Circulation: Heart Failure

ORIGINAL ARTICLE

Heart Failure With Preserved Ejection Fraction Infrequently Evolves Toward a Reduced Phenotype in Long-Term Survivors

A Long-Term Prospective Longitudinal Study

See Editorial by Paulus

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BACKGROUND: Long-term trajectories of left ventricular ejection fraction (LVEF) in heart failure (HF) patients with preserved EF (HFpEF) remain unclear. Our objective was to assess long-term longitudinal trajectories in consecutive HFpEF patients and the prognostic impact of LVEF dynamic changes over time.

METHODS AND RESULTS: Consecutive ambulatory HFpEF patients admitted to a multidisciplinary HF Unit were prospectively evaluated by 2-dimensional echocardiography at baseline and at 1, 3, 5, 7, 9, and 11 years of follow-up. Exclusion criteria were patients having a previous known LVEF <50%, patients undergoing only 1 echocardiogram study, and those with a diagnosis of dilated, noncompaction, alcoholic, or toxic cardiomyopathy. One hundred twenty-six patients (age, 71±13 years; 63% women) were included. The main pathogeneses were valvular disease (36%) and hypertension (28%). Atrial fibrillation was present in 67 patients (53%). The mean number of echocardiographies performed was 3±1.2 per patient. Locally weighted error sum of squares curves showed a smooth decrease of LVEF during the 11-year follow-up that was statistically significant in linear mixed-effects modeling (P=0.01). Ischemic patients showed a higher decrease than nonischemics. The great majority (88.9%) of patients remained in the HFpEF category during follow-up; 9.5% evolved toward HF with midrange LVEF, and only 1.6% dropped to HF with reduced LVEF. No significant relationship was found between LVEF dynamics in the immediate preceding period and mortality.

CONCLUSIONS: LVEF remained ≥50% in the majority of patients with HFpEF for ≤11 years. Only 1.6% of patients evolved to HF with reduced LVEF. Dynamic LVEF changes were not associated with mortality.

Key Words: ejection fraction ■ follow-up studies ■ heart failure ■ humans ■ ventricular function

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WHAT IS NEW?

- Left ventricular ejection fraction (LVEF) trajectories in heart failure with preserved ejection fraction are not well elucidated.
- Previous data based on clinically driven LVEF measurements may be biased toward a higher proportion of patients with left ventricular functional deterioration.
- This prospective protocol-fixed LVEF assessment suggests that heart failure with preserved ejection fraction infrequently evolves toward an heart failure with preserved ejection fraction–declined phenotype.
- Mortality was not associated with a declining LVEF in the preceding period.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Contemporary medical treatments have not significantly changed the prognosis of patients with heart failure with preserved ejection fraction.
- Because longitudinal LVEF assessment does not seem to play a crucial role in mortality, new treatment targets are necessary, such as comorbidities, inflammation, vascular stiffness, endothelial dysfunction, and others.

The main terminology used to describe heart failure (HF) is based on the measurement of left ventricular ejection fraction (LVEF). A wide range of patients have HF, including those with normal LVEF (typically considered as ≥50%; HF with preserved ejection fraction [HFpEF]) to those with reduced LVEF (typically considered as <40%; HF with reduced ejection fraction [HFrEF]).[1] Patients with an LVEF in the range of 40% to 49% represent a gray area, defined in the most recent European Society of Cardiology guidelines as HF with midrange LVEF (HFmrEF).[1] Patients with HFpEF are a heterogeneous group with various underlying pathogeneses and pathophysiological abnormalities, and the diagnosis is more challenging than for HFrEF because it largely involves excluding other potential noncardiac causes of symptoms suggestive of HF.[1,2]

Although the proportion of patients with HFpEF ranges from 22% to 73%, depending on the definition,[1,2] the long-term LVEF longitudinal trajectories in patients with HFpEF are unclear. Most data come from retrospective analyses in which subsequent LVEF assessments were clinically driven and thus susceptible to important indication bias, rather than because of a prospective fixed protocol[3,4] and had limited follow-up.[3–5] We recently reported the longitudinal dynamics of LVEF in patients with HFrEF and HFmrEF.[6] In the current report, our aim was to prospectively assess LVEF longitudinal trajectories in the long term (≤11 years) in a consecutive real-life cohort of patients with HFpEF.

