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ORIGINAL RESEARCH

In-Hospital Improved Left Ventricular Ejection Fraction and Prognosis in Acute Heart Failure

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BACKGROUND: The in-hospital trajectories of left ventricular ejection fraction (LVEF) in patients admitted for acute heart failure have been poorly investigated. We sought to assess the rate of heart failure with improved ejection fraction (HFimpEF) at discharge in acute heart failure, to identify predictors of HFimpEF and to evaluate the association of HFimpEF with outcome.

METHODS: We retrospectively enrolled patients admitted for acute heart failure, with ≥2 in-hospital echocardiographic evaluations of LVEF and with LVEF ≤40% at admission. HFimpEF was defined as LVEF >40% at discharge, with an improvement in LVEF ≥10%. The primary end point was 1-year all-cause death. Trajectories of LVEF were also assessed at follow-up ambulatory visit at 1 year after discharge.

RESULTS: The overall population included 779 patients with LVEF ≤40% at admission; at discharge, 14.9% had HFimpEF. The independent predictors of HFimpEF were valvular heart disease (odds ratio, 3.460; *P*=0.001), lower left ventricular volumes (odds ratio, 0.957 per 1 mL/m^2 increase; *P*<0.001), and absence of right ventricular dysfunction (odds ratio, 0.518; *P*=0.017). LVEF at admission was not associated with 1-year all-cause death. When patients were classified according to the in-hospital LVEF trajectory, HFimpEF was independently associated with a lower risk of 1-year (hazard ratio [HR], 0.324; *P*=0.008) and 5-year all-cause death (HR, 0.584; *P*=0.013). Among patients discharged with HFimpEF who were reevaluated after 12 months, 86% maintained LVEF >40%, while 14% showed again LVEF ≤40%.

CONCLUSIONS: In patients with acute heart failure admitted with LVEF ≤40%, 15% had HFimpEF at predischarge reassessment. Valvular pathogenesis of heart failure with reduced ejection fraction, absent right ventricular dysfunction and less severe left ventricular remodeling were associated with higher likelihood of in-hospital HFimpEF. One-year and 5-year mortality risk was lower in patients with HFimpEF compared with patients with nonimproved LVEF.

Key Words: acute heart failure ■ left ventricular ejection fraction ■ death ■ outcomes ■ systolic function ■ trajectories

See Editorial by XXX.

Left ventricular ejection fraction (LVEF) is the most common parameter used to quantify global left ventricular (LV) systolic function.[1,2] There is a growing interest in dynamic changes and trajectories of LVEF over time,[3,4] in particular, since the value of LVEF may guide medical therapy for chronic heart failure (HF). Longitudinal improvement or fluctuating course of LVEF raises the question whether guideline-directed medical therapy for HF with reduced ejection fraction (HFrEF) should be prolonged after normalization of

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CLINICAL PERSPECTIVE

What Is New?

- In patients hospitalized for acute heart failure with reduced ejection fraction, improvement in left ventricular ejection fraction occurred in ≈15% and was predicted by valvular pathogenesis of heart failure, smaller left ventricular volumes, and absence of right ventricular dysfunction, suggesting more reversible disease mechanisms.
- Early improvement in left ventricular ejection fraction was independently associated with lower short- and long-term mortality rates, whereas baseline left ventricular ejection fraction at admission was not prognostic.

What Are the Clinical Implications?

- Routine echocardiographic reassessment of left ventricular ejection fraction before discharge may refine early risk stratification and help tailor post-discharge follow-up intensity.

Nonstandard Abbreviations and Acronyms

ESC HF III	European Society of Cardiology Heart Failure III
HFH	heart failure rehospitalization
HFimpEF	heart failure with improved ejection fraction
HFrEF	heart failure with reduced ejection fraction
MR	mitral regurgitation
RVD	right ventricular dysfunction

LVEF,[5,6] even when overt systolic dysfunction was only transient.[7]

In both chronic and acute HF (AHF), LVEF has a dynamic nature,[8] since systolic function reflects not only intrinsic contractility of LV but also the influence of the pressure and volume overload, which might be affected by several clinical and hemodynamic conditions, like fluid retention, rise in arterial and intraventricular pressure, concurrent ischemia, and, notably, medical therapy.[9] For these reasons, LVEF assessment at a single time point may not be sufficient for long-term risk stratification, especially during an episode of AHF.[10] The longitudinal course of LVEF has been demonstrated to predict events, both in chronic HF with reduced ejection fraction (HFrEF)[11] and during follow-up after an AHF episode.[12,13] HF with improved ejection fraction (HFimpEF) has recently been recognized as a distinct clinical phenotype, reflecting patients with prior HFrEF who experience a significant recovery of systolic function. According to current definitions, HFimpEF is characterized by an initial LVEF ≤40%, a ≥10% absolute increase, and a subsequent LVEF >40%. This entity has gained increasing attention because it is associated with more favorable outcomes compared with persistent HFrEF.[14,15] However, in-hospital trajectories of LVEF during AHF admission remain poorly explored.[16]

We sought (1) to explore the prevalence and characteristics of HFimpEF in a cohort of patients admitted for AHF, (2) to find predictors of early LVEF improvement, and (3) to assess the relation of HFimpEF with short-term and long-term outcomes.

METHODS

Study Design and Data Collection in TRI-AHF Registry

The data that support the findings of this study are available from the corresponding author upon reasonable request.

In this retrospective longitudinal study, we analyzed patients from the TRI-AHF (Tricuspid - Acute Heart Failure) registry. As previously described,[17] the registry includes patients hospitalized for AHF between November 2010 and June 2022 at our center (Azienda Sanitaria Universitaria Giuliano-Isontina—and University Hospital of Trieste, Italy). Patients with AHF secondary to acute myocardial infarction, pulmonary embolism, type I pulmonary arterial hypertension, congenital heart disease, or endocarditis were not enrolled in the registry. Patients enrolled in the database were categorized according to the type of AHF ("de novo" versus "acutely decompensated chronic HF"), the primary etiology and triggering factor, if identifiable. Collected information included data concerning medical history, clinical presentation, ECG, transthoracic echocardiography, laboratory findings, and in-hospital treatment. Information on medical therapy before admission and at discharge was also collected, including dosages of antineurohormonal medications for HFrEF (ie, renin–angiotensin system inhibitors/angiotensin receptor–neprilysin inhibitors, β-blockers, mineralocorticoid receptor antagonists), reported as percentage of patients treated with ≥50% versus <50% of target dose (as indicated by European Society of Cardiology HF guidelines[18]), and of loop diuretics, divided into ≥50 mg versus <50 mg of furosemide or equivalent.

