization-related results. Thirdly, LVEF can be influenced by several conditions, which may affect research results. We have adjusted covariates with statistical significance and clinically relevant variables in regression analysis, but information bias and confounding bias can not be completely avoided. Finally, considering the relatively small sample size of this study, future large-scale prospective studies are necessitated to validate our findings.

Conclusions

HFimpEF does not represent HF completely recovery, given that patients with HFimpEF had different LVEF trajectories. Moreover, patients with persistent HFimpEF experienced better clinical outcomes, highlighting the need for clinicians to identify modifiable clinical factors for LVEF improved and concurrently minimize the risk of adverse outcomes in the future.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-024-04288-x.

Supplementary Material 1

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Author contributions

Yang Jiang: Conceptualization, Methodology, Investigation, Writing – Original Draft. Xuefu Chen: Investigation, Statistical Analysis, Writing – Review & Editing. Xinxin Zhang: Writing – Review & Editing. Shuang Dong: Investigation. Ying Liu: Writing – Review & Editing.

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Data availability

The data supporting the findings of this study have been deposited in the First Affiliated Hospital of Dalian Medical University, which are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

All participants provided informed consent before entering the study. This study was approved by both the institutional review board of First Affiliated Hospital of Dalian Medical University (PJ-KS-KY-2024-375) and the institutional review board of Central Hospital of Dalian University of Technology (YN2024-018-01). The Clinical Trial Number is ChiCTR2400086622.

Competing interests
The authors declare no competing interests.

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