METHODS

Study Population

Consecutive ambulatory patients with HFpEF referred to an HF clinic between August 2001 and December 2015 were considered for the study. The main inclusion criteria were having an initial LVEF ≥50%, at least 1 hospital admission for HF, and having at least 2 echocardiography measurements during the study period. Exclusion criteria were as follows: having a previous known LVEF <50% (the so-called HF with recovered LVEF), undergoing only 1 echocardiogram (death before 1 year of follow-up or not attending the scheduled echocardiography tests), and having a diagnosis of dilated, noncompaction, alcoholic, or toxic cardiomyopathy.

Planned follow-up visits and scheduled echocardiogram tests included a minimum of 1 visit with a nurse every 3 months and 1 visit with a physician (cardiologist, internist, or family physician) every 6 months, as well as optional visits with specialists in geriatrics, psychiatry, and rehabilitation. The LVEF measurements were prospectively scheduled at baseline, 1 year afterward, and then every 2 years and were performed using 2-dimensional echocardiography by cardiologists who were imaging experts. The LVEF was obtained from apical 2- and 4-chamber views and calculated using the Simpson method. All echocardiograms were revised for accuracy by expert staff. During the baseline visit, patients provided written consent for the use of their clinical data for research purposes. The study was performed in compliance with the law protecting personal data in accordance with the international guidelines on clinical investigation of the World Medical Association Declaration of Helsinki.

Statistical Analysis

Categorical variables were expressed as absolute numbers and percentages. Continuous variables were expressed as the mean (SD) or median (quartiles Q1–Q3) according to normal or non-normal distributions. Normal distribution was assessed with normal Q to Q plots. Locally weighted error sum of squares (Loess) curves—a nonparametric approach developed in 1988—were plotted for the whole cohort.[7] Loess curves are useful to observe trends or relationships in nonlinear data observed over time. Loess moves along data looking at chunks at a time, fitting a set of local regression lines computed using the observed data (missing values are omitted) and connecting these lines to make a smooth line. Missing data because of loss to follow-up were assumed to be at random because there was no evidence that not attending the scheduled visit had anything to do with LVEF. Locally weighted regression is based on a weight function, which gives the greatest weight to observations that are the closest to the focal observation.

Statistical analyses of the LVEF change over time were performed by linear mixed-effects (LME) modeling, which takes into account the group-level structure in the data by simultaneously assessing effects within and across groups. The LME models incorporate both fixed effects and random effects and describe the relationship between a response and

Table. Demographic, Clinical, Echocardiographic Characteristics and Treatment of Patients at Baseline and Treatments During Follow-Up

	Total Cohort	N
Age, y	71±13	126
Women, n (%)	79 (62.7)	126
White	125 (99.2)	126
Pathogenesis		126
Ischemic heart disease	18 (14.3)	
Hypertensive	35 (27.8)	
Hypertrophic cardiomyopathy	15 (11.9)	
Valvular	45 (35.7)	
Other	13 (10.3)	
HF duration, mo	12 (2.8–36.5)	126
≥1 HF admission in previous year	87 (69)	126
NYHA class		126
I	9 (7.1)	
II	67 (53.2)	
III	48 (38.1)	
IV	2 (1.6)	
LVEF, %	63±8	126
LV end-diastolic diameter, mm	49.2±7	120
LV end-systolic diameter, mm	32.1±7.6	118
IVS, mm	13.4±3.2	102
PW, mm	12.2±2	102
LA diameter, mm	50 (45–56)	124
PAP, mm Hg	49±14	98
Mitral regurgitation, n (%)		126
Mild	62 (50)	
Moderate	22 (17)	
Severe	16 (13)	
Hypertension, n (%)	94 (74)	126
Diabetes mellitus, n (%)	50 (40)	126
COPD, n (%)	17 (13.5)	126
Peripheral arteriopathy, n (%)	11 (8.7)	126
Atrial fibrillation, n (%)	67 (53)	126
Anemia, n (%)*	64 (50.8)	123
Renal insufficiency, n (%)†	70 (55.6)	124
Blood pressure, mm Hg	138.1±26.3	126
Heart rate, bpm	70.1±14.3	126
BMI, kg/m^2	27.1 (24.3–31)	125
NT-proBNP, ng/L	1490 (628–2797)	96
Treatment (baseline), n (%)		
ACE inhibitor or ARB	91 (72.2)	126
β-Blocker	68 (54)	126
MRA	27 (21.4)	126
Loop diuretic	99 (78.6)	126
Digoxin	31 (24.6)	126
ICD	3 (2.4)	126
Treatment (F-U), n (%)		
ACE inhibitor or ARB	88 (70)	126
β-Blocker	97 (77)	126
MRA	69 (54.8)	126
Loop diuretic	116 (92.1)	126
Digoxin	54 (42.9)	126
ICD	5 (4)	126

Data represent the mean±SD, median (quartiles Q1–Q3), or n (%). ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; F-U, follow-up; HF, heart failure; ICD, implantable cardioverter-defibrillator; IVS, interventricular septum; LA, left atrium; LV, left ventricle; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAP, pulmonary artery pressure; PW, posterior wall; and WHO, World Health Organization.