Only for patients with an available echocardiographic examination 1 year after the index hospitalization (range, 6–18 months), we also collected data on LVEF trajectories and guideline-directed medical therapy during follow-up.

Subjects gave informed consent for the study, and the institutional ethics board approved the study, which complied with institutional review board policies of hospital administration.

Inclusion and Exclusion Criteria

Among patients enrolled in TRI-AHF registry, for the present study, we included only patients with LVEF ≤40% at admission, and with ≥2 echocardiographic evaluations of LVEF during hospitalization (the first at admission, and the second before discharge, when all intravenous medications were suspended, at least 48 hours later than the first evaluation); patients with LVEF >40% at admission, as well as patients with LVEF ≤40% without a predischarge reevaluation, were excluded. Moreover, we excluded patients who underwent coronary revascularization (either percutaneous or surgical), valvular repair or replacement, or implantation of a cardiac resynchronization therapy device during the index hospitalization (Figure 1A).

Echocardiographic Examination and Assessment of LVEF

Echocardiograms were recorded by experienced operators on digital media storage devices at the echocardiographic core laboratory of our institution and reviewed and reanalyzed offline (according to current international guidelines[19,20]) by 2 level 3–trained echocardiographers.

LV volumes (indexed end-diastolic volume) and LVEF were consistently calculated by Simpson's biplane method from apical views, in accordance with current international echocardiographic guidelines.[19] LVEF was reported as an integer value (1% steps), without predefined rounding categories. Given that all included patients had LVEF ≤40% at admission, HFimpEF was defined as LVEF >40% at the predischarge reevaluation, plus an improvement in LVEF of at least 10%.[12,14,15] The remaining patients, with LVEF ≤40% at discharge or with an improvement <10%, were categorized as non-improved ejection fraction (EF).

For exploratory purposes, patients with an available echocardiographic examination at 1-year follow-up were categorized according to LVEF trajectories. Patients with non-improved EF during the index hospitalization were classified into late HFimpEF and persistent HFrEF, according to the same criteria exposed previously; patients discharged with HFimpEF were classified as maintaining LVEF >40% or having LVEF ≤40%.

Right ventricular dysfunction (RVD) was defined as fractional area change <35%; in a limited number of cases in which right ventricular fractional area change was not feasible or reliable, right ventricular function was evaluated by tricuspid annular plane systolic excursion, with RVD defined as tricuspid annular plane systolic excursion <17 mm. Data concerning severity of mitral (MR) and tricuspid regurgitation, defined as trivial or mild versus moderate or severe grade, were also collected, as well as the evaluation of E/E′ and pulmonary arterial systolic pressure.

Study End Points

The primary end point was 1-year all-cause death. Secondary end points were 5-year all-cause death, 1-year HF rehospitalization (HFH) and a composite of 1-year all-cause death or HFH. Information on outcomes was obtained from official hospital reports and regional health care archives and death registries; additional information from patients' families or general practitioners was used only when administrative data were incomplete.

Statistical Analysis

Continuous normally distributed data are displayed as mean±SD, and comparisons were made using ANOVA; data with skewed distributions are presented as median with interquartile range, and comparisons were made using the Mann–Whitney *U* test. Digit preference for LVEF was evaluated by analyzing terminal digit distribution using a χ^2 goodness-of-fit test (expected uniform distribution, 0–9).

To identify independent predictors of HFimpEF, binary logistic regression analyses were performed; association of all baseline characteristics with HFimpEF was assessed at the univariable logistic regression analysis; and variables significantly associated with HFimpEF in the univariable logistic regression analysis were included in the multivariable analysis.

Cumulative event-free survival estimates were plotted using the Kaplan–Meier estimator, and differences between survival curves were tested with the log-rank test. Univariable and multivariable Cox regression analyses were fitted to define the association of LVEF at admission, LVEF at discharge and of HFimpEF with the outcomes. In the multivariable Cox regression models, we included the covariates previously validated in the first outcome model performed on this registry[17] (ie, ischemic heart disease, diabetes, peripheral artery disease, systolic blood pressure, atrial fibrillation, serum creatinine, serum urea, natriuretic peptides above the median, presence of RVD, moderate–severe MR, moderate–severe tricuspid regurgitation, pulmonary arterial systolic pressure), including also sex and age. All Cox proportional hazards analyses were performed on the complete-case population, as shown in Figure 1A; no additional exclusions were applied for the multivariable models. The proportional hazards assumption for HFimpEF was assessed by including a time-dependent interaction term between HFimpEF and log(time) in the Cox model. To explore

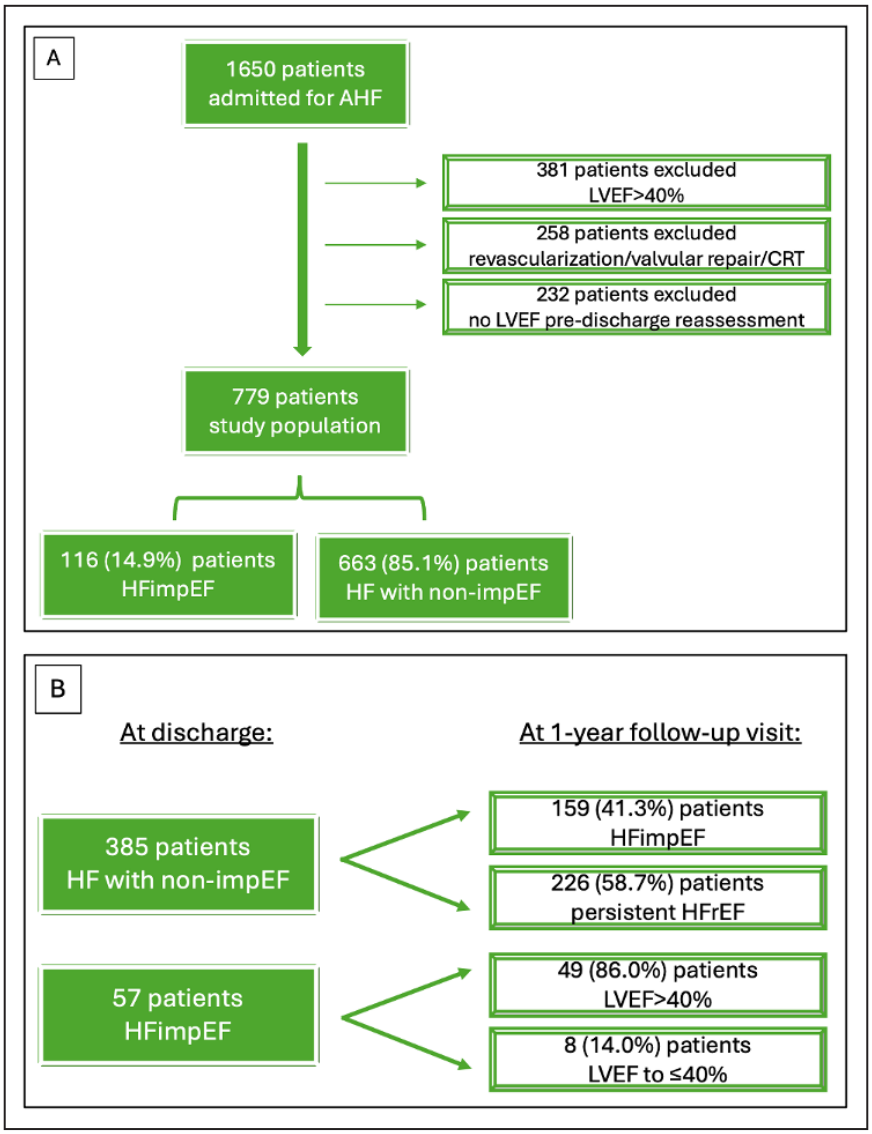

Figure 1. LVEF trajectories during hospitalization and 1 year after discharge.
A, Study population enrollment and exclusion criteria. Of 1650 patients admitted for AHF in the study period, 779 were finally enrolled. Of them, 14.9% had HFimpEF and 85.1% had nonimproved EF. **B**, Among 385 patients discharged with HFrEF and reevaluated at the follow-up visit, 41.3% showed HFimpEF, while 58.7% maintained LVEF ≤40%. Among 57 patients discharged with HFimpEF and reevaluated after 12 months, 86.0% maintained LVEF >40%, while 14.0% showed a decrease in LVEF to ≤40%. AHF indicates acute heart failure; HFimpEF, heart failure with improved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and LVEF, left ventricular ejection fraction.

potential nonlinearity of continuous covariates (age, systolic blood pressure, creatinine, and urea), these variables were additionally modeled as quartiles.

To explore the shape of the association between in-hospital change in LVEF (ΔLVEF) and 1-year death, we modeled ΔLVEF as a continuous variable using restricted cubic splines. Restricted cubic splines were modeled using 3 *df*, with knots placed at equally spaced quantiles of the ΔLVEF distribution. We compared linear versus spline models using likelihood-ratio and Wald tests and assessed potential nonlinearity and thresholds. Model performance was evaluated through discrimination (concordance index).

Only for exploratory purposes, for patients who had an available echocardiographic examination at 1-year follow-up, the long-term (5-year) mortality rate was assessed for each subgroup according to LVEF trajectories.

Given the low proportion of missing data, analyses were conducted using complete-case analysis

without imputation, as previously described for the TRI-AHF registry.[17] A 2-tailed *P* value of <0.05 was considered statistically significant. SPSS Statistics software version 26.0 (IBM, Armonk, NY) and Stata version 14.2 (StataCorp, College Station, TX) were used for analysis.

RESULTS

Patient Characteristics and Clinical Presentation

Among 1650 patients hospitalized for AHF during the registry period, 779 were enrolled in this study. A total of 381 patients were excluded because they had LVEF >40%; 258 were excluded because they underwent coronary revascularization, valvular repair or replacement, or implantation of a cardiac resynchronization therapy device; and 232 were excluded because they did not have an echocardiographic reevaluation before discharge (Figure 1A). Baseline characteristics of the study population are presented in Tables 1 and 2. Mean age was 68±12 years, 73% were men, and 41% had a history of chronic HF. Mean LVEF at admission was 29±9%. Terminal digit analysis (Table S1) showed digit preference, with disproportionate frequency of values ending in 0 or 5 (χ^2 *P*=0.015), suggesting rounding tendencies in LVEF reporting.

Trajectories of LVEF During Hospitalization

Among the 779 patients enrolled, at discharge, 116 (14.9%) had LVEF >40% with an improvement in LVEF of at least 10% (HFimpEF), while 663 (85.1%) had non-improved EF (Figure 1A). Patients with HFimpEF were slightly older than patients with non-improved EF (70 versus 67 years old; *P*=0.039); as regards HF pathogenesis, they had more frequently valvular heart disease (26% versus 9%; *P*<0.001) and less frequently a diagnosis of cardiomyopathy (6% versus 17%; *P*=0.002). Sustained supraventricular tachyarrhythmia as the triggering factor was more common in patients with HFimpEF (35% versus 20%; *P*<0.001). The median length of hospitalization was similar between the 2 groups (13 [interquartile range, 9–19] days for patients with HFimpEF versus 12 [interquartile range, 9–19] days for non-improved EF; *P*=0.601). At the predischarge echocardiogram, patients with HFimpEF versus patients with non-improved EF had smaller LV indexed end-diastolic volume (59 versus 87 mL/m^2), lower prevalence of RVD (20% versus 50%) and significant MR (22% versus 41%), lower E/E' (14 versus 18), and lower pulmonary arterial systolic pressure (38 versus 41 mmHg).

With regard to medical therapy before admission, no differences were found between the 2 groups. At discharge, patients with HFimpEF (compared with patients with non-improved EF) received slightly lower dosages of renin–angiotensin system inhibitors/angiotensin receptor–neprilysin inhibitors (29% versus 39% patients receiving ≥50% of target dose; *P*=0.035) and similar dosages of β-blockers (13% versus 16% receiving ≥50% of target dose; *P*=0.487) but were less frequently prescribed mineralocorticoid receptor antagonists (47% versus 66% receiving ≥50% of target dose; *P*<0.001) and loop diuretics (34.5% versus 60% patients receiving ≥50 mg/day; *P*<0.001).