*According to WHO criteria (<13 g/dL in men and <12 g/dL in women).

†Estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration equation) <60 mL/min per 1.73 m^2.

covariates that have been observed along with the response.[8] In this study, LME models were built using the nlme package[9] to evaluate the effect of time on LVEF change. We hypothesized that there are important individual-level effects and that patients have similar rates of change over time; thus, we fitted random intercept LME models. In this type of LME model, the measured value of LVEF is assumed to have a set of fixed parameters across individuals, but there is a specific random effect per individual. Also, we performed mean paired data comparisons between each predefined study time point. Finally, changes in the LVEF categories established in the 2016 HF Guidelines of the European Society of Cardiology were analyzed between the baseline LVEF and the last obtained LVEF for each patient. Statistical analyses were performed using SPSS 21 (SPSS, Inc, Chicago, IL) and R (A Language and Environment for Statistical Computing) by the R Core Team (2017; R Foundation for Statistical Computing, Vienna, Austria). For LME models, we used the nlme R package, version 3.1-131.1.[9] A 2-sided $P<0.05$ was considered significant. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. J.L. had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

RESULTS

A total of 265 patients with LVEF ≥50% were admitted to the outpatient HF Unit. Seventeen patients were excluded because of a previous known LVEF <50%, 106 were excluded because they had only 1 echocardiogram study (45 died during the first year, and 61 did not attend the scheduled echocardiography exams), and 15 were excluded because of an etiology diagnosis considered a phenotype not related to HFpEF (3 dilated, 4 noncompaction, 3 alcoholic, and 5 drug-derived cardiomyopathies). Table I in the Data Supplement compared

the studied cohort and patients who died during the first year of follow-up and those who did not attend the scheduled echocardiography exams. Patients who died during the first year had a significantly worse clinical profile, whereas those who did not come back for their repeat echocardiogram were clinically similar to the included patients. Thus, 126 patients (age, 71±13 years; 63% women) were finally included in the present report. The main HF pathogeneses were valvular disease (36%) and hypertensive cardiomyopathy (28%; Table). Sixty-seven patients (53%) were in atrial fibrillation. Treatments at baseline and during follow-up are depicted in the Table. Notably, β-blocker, mineralocorticoid receptor antagonists, and digoxin were significantly increased during follow-up. Thirteen electrical cardioversions and 3 atrial ablations were performed, but at the last follow-up, only 3 such patients remained in sinus rhythm. Sixteen revascularization procedures were performed in 10 ischemic patients. Figure I in the Data Supplement shows the distribution of echocardiograms performed on the patients. The LVEF measurements were obtained from 126, 108, 73, 43, 22, 11, and 8 patients at the predefined time points, accounting for 100%, 86%, 82%, 75%, 73%, 85%, and 89% of the patients alive at each time point. The mean number of echocardiography measurements performed was 3±1.3 per patient. All-cause mortality at 11 years was 89%. Table II in the Data Supplement shows the causes of death for the whole cohort.

Figure 1A shows the Loess curve of the LVEF dynamic trajectory of the entire cohort at every study time point. A smooth decrease was observed during follow-up. Although numerically small, the LME model showed that changes in LVEF were statistically significant during the 11-year follow-up (P=0.01). The mean LVEF at each study time point was 63±8%, 62±9%, 61±9%, 61±7%, 61±7%, 61±8%, and 58±6%. Figure II in the Data Supplement shows violin plots of LVEF at each study time point. Paired data comparisons showed no statistical differences between study periods (Table III in the Data Supplement). Table IV in the Data Supplement shows trajectories of other available echocardiography data beyond LVEF. Remarkably, the great majority of patients remained in the HFpEF category (88.9%) at their last echocardiography, whereas 9.5% went down to HFmrEF and 1.6% dropped to HFrEF (or HFpEF declined; Figure 1B). None of the patients of ischemic pathogenesis declined to HFrEF, but 27.8% declined to HFmrEF, versus 6.6% of nonischemic pathogeneses (P=0.005). Eight of the 12 patients (67%) who declined to HFmrEF had a baseline LVEF between 50% and 55%; the 2 patients who went down to HFrEF had a baseline LVEF ≥65%. As triggers for LVEF declining in such patients, 5 experienced a new myocardial infarction, 1 developed severe senile amyloidosis, 1 had breast neoplasm metastases, 1 developed permanent atrial fibrillation, 1 developed