Predictors of LVEF Improvement

Among the baseline variables significantly associated with HFimpEF at univariable analysis (Table S2), the variables independently associated with higher likelihood of HFimpEF at multivariable analysis (Table 3) were valvular heart disease (odds ratio, 3.460 [95% CI, 1.672–7.143]; *P*=0.001), lower LV indexed end-diastolic volume (odds ratio, 0.957 per 1 mL/m^2 increase [95% CI, 0.943–0.970]; *P*<0.001) and absence of RVD (odds ratio, 0.518 [95% CI, 0.302–0.890]; *P*=0.017). Age, diagnosis of cardiomyopathy, atrial fibrillation, LVEF, and MR were not independently associated with HFimpEF.

Association of HFimpEF With Outcomes

During the first year after discharge, 99 (12.7%) patients died: 8 (6.9%) patients with HFimpEF and 91 (13.7%) patients with non-improved EF. In the overall population, rates of 5-year all-cause death, of 1-year HFH, and of 1-year death/HFH were 251 (32.2%), 131 (16.8%), and 201 (25.8%), respectively.

At univariable Kaplan–Meier analysis, patients with HFimpEF, compared with patients with non-improved EF, showed a lower 1-year mortality rate (*P*=0.047) and a similar 5-year mortality rate (*P*=0.296) and 1-year HFH rate (*P*=0.950), and 1-year mortality/HFH rate (*P*=0.317) (Figure 2). Similarly, at univariable Cox regression analyses (Table S3), HFimpEF was associated with 1-year death but not with secondary end points.

At multivariable analysis, LVEF at admission was not associated with 1-year all-cause death (hazard ratio [HR], 0.993 per 1% increase [95% CI, 0.967–1.020]; *P*=0.625; Table S4). However, when patients were classified according to in-hospital LVEF trajectory, HFimpEF (versus non-improved EF) was significantly associated with a lower risk of 1-year all-cause death (HR, 0.324 [95% CI, 0.141–0.741]; *P*=0.008; Table 4). No significant violation of the proportional hazards assumption was observed for HFimpEF (*P*=0.652). Modeling continuous covariates as quartiles confirmed a consistent trend across categories, supporting the linearity assumption. Consistently, higher LVEF at discharge was also independently related with lower

Table 1. Patient Characteristics of the Overall Study Population and of Patients With HFimpEF Versus Non-improved EF (Clinical Features)

	Overall	HFimpEF	HF with non-improved EF	
	n=779	n=116 (14.9%)	n=663 (85.1%)	*P* value
Demographics and past medical history				
Age, y	68±12	70±13	67±12	0.039†
Male sex	568 (72.9)	77 (66.4)	491 (74.1)	0.086
Body mass index, kg/m^2	27±5	28±5	27±5	0.247
Decompensated chronic HF	322 (41.3)	46 (39.7)	276 (41.6)	0.690
Etiology: Ischemic heart disease	348 (44.7)	51 (44.0)	297 (44.8)	0.868
Etiology: Hypertensive heart disease	168 (21.6)	19 (16.4)	149 (22.5)	0.141
Etiology: Cardiomyopathy	120 (15.4)	7 (6.0)	113 (17.0)	0.002†
Etiology: Valvular heart disease	93 (11.9)	30 (25.9)	63 (9.5)	<0.001†
Triggering factor: Tachyarrhythmia	175 (22.5)	41 (35.3)	134 (20.2)	<0.001†
Triggering factor: Myocardial ischemia	83 (10.7)	11 (9.5)	72 (10.9)	0.657
Triggering factor: Infections	56 (7.2)	12 (10.3)	44 (6.6)	0.154
Triggering factor: Hypertensive crisis	33 (4.2)	4 (3.4)	29 (4.4)	0.648
Diabetes	281 (36.1)	44 (37.9)	237 (35.7)	0.651
Previous myocardial infarction	162 (20.8)	17 (14.7)	145 (21.9)	0.077
Previous revascularization	124 (15.9)	14 (12.1)	110 (16.6)	0.219
Previous device implantation	78 (10.0)	6 (5.2)	72 (10.9)	0.060
Peripheral artery disease	163 (20.9)	30 (25.9)	133 (20.1)	0.156
Previous stroke/transient ischemic attack	71 (9.1)	13 (11.2)	58 (8.7)	0.396
Chronic kidney disease	201 (25.8)	31 (26.7)	170 (25.6)	0.806
Chronic obstructive pulmonary disease	101 (13.0)	16 (13.8)	85 (12.8)	0.774
Clinical presentation at admission and in-hospital treatments				
Systolic blood pressure, mmHg	134±28	133±31	134±28	0.764
Heart rate, bpm	100±28	105±29	99±28	0.019†
Signs of hypoperfusion	171 (22.0)	23 (19.8)	148 (22.3)	0.549
Pulmonary edema	127 (16.3)	18 (15.5)	109 (16.4)	0.804
Atrial fibrillation	224 (28.8)	47 (40.5)	177 (26.7)	0.002†
Left or right bundle-branch block	243 (31.2)	33 (28.4)	210 (31.7)	0.489
Length of hospitalization, d	12 [9–19]	13 [9–19]	12 [9–19]	0.601
Inotropes or vasopressors	238 (30.6)	28 (24.1)	210 (31.7)	0.104
Vasodilators (intravenous)	195 (25.0)	26 (22.4)	169 (25.5)	0.480
Medical therapy before admission				
RASi/ARNi ≥50% of target dose	201 (26.2)	25 (21.9)	176 (27.0)	0.260
β blockers ≥50% of target dose	115 (14.9)	13 (11.2)	102 (15.5)	0.228
MRA ≥50% of target dose	85 (11.0)	10 (8.6)	75 (11.4)	0.380
Furosemide ≥50 mg/d	151 (19.6)	18 (15.8)	133 (20.3)	0.263
Medical therapy at discharge				
RASi/ARNi ≥50% of target dose	283 (37.5)	32 (28.6)	251 (39.0)	0.035†
β blockers ≥50% of target dose	117 (15.5)	15 (13.3)	102 (15.8)	0.487
MRA ≥50% of target dose	474 (62.8)	53 (46.9)	421 (65.6)	<0.001†
Furosemide ≥50 mg/d	425 (56.4)	39 (34.5)	386 (60.3)	<0.001†

Values are reported as mean±SD or n (%).