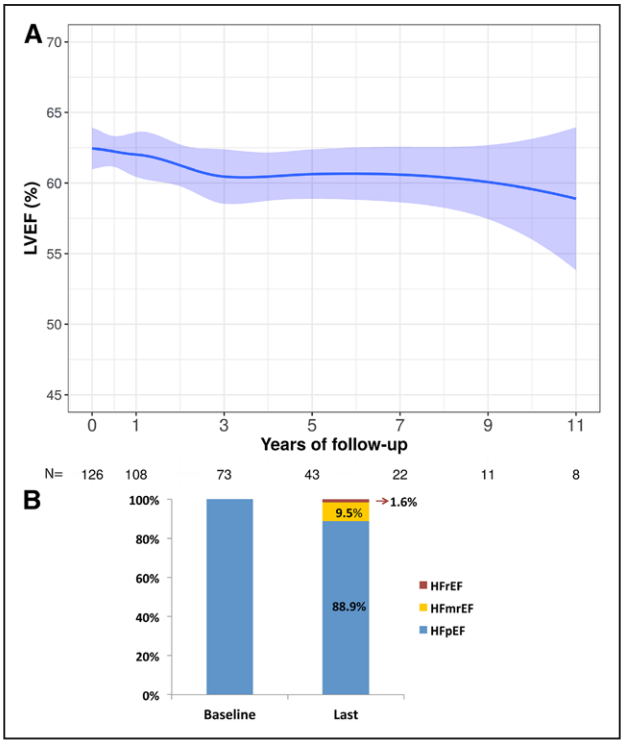

Figure 1. Left ventricular ejection fraction (LVEF) trajectories and changes during follow-up.
A, Loess curve of the LVEF longitudinal trajectory for the total cohort; P=0.01. Shaded regions displayed around curves represent the 95% CI. **B**, Changes from heart failure with preserved ejection fraction (HFpEF) at baseline to heart failure with midrange LVEF (HFmrEF) or heart failure with reduced ejection fraction (HFrEF) at the last observation for every patient.

severe renal insufficiency, and 2 patients with severe valvular disease were rejected for surgery, with progressive deterioration.

The patients with HFpEF with an ischemic pathogenesis had an ominous outcome; all died within 5 years, and they had a steeper declining LVEF slope during the first 5 years (Figure 2); in the LME model, a significant interaction was found between ischemic pathogenesis and LVEF trajectory (P=0.03). A significant interaction was also found between LVEF trajectories and sex (P=0.04; Figure 3A) but not with age (≤75 versus >75 years; P=0.75), Figure 3B) or HF duration (≤1 versus >1 year; P=0.6; Figure 3C). We did not find a relationship between worse LVEF dynamics in the preceding study period (changes between the 2 previous LVEF values) and mortality (Figure 4A) or for the different trajectories between survivors and nonsurvivors during follow-up (P for interaction, 0.69), Figure 4B). Tables V to X in the Data Supplement show LME model formulas and regression results.

DISCUSSION

This is the first long-term assessment of LVEF trajectories using a prespecified and fixed prospective echocardiography protocol in patients with HFpEF. Two main findings emerged: (1) the LVEF dynamics in HFpEF did

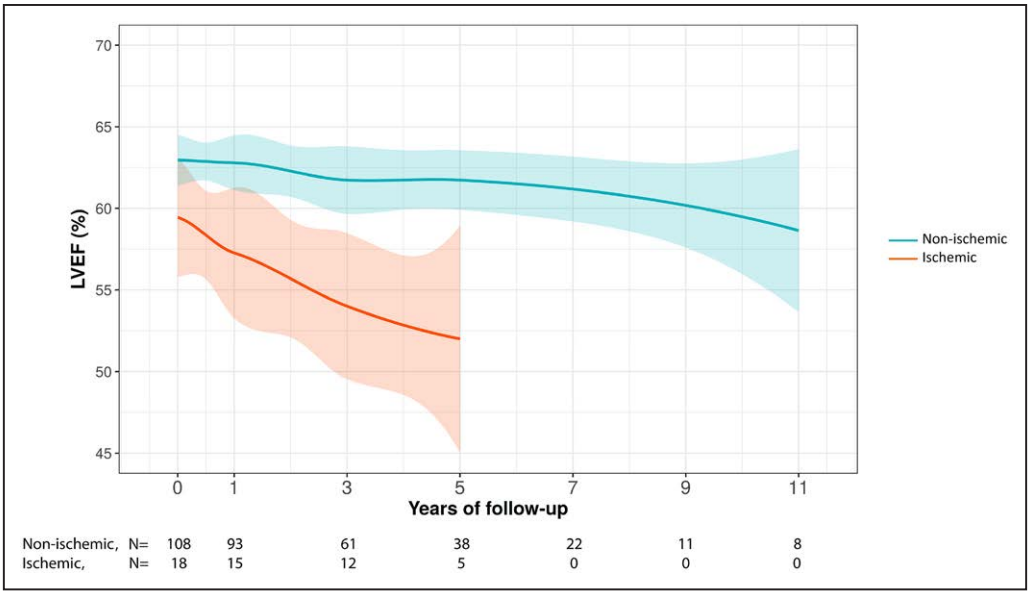

Figure 2. Loess spline curves for the long-term left ventricular ejection fraction (LVEF) trajectories based on the pathogenesis of heart failure. Ischemic (orange) vs nonischemic (blue); in the linear mixed-effects model, a significant interaction was found between ischemic and LVEF trajectory (*P*=0.03). Shaded regions displayed around curves represent the 95% CI.

not show significant changes toward reduced HF phenotypes during follow-up in the great majority of long-term survivors, although a smooth decline in LVEF was observed; and (2) the LVEF dynamics in the immediate preceding period were not associated with mortality, which, nevertheless, was unacceptably high (89% at 11 years). These data showed relevant differences in the LVEF trajectories in patients with HFrEF and HFmrEF,[6] as well as with previous studies that examined LVEF trajectories in HFpEF subjects in a retrospective and clinically driven manner.[3,4]

Regarding LVEF trajectories in different HF settings, we recently reported significant LVEF changes during follow-up in patients with depressed LVEF (EF <50%). In brief, we reported a steep LVEF increase during the first year, a plateau during the decade after, and a slow decline thereafter.[6] In these patients, LVEF trajectories showed significant differences according to sex, ischemic pathogenesis, and HF duration.[6] In the current HFpEF study, LVEF trajectories showed a smooth decrease but remained markedly above 50% during follow-up (Figure 1A) in the whole cohort. Remarkably, a significant interaction was found between LVEF trajectories and ischemic pathogenesis and sex. The differences found between LVEF trajectories in different HF phenotypes (namely HF with depressed or preserved LVEF) were not unexpected given the distinct pathobiology underlying both conditions, patterns of ventricular remodeling, and clinical characteristics.[10–13] In addition, huge differences have been reported for the effects of treatments on LVEF trajectories and outcomes as medications that produce unequivocal benefits in patients with HFrEF have not improved patients with HFpEF.

Previous reports have examined LVEF trajectories in HFpEF. Dunlay et al,[3] in a retrospective community-based cohort of incident HF patients, found that an LVEF decline to <50% was found in 38.5% of patients with HFpEF during follow-up, and 25.1% had a decline in LVEF to <40%. On average, the authors reported an LVEF decrease of 5.8% during 5 years with greater declines in older individuals and those with coronary disease. A major limitation of this study, pointed out by the authors, is that "all echocardiograms were obtained at the discretion of the patient's providers rather than at prespecified intervals." This is a source of potential bias with ejection fraction assessment being influenced by clinical status, age, provider, and therapeutic era.[3] Indeed, the authors highlighted the need for prospective longitudinal studies, such as that reported here. Clarke et al[4] studied a cohort of patients with HFpEF with a primary hospital discharge diagnosis of HF and 2 LVEF tests over 30 days apart. For similar patients with HFpEF, after 5 years of follow-up, there was a 15% probability they would remain as HFpEF and a 33% probability they would decline to HFrEF. Again, the authors recognized limitations because these data were observational and the times of ascertainments of LVEF were clinically driven rather than following a fixed prospective protocol. In this study, patients were more likely to have LVEF measured when they were less well, resulting in an upward bias in the estimated hazard for transitioning from HFpEF to HFrEF or less likely to have the LVEF measured when they were nearing end of life, which could result in a downward bias.