ARNi indicates angiotensin receptor–neprilysin inhibitor; EF, ejection fraction; HF, heart failure; HFimpEF, heart failure with improved ejection fraction; and RASi, renin–angiotensin system inhibitor.

†Indicates statistical significance.

Table 2. Patient Characteristics of the Overall Study Population, and of Patients With HFimpEF Versus Nonimproved EF (Laboratory and Echocardiographic Examinations)

	Overall	HFimpEF	HF with non-improved EF	
	n=779	n=116 (14.9%)	n=663 (85.1%)	*P* value
Laboratory examinations at admission				
Creatinine, mg/dL	1.10 (0.90–1.39)	1.08 (0.89–1.38)	1.10 (0.90–1.40)	0.671
eGFR (CKD-EPI), mL/min per 1.73 m^2	64±24	63±25	64±23	0.584
Urea, mg/dL	46 (35–62)	45 (34–63)	46 (35–62)	0.893
Sodium, mEq/L	138±4	138±4	138±4	0.503
Potassium, mEq/L	4.03±0.56	4.07±0.53	4.03±0.57	0.491
Hemoglobin, g/dL	13.4±2.1	12.9±2.6	13.4±2.0	0.035†
High NPs (BNP or NT-proBNP greater than median)*	390 (50.1)	51 (44.0)	339 (51.1)	0.154
Laboratory examinations at discharge				
Creatinine, mg/dL	1.13 (0.93–1.42)	1.09 (0.91–1.39)	1.14 (0.94–1.43)	0.178
eGFR (CKD-EPI), mL/min per 1.73 m^2	62±23	63±23	62±23	0.812
Urea, mg/dL	53 (40–71)	48 (35–67)	54 (41–72)	0.066
Sodium, mEq/L	138±3	139±3	138±3	0.257
Potassium, mEq/L	4.21±0.44	4.12±0.43	4.22±0.43	0.033†
Hemoglobin, g/dL	12.7±2.2	12.1±2.3	12.7±2.1	0.006†
High NPs (BNP or NT-proBNP greater than median)*	89 (21.0)	7 (13.7)	82 (22.0)	0.174
Echocardiographic exam at admission				
LV indexed end-diastolic volume, mL/m^2	85±30	63±24	88±30	<0.001†
LVEF, %	29±9	31±7	29±9	0.004†
Right ventricular dysfunction	411 (53.0)	41 (35.3)	370 (56.1)	<0.001†
Mitral regurgitation (moderate–severe)	381 (49.5)	40 (34.8)	341 (52.1)	0.001†
Tricuspid regurgitation (moderate–severe)	174 (22.6)	22 (19.0)	152 (23.2)	0.314
E/E′	20 (15–25)	18 (14–23)	20 (15–26)	0.168
Pulmonary arterial systolic pressure, mmHg	43±13	41±12	43±13	0.160
Echocardiographic examination at discharge				
LV indexed end-diastolic volume, mL/m^2	83±30	59±22	87±29	<0.001†
LVEF, %	33±11	53±8	30±7	<0.001†
Right ventricular dysfunction	339 (45.1)	23 (19.8)	316 (49.8)	<0.001†
Mitral regurgitation (moderate–severe)	285 (37.9)	25 (21.6)	260 (40.9)	<0.001†
Tricuspid regurgitation (moderate–severe)	104 (13.8%)	16 (13.8%)	88 (13.9%)	0.985
E/E′	18 (13–23)	14 (11–20)	18 (13–23)	0.001†
Pulmonary arterial systolic pressure, mmHg	41±13	38±11	41±13	0.021†

Values are reported as mean±SD, median (interquartile range), or n (%).

BNP indicates B-type natriuretic peptide; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HFimpEF, heart failure with improved ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction; NP, natriuretic peptide; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*Median value for BNP=915pg/mL, median value for NT-proBNP=6291pg/mL.

†Indicates statistical significance.

1-year all-cause death (HR, 0.964 per 1% increase [95% CI, 0.941–0.988]; *P*=0.003; Table S5).

When ΔLVEF was analyzed as a continuous variable using restricted cubic splines, no significant nonlinear association with 1-year death was detected (likelihood ratio *P*=0.20; Wald *P*=0.30). The spline model did not improve model fit compared with a linear specification ($\Delta\chi^2$=2.33 on 2 *df*; *P*=0.312), and discrimination was similar (concordance index spline 0.533 versus. linear 0.531; Figure 3).

As regards secondary end points, HFimpEF was also independently associated with a lower risk of 5-year all-cause death (HR, 0.584 [95% CI, 0.382–0.895]; *P*=0.013; Table S6); however, it was not associated

Table 3. Independent Predictors of HFimpEF at Multivariable Analysis

	Odds ratio	95% CI	*P* value
Age (per 1- y increase)	0.987	0.963–1.011	0.295
Etiology: Cardiomyopathy	0.546	0.208–1.435	0.220
Etiology: Valvular heart disease	3.460	1.672–7.143	0.001
Triggering factor: Tachyarrhythmia	1.669	0.824–3.378	0.155
Previous valvular surgery/repair	1.529	0.572–4.098	0.397
Heart rate (per 1 bpm increase)	0.999	0.989–1.009	0.840
Atrial fibrillation	1.326	0.720–2.445	0.364
Hemoglobin (per 1 g/dL increase)	0.904	0.798–1.024	0.113
LV indexed end-diastolic volume (per 1 mL/m^2 increase)	0.957	0.943–0.970	<0.001
LVEF (per 1% increase)	0.970	0.941–1.001	0.058
Right ventricular dysfunction	0.518	0.302–0.890	0.017
Mitral regurgitation (moderate–severe)	0.931	0.547–1.585	0.792

HFimpEF indicates heart failure with improved ejection fraction; LV, left ventricular; and LVEF, left ventricular ejection fraction.

with a lower risk of 1-year HFH (HR, 0.961 [95% CI, 0.556–1.659]; *P*=0.885; Table S7) and of 1-year all-cause death or HFH (HR, 0.729 [95% CI, 0.452–1.177]; *P*=0.197; Table S8).

Trajectories of LVEF at 1-Year Follow-Up

LVEF reevaluation at 12-month follow-up (range, 6–18 months) was available for 442 (57%) patients (Figure 1B).

Among patients discharged with non-improved EF (n=663), 385 were reevaluated at 12 months; of them, 159 (41.3%) showed late HFimpEF, while 226 (58.7%) maintained LVEF≤40% or showed an improvement in LVEF <10%. Patients with late HFimpEF (compared with patients with persistent HFrEF) were treated with similar dosages of renin–angiotensin system inhibitors/angiotensin receptor–neprilysin inhibitors (59.5% versus 50% patients receiving ≥50% of target dose) and of β-blockers (35% versus 26%), but with significantly lower dosages of mineralocorticoid receptor antagonists (39% versus 50%) and of loop diuretics (23% versus 54%) (Table S9). Incidence of all-cause death, in the first 5 years after the follow-up visit, was 13.2% in patients with late HFimpEF and 32.7% in patients with persistent HFrEF.

Among patients discharged with HFimpEF (n=116), 57 had LVEF reevaluation after 12 months; 49 (86.0%) maintained LVEF>40%, while 8 (14.0%) showed a decrease in LVEF to ≤40%. Thirteen of 49 (26.5%) patients with LVEF >40% and 3 of 8 (37.5%) patients with LVEF ≤40% died during the 5 years after the follow-up visit.

DISCUSSION

The dynamic change of LVEF over time has largely been described, especially in patients with chronic HFrEF: While a progressive decline in systolic function correlates with poor prognosis,[21] the improvement in LVEF and the transition from HFrEF to HF with mildly reduced or preserved EF was associated with better outcomes.[11,14,15,22] LVEF fluctuations are even more evident in the acute setting; however, few previous studies have focused on LVEF improvement in AHF but comparing LVEF assessment during the index hospitalization and during subsequent follow-up after discharge. In this study, we sought to specifically evaluate in-hospital trajectories of LVEF to assess baseline predictors and prognostic correlates of HFimpEF at the moment of discharge, rather than during follow-up. The main results were that: (1) of 779 patients with LVEF ≤40% at admission, 14.9% showed HFimpEF at discharge; (2) predictors of HFimpEF were valvular heart disease, lower LV volumes, and absence of RVD; and (3) HFimpEF (but not LVEF at admission) was associated with a lower risk of 1-year all-cause death after discharge.

Prevalence of HFimpEF in AHF

In our cohort, 15% of patients admitted with LVEF ≤40% had improved EF at the predischarge reevaluation. This prevalence is newly described, to the best of our knowledge, since former data mainly assessed the changes in LVEF 1 year after discharge. Only 1 previous study[16] explored the variation of LVEF during a hospitalization for AHF; however, this study showed an association between in-hospital improvement in LVEF and outcome only in patients with HFpEF; moreover, LVEF improvement was analyzed as an absolute value, and the entity of HFimpEF was not considered. Given the known limitations of LVEF, it is conceivable that the prevalence of HFimpEF could be easily overestimated in the case of an erroneous evaluation of LVEF at admission. For this reason, we defined HFimpEF as LVEF transitioning from ≤40% at admission to >40% at discharge but along with an improvement in LVEF

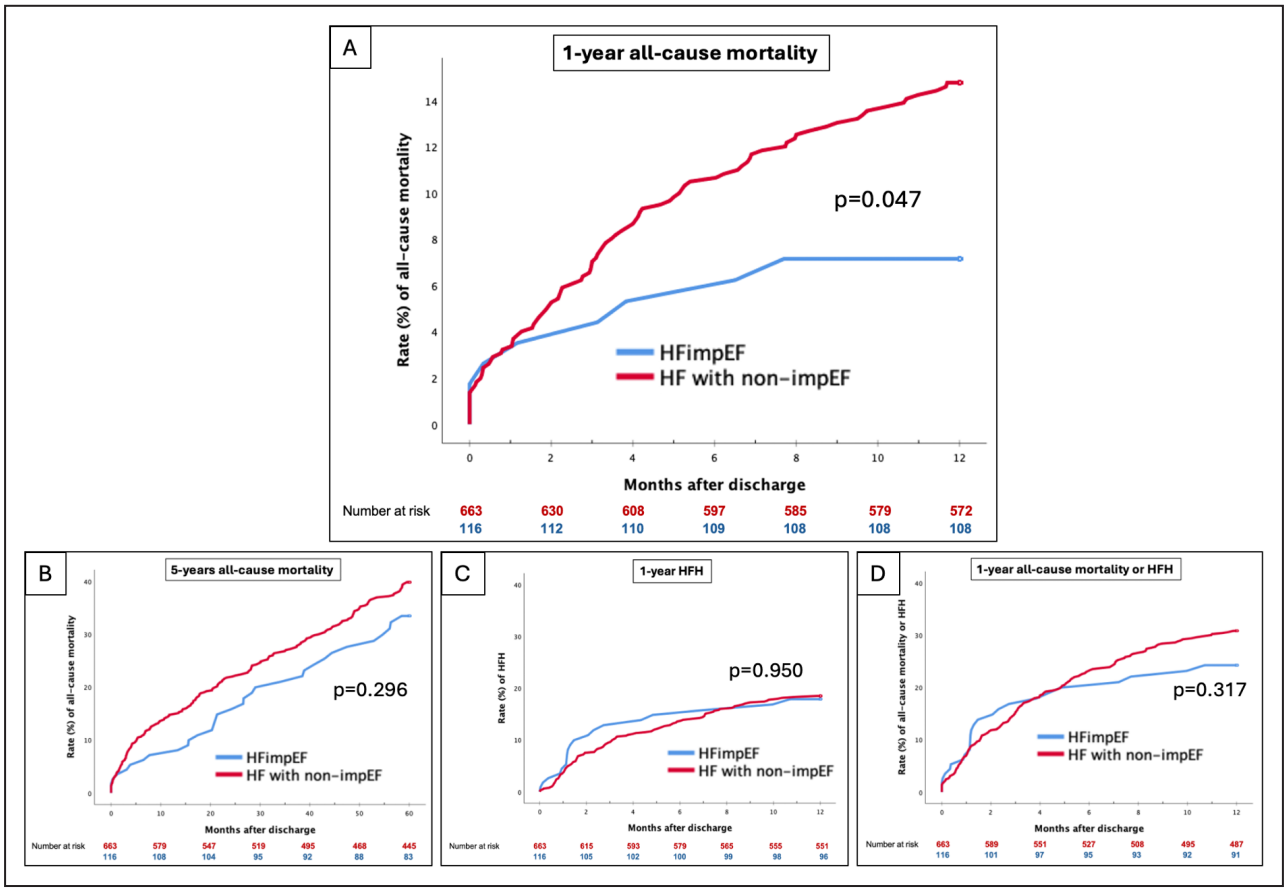

Figure 2. Kaplan–Meier curves for HFimpEF vs non-improved EF at discharge.
Patients were stratified according to HFimpEF vs non-improved EF at predischarge evaluation. **A**, 1-year all-cause death (primary end point). **B**, 5-year all-cause death (secondary end point). **C**, 1-year HFH (secondary end point). **D**, 1-year all-cause death or HFH (secondary end point). EF indicates ejection fraction; HFH indicates heart failure rehospitalization; HFimpEF, heart failure with improved ejection fraction; and HFrEF, heart failure with reduced ejection fraction.