In contrast to these previously discussed reports, and more in agreement with our data, is the report by Tsuji et al[5] in the CHART-2 study (Chronic Heart Failure Registry

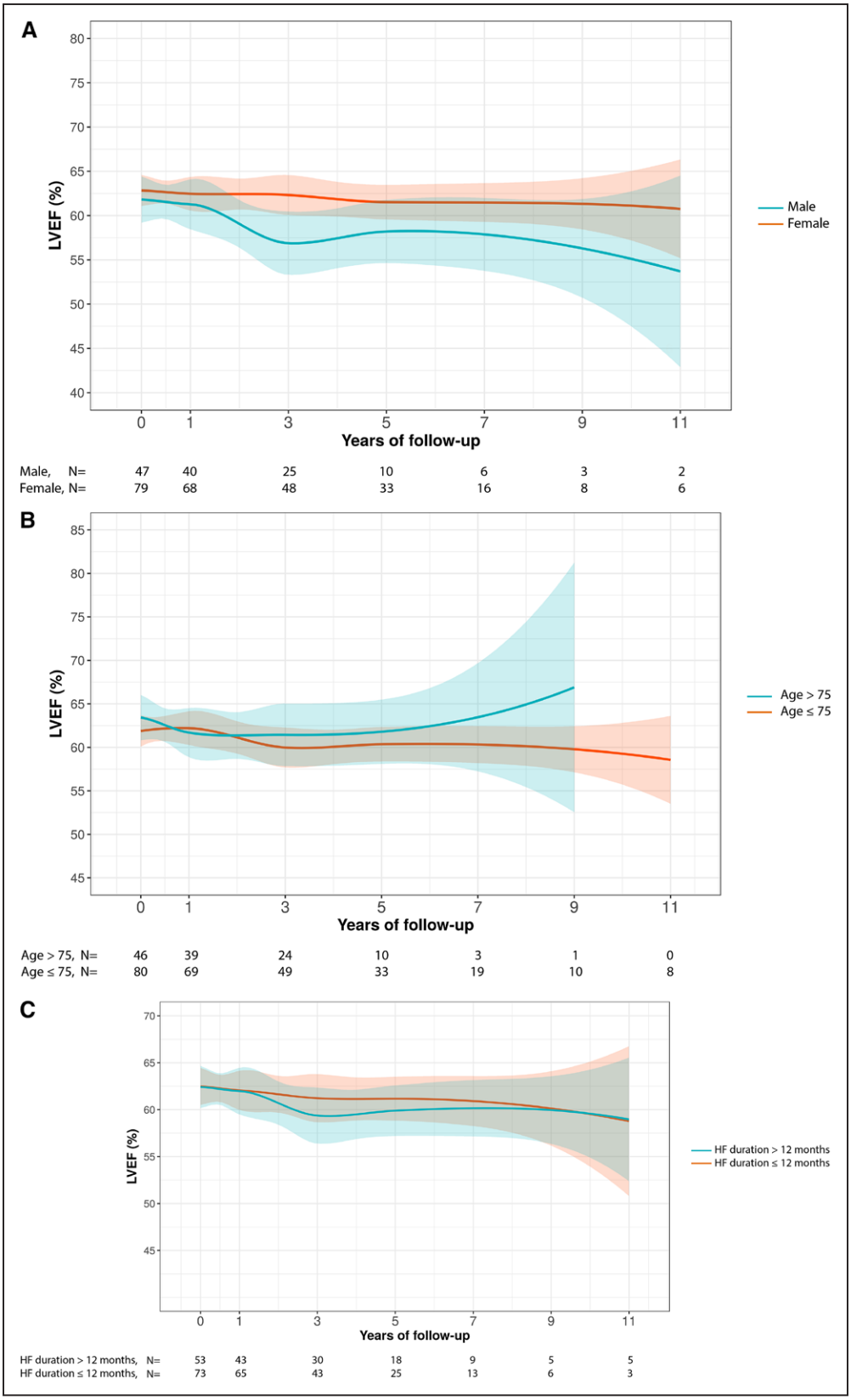

Figure 3. Loess spline curves for the long-term left ventricular ejection fraction (LVEF) trajectories based on several characteristics of patients. **A**, Sex: women (orange) vs men (blue); *P*=0.04 for the interaction between sex and LVEF trajectory in the linear mixed-effects (LME) model. **B**, Age: ≤75 y (orange) vs >75 y (blue); *P*=0.75 for the interaction between age group and LVEF trajectory in the LME model. **C**, Duration of heart failure (HF): ≤12 mo (orange) vs >12 mo (blue); *P*=0.6 for the interaction between HF duration group and LVEF trajectory in the LME model. Shaded regions displayed around curves represent the 95% CI.