of at least 10%, to exclude or limit the influence of inter- and intra-observer variability, to intercept patients with a great improvement in systolic function despite a predischarge LVEF between 41% and 49%, and to avoid classifying as HFimpEF those patients with small change in LVEF around 40%.[23]

Moreover, we excluded patients who underwent coronary revascularization (either percutaneous or surgical), valvular repair or replacement, and implantation of cardiac resynchronization therapy during the index hospitalization, to evaluate the LVEF trajectories more directly related to decongestive treatment and hemodynamic stabilization and to assess the prognostic implication of LVEF change unrelated to these specific disease-modifying treatments.

Patients with HFimpEF were older and more frequently had reversible causes of LV dysfunction such as supraventricular tachyarrhythmias, with less pronounced ventricular remodeling. Medical therapy before admission was similar in both groups. Conversely, at discharge, patients with improved LVEF were slightly less often treated with renin–angiotensin system inhibitors/angiotensin receptor–neprilysin inhibitors. These patients needed lower dosages of diuretics and showed surrogate markers of better decongestion at discharge (eg, lower prevalence of RVD and significant MR, lower pulmonary arterial systolic pressure and E/E′, slightly lower natriuretic peptides) and less evident obstacles to guideline-directed medical therapy implementation (eg, lower creatinine and serum potassium); hence, in our opinion, poor uptitration of medical therapy in patients with HFimpEF could be explained by the weaker strength of recommendation of these medications in the absence of persistent LVEF ≤40%, especially for patients with de novo HF. Few recent studies[24,25] tried to explore whether patients with only transient systolic dysfunction that improves before discharge may benefit from long-term administration of drugs recommended for HFrEF; however, more robust evidence is needed.

Table 4. Association of HFimpEF With 1-Year All-Cause Death (Multivariable Analysis)

	Hazard ratio	95% CI	*P* value
HFimpEF (vs HF with non-improved EF)	0.324	0.141–0.741	0.008
Age (per 1-y increase)	1.047	1.021–1.073	<0.001
Male sex	1.050	0.618–1.785	0.856
Ischemic heart disease	0.477	0.289–0.789	0.004
Diabetes	1.289	0.807–2.057	0.288
Peripheral artery disease	1.645	1.007–2.687	0.047
Systolic blood pressure (per 1 mmHg increase)	0.984	0.974–0.994	0.002
Atrial fibrillation	1.259	0.784–2.021	0.340
Creatinine (per 1 mg/dL increase)	1.039	0.830–1.300	0.740
Urea (per 1 mg/dL increase)	1.012	1.006–1.019	<0.001
High NPs (BNP or NT-proBNP greater than median)*	1.595	0.985–2.584	0.058
Right ventricular dysfunction	0.790	0.477–1.309	0.361
Mitral regurgitation (moderate–severe)	0.620	0.377–1.021	0.060
Tricuspid regurgitation (moderate–severe)	1.386	0.797–2.410	0.248
Pulmonary arterial systolic pressure (per 1 mmHg increase)	1.005	0.987–1.024	0.601

BNP indicates B-type natriuretic peptide; EF, ejection fraction; HF, heart failure; HFimpEF, heart failure with improved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NP, natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*Median value for BNP, 915 pg/mL; median value for NT-proBNP, 6291 pg/mL.

Predictors of HFimpEF in AHF

Lower LV dimensions at admission were strongly associated with HFimpEF, as previously reported.[12] It is intuitive that larger LV volumes frequently denote long-term (and possibly irreversible) adaptation that is less prone to reverse remodeling and improvement in LVEF,[26,27] and is more likely in irreversible cases of LV dysfunction. Moreover, at higher baseline values of indexed end-diastolic volume, larger absolute increase in stroke volumes and larger absolute decrease in systolic volumes are necessary to reach the same change in LVEF.

Baseline RVD was an adverse predictor of HFimpEF, with almost halved probability of HFimpEF in those patients. Presence of RVD is again a marker of more advanced disease and less reversible LV dysfunction.[28]

Finally, valvular heart disease was another predictor of HFimpEF, although patients undergoing valvular repair or replacement were excluded. It is possible that in patients with severe valvular disease, like primary MR, aortic regurgitation, and stenosis, hemodynamic compromise and HF decompensation are mainly sustained by pressure and volume overload, which are more easily reversible with medical therapy, such as diuretics and vasodilators; viable cardiomyocytes also more likely respond to inotropic stimulations and recover systolic dysfunction, while nonvalvular pathogeneses of HF (mainly ischemic heart disease and cardiomyopathies) often subtend irreversible histological alteration, cellular damage, and replacement fibrosis, reducing the chance of reverse remodeling.[29,30]

At descriptive analyses, patients with HFimpEF had atrial fibrillation and tachyarrhythmias more frequently as a precipitating factor, as well as higher heart rate; surprisingly, neither of these variables were independent predictors of HFimpEF. We hypothesized that, after rate control and sinus rhythm restoration, LVEF improvement requires longer intervals.

Prognostic Implication of Early HFimpEF in AHF

In this study, we found that in-hospital LVEF improvement was associated with a lower risk of short- and long-term all-cause death. The relief of systolic dysfunction before discharge may be representative of treatment effectiveness and successful decongestion. Moreover, it denotes less advanced structural impairment. All these aspects predispose to better outcomes. Our findings can be relevant for the early risk stratification of patients with AHF, who are exposed to the highest risk in the first weeks after discharge, and may guide the indication to very early clinical reassessment in patients discharged with persistent HFrEF versus more delayed follow-up in those with improved LVEF. Both discharge LVEF and in-hospital improvement in LVEF showed independent associations with outcomes. The consistency of these results reinforces the concept that, although admission LVEF is essential for the initial clinical, diagnostic, and therapeutic framing of the patient, it is the discharge LVEF and the in-hospital trajectory of LVEF that more strongly reflect the patient's true recovery potential during the acute phase and therefore provide more accurate prognostic information.