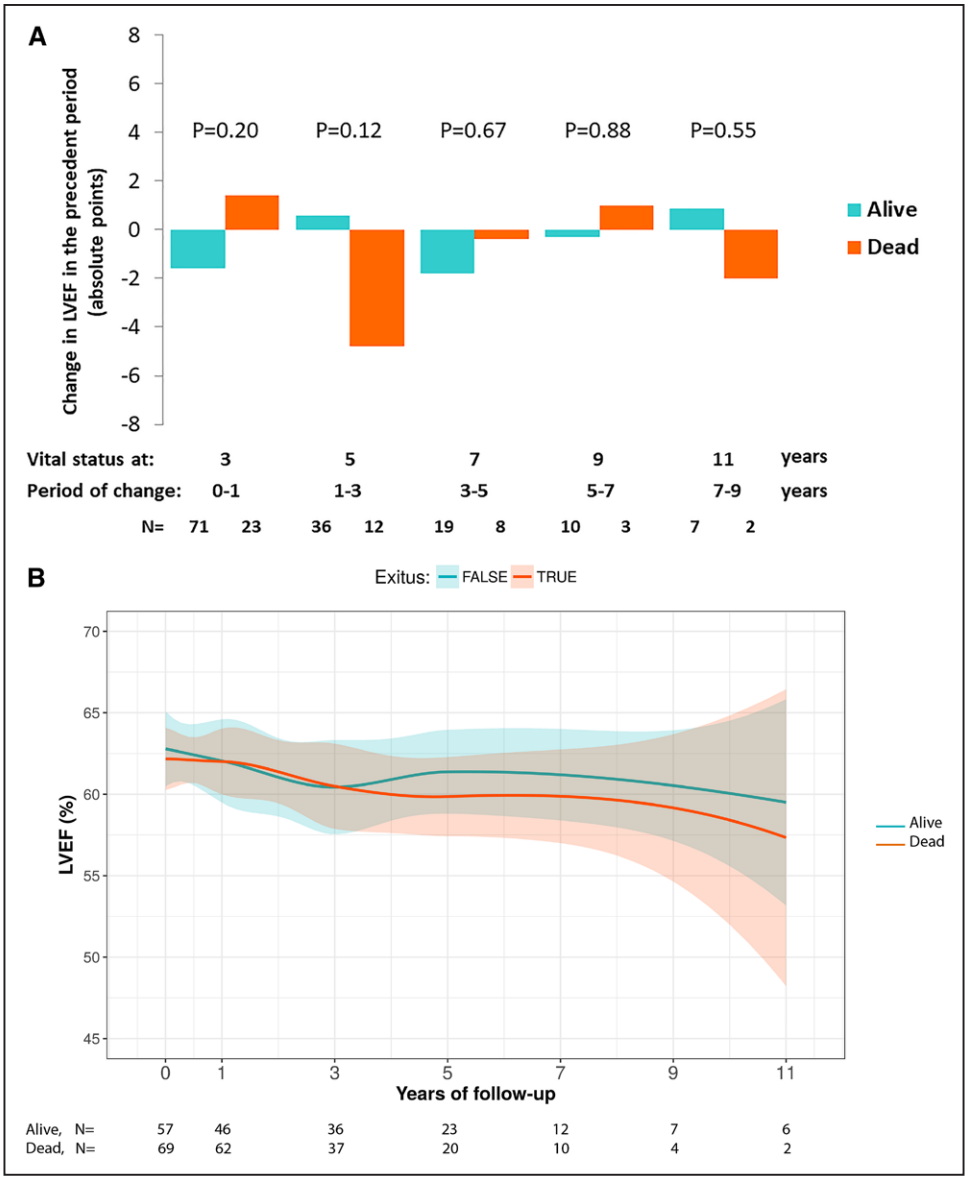

Figure 4. Trajectories and changes in left ventricular ejection fraction (LVEF) and survival.
A, Changes between the last 2 echocardiograms before the analyzed study period according to vital status. Orange represents those patients who died in the subsequent study period, and blue represents those who survived for the entire subsequent period. **B**, Loess spline curves of long-term LVEF trajectories relative to vital status during follow-up. Patients who died during follow-up (orange) vs patients alive at the end of follow-up (blue); *P*=0.69 for the interaction between vital status at the end of follow-up and LVEF trajectory. Shaded regions displayed around curves represent the 95% CI.

and Analysis in the Tohoku District 2), although this study is limited by a shorter follow-up, with prospective LVEF assessments at baseline, 1, 2, and 3 years. These authors found that patients with HFpEF transitioned to HFmrEF and HFrEF by 8% and 2% at 1 year and by 8% and 4% at 3 years, respectively.[5] These results confirm that the LVEF trajectories in HFpEF, when assessed according to a fixed protocol, infrequently evolve toward an HFpEF-declined phenotype. Differences in cohorts' characteristics may also account, at least in part, for the differences found relative to retrospective studies.