Modeling ΔLVEF as a continuous variable using splines showed no evidence of nonlinear dose–response patterns or prognostic thresholds. While any improvement in LVEF was associated with better outcomes, supporting HFimpEF as a favorable phenotype, the magnitude of improvement did not act as a graded quantitative predictor of risk. This suggests that ΔLVEF functions primarily as a phenotypic marker (improved versus not improved) rather than a continuous prognostic metric, indicating that early LVEF improvement is informative for risk stratification but should not be interpreted as linearly prognostic.

The association between HFimpEF and 5-year mortality rate was not significant at univariable analyses but

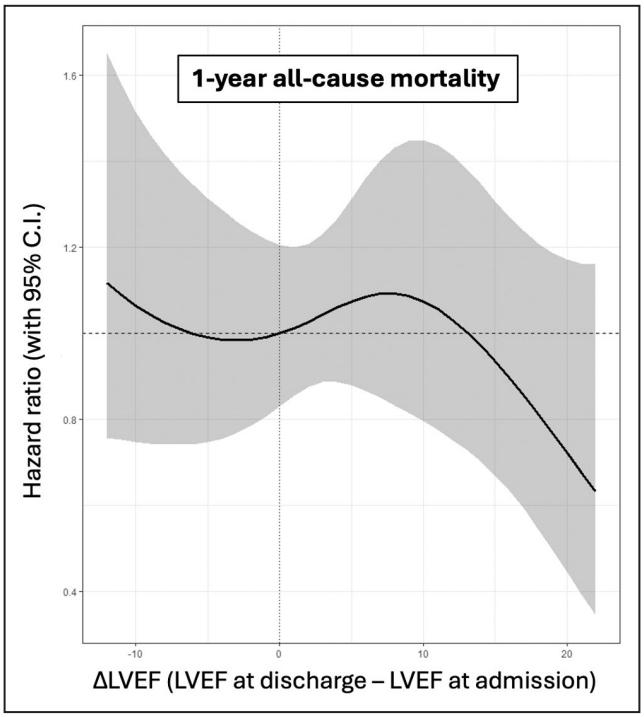

Figure 3. Cubic splines curves for the association of ΔLVEF with 1-year all-cause death.
No significant nonlinear association with 1-year mortality rate was detected (likelihood ratio *P*=0.20; Wald *P*=0.30). LVEF indicates left ventricular ejection fraction.

became significant after multivariable adjustment, suggesting that confounding factors may obscure its prognostic impact in unadjusted models, particularly over longer follow-up. We consider the adjusted analyses more informative, as they account for established determinants of long-term outcome. Conversely, HFimpEF was not associated with 1-year HFH nor with the composite end point of 1-year death/HFH. This finding is clinically plausible, as early improvement in LVEF may reflect lower risk of death without necessarily preventing recurrent decompensation episodes, which are influenced by comorbidities and postdischarge management rather than systolic function alone.

Finally, among patients with in-hospital improved EF, 14% experienced a further deterioration in LVEF at 1-year reassessment and were burdened by a high mortality rate, confirming the importance of serial echocardiographic reassessment over time. However, given the limited number of patients with an available echocardiographic reassessment at 1-year follow-up, their analyses should only be considered exploratory.

Limitations

This study has several limitations. Larger and prospective studies are needed to confirm our results, which are based on observational retrospective analyses.

Patients were enrolled in a single tertiary care Centre for the management of HF and cardiomyopathies; however, only 15.4% of patients had a cardiomyopathy, and the primary pathogenesis of HF in our cohort reflects data reported by large multicenter studies.[31,32] The mean age of our cohort was slightly lower than that reported in larger European AHF registries, such as the ESC HF III (European Society of Cardiology Heart Failure III) registry[33]; this modest difference may reflect a degree of selection bias related to recruitment in a single tertiary-care center, where younger and more complex patients are often referred.

The exclusion of patients with LVEF >40% at admission might have generated a selection bias, since patients with subsequent development of systolic dysfunction and patients with erroneously evaluated preserved LVEF were not encompassed in this population; however, this study was specifically designed to evaluate trajectories of LVEF in patients with reduced LVEF at the first in-hospital evaluation. The lack of predischarge echocardiographic reassessment in 232 patients is a further limitation; fortunately, they represented only a small proportion of the hypothetically eligible patients.

Given the retrospective nature of the study, echocardiographic assessments were not blinded and formal reproducibility testing was not performed; therefore, particularly in the acute setting, measurement variability

(both intra- and interobserver) may have led to some degree of misclassification. A significant digit preference was observed, with clustering of LVEF values at 5% to 10% multiples, consistent with prior reports.[34] While this rounding tendency may reduce granularity in the continuous distribution of LVEF, it is unlikely to have materially influenced our categorical classification of HFimpEF, which required both crossing the 40% threshold and an absolute ≥10% increase. Nonetheless, digit bias should be acknowledged as a potential limitation when interpreting small numerical LVEF changes and may partly contribute to the lack of a linear continuous effect in spline analysis.

Medical therapy at discharge was not included in the multivariable models, as we adopted a previously validated prognostic framework; therefore, residual confounding related to treatment differences cannot be entirely excluded.

Finally, the reevaluation of LVEF during follow-up was restricted to a single time point; further studies might assess more carefully longitudinal changes in systolic function over time, while our aim was specifically focused on in-hospital LVEF trajectories.

CONCLUSIONS

In this cohort of patients hospitalized for AHF, 15% of patients with HFrEF showed HFimpEF at the predischarge reevaluation. Reversible causes of HFrEF (in particular, valve disease) and less severe cardiac remodeling were associated with higher likelihood of early LVEF improvement. HFimpEF was associated with a marked decrease in 1-year mortality risk, supporting the definition of a specific subtype of HFimpEF. These findings provide a rationale for future prospective trials aimed at optimizing postdischarge management and guideline-directed medical therapy strategies in patients with early HFimpEF.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S9

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