Of interest, Ueda et al,[14] in a retrospective analysis of 100 patients admitted because of acute HF, found that an initial LVEF ≤55% was key for transitioning from HFpEF to HFmrEF (10 of 13 versus 1 of 87 with initial LVEF >55%; *P*<0.001). In our prospective assessment, we also found that 8 of 12 patients (67%) who transitioned to HFmrEF had a baseline LVEF ≤55%. Using 50% as the cutoff for HFpEF is arbitrary and eventually the range of 50% to 55% LVEF may represent, at least in some patients, an incipient degree of systolic dysfunction rather than a true HFpEF phenotype. Indeed normal LVEF by 2-dimensional echocardiography is probably the nearest to 55% than 50%,[15,16] and most LVEF follow-up studies have been performed by 2-dimensional echocardiogram.

The value of LVEF dynamics in predicting mortality risk also differed between depressed and preserved

HF phenotypes. In our previous study, we found that patients with LVEF <50% who died had worse LVEF dynamics in the preceding study period,[6] whereas we did not find such a relationship in the present HFpEF cohort. Differences in the causes of death might play an important role in this discrepancy. Noncardiovascular death occurred in ≈15% of all patients with depressed HF in our previous study, whereas in the present HFpEF cohort, >25% of patients died from noncardiovascular causes. As the longitudinal LVEF assessment does not seem to play a crucial role in mortality in HFpEF, new treatment targets are needed, including comorbidities, inflammation, vascular stiffness, endothelial dysfunction, and others.

This study is not without limitations. The study sample size is limited, and patients were treated at a specific multidisciplinary HF clinic in a tertiary-care hospital, with patients referred after at least 1 hospital admission or with a history of difficult management. That means they are highly selected patients, so we cannot disregard selection bias by disease severity. LVEF was assessed by transthoracic echocardiography in routine clinical care. However, in the current study, all echocardiograms were scheduled and analyzed prospectively and at prespecified intervals and not at the discretion of the patient's physician. We acknowledge that the intraobserver and interobserver variabilities of echocardiogram-derived LVEF are ≈5%. However, we assume that such variability was randomly distributed during follow-up. Further, contrast echocardiography may be superior in the evaluation of left ventricular remodeling parameters. However, it is infrequently used in clinical practice, usually only in selected patients. Three-dimensional echocardiography and cardiac magnetic resonance imaging would evaluate left ventricular function and volumes more precisely, but they are not broadly used in clinical practice and even less so in HFpEF. As in all published studies of changes in left ventricular function during follow-up, our analyses were performed in completers, that is, patients with data available from both baseline and at least the 1-year echocardiography. We cannot fully discard that excluded patients eventually experienced a drop in their LVEF, but we found no evidence to support such possibility. Nevertheless, these results can only apply to subjects on whom we had long-term data. The limited proportion of patients with HF of ischemic pathogenesis (14%) could influence the reported data because their trajectories showed a significantly steeper slope without reaching the HFrEF cut-point. Finally, we cannot fully exclude some bias in the Loess spline curves due to dropout because we could not statistically distinguish between autonomous time trends and pseudo upward trends due to successive dropouts (because of fatalities) with lower initial LVEF values. Missing values because of patients' loss to follow-up were assumed to be at random. Furthermore, Loess spline curve estimations at the end of follow-up are less robust because of the limited number of patients.

CONCLUSIONS

LVEF remained ≥50% in the majority of patients with HFpEF for ≤11 years, whereas 9.5% of patients evolved to HFmrEF and 1.6% to HFrEF during long-term follow-up. In patients with HFpEF of ischemic pathogenesis, the evolution to HFmrEF reached 27.8% during follow-up. No significant relationship was found between the LVEF trajectory or LVEF dynamics in the immediate preceding period and mortality.

ARTICLE INFORMATION

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Disclosures

None.

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