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【 ORIGINAL ARTICLE 】

Changes in the Left Ventricular Ejection Fraction and Outcomes in Hospitalized Heart Failure Patients with Mid-range Ejection Fraction: A Prospective Observational Study

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Abstract:

Objective Current clinical guidelines have proposed heart failure (HF) with mid-range ejection fraction (HFmrEF), defined as a left ventricular ejection fraction (LVEF) of 40-49%, but the proportion and prognosis of patients transitioning toward HF with a reduced LVEF (LVEF <40%, HFrEF) or HF with a preserved LVEF (LVEF ≥50%, HFpEF) are not fully clear. The present study prospectively evaluated the changes in the LVEF one year after discharge and the outcomes of hospitalized patients with HFmrEF.

Methods We prospectively studied 259 hospitalized patients with HFmrEF who were discharged alive at our institutions between 2015 and 2019. Among them, 202 patients with HFmrEF who underwent echocardiography at the one-year follow-up were included in this study. Patient characteristics, echocardiographic data and all-cause death were collected.

Results Eighty-seven (43%) patients transitioned to HFpEF (improved group), and 35 (17%) transitioned to HFrEF (worsened group). During a median follow-up of 33 months, 27 (13%) patients died. After adjustment, patients in the worsened group had an increased risk of all-cause mortality compared with those in the improved group [hazard ratio 7.02, 95% confidence interval (CI) 1.13-43.48]. The baseline LVEF (per 1% decrease) and tricuspid annular plane systolic excursion (per 1 mm decrease) were independent predictors of the worsened LVEF category (odds ratio 2.13, 95% CI 1.25-3.63 and odds ratio 1.31, 95% CI 1.01-1.70, respectively).

Conclusion Our study showed that a worsened LVEF one year after discharge was associated with a poor prognosis in hospitalized patients with HFmrEF.

Key words: heart failure, hospitalized, left ventricular ejection fraction, mid-range, outcome

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Introduction

Heart failure (HF) has been historically categorized based on the left ventricular ejection fraction (LVEF) into HF with a reduced EF (HFrEF), defined as an LVEF ≤40%, and HF with a preserved EF (HFpEF), defined as the opposite category (normal or near normal LVEF) (1-3). However, the optimal cut-off value for defining a preserved or reduced EF has been unclear (40% or 50%), and how to classify patients who are in the 'gray zone' (40-49%) remains controversial (4, 5). The European Society of Cardiology (ESC) has proposed mid-range EF (HFmrEF) as a new category of HF that includes patients with an LVEF of 40-49% (6). Recent studies have suggested that HFmrEF patients show intermediate clinical characteristics between HFrEF and HFpEF patients (7).

This classification is not consistent with the same category over the long term for HF patients. Previous reports have shown that patients with HFmrEF partially transition to

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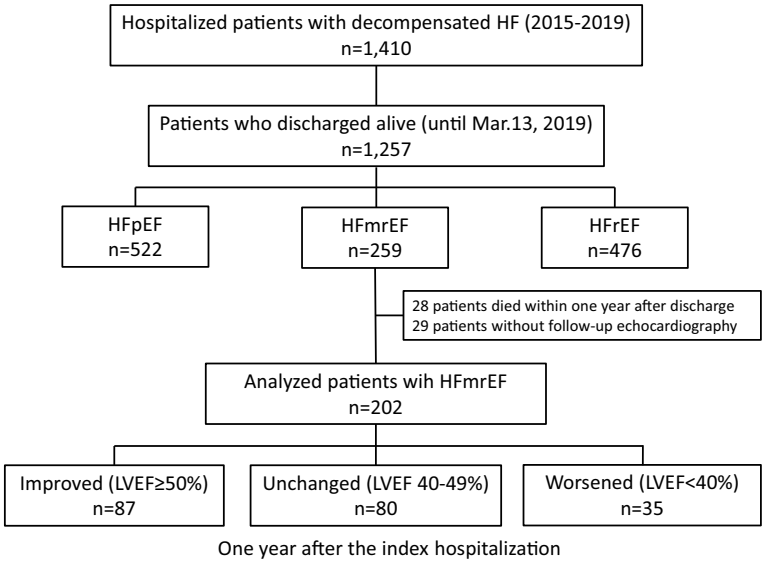

Figure 1. Flow diagram of the study patients. HF: heart failure, HFmrEF: heart failure with a mid-range ejection fraction, HFpEF: heart failure with a preserved ejection fraction, HFrEF: heart failure with a reduced ejection fraction, LVEF: left ventricular ejection fraction

other categories over time, such as HFpEF (improved) and HFrEF (worsened) (8, 9). Management of HFmrEF is required to identify high-risk patients for additional risk stratification and treatment (7). However, the proportion and prognosis of patients who transition toward a reduced LVEF category (LVEF <40%, HFrEF) or a preserved LVEF category (LVEF ≥50%, HFpEF) are not fully clear. Patients who transition from HFmrEF to HFrEF (worsened) have been reported to be associated with a poor prognosis (8-10), whereas there is no association between LV transition and the prognosis (11).

In a multicenter retrospective observation study, we previously reported that 38% of hospitalized patients with HFmrEF had an increased LVEF (HFpEF category), and 16% of them had a decreased LVEF (HFrEF category) after hospital discharge, although this information was only available in the follow-up echocardiographic data (12). However, whether or not LVEF transition in these patients was associated with their prognosis was not evaluated.

The present study prospectively evaluated the changes in the LVEF one year after discharge and the outcomes in patients with HFmrEF who were discharged alive after index HF hospitalization.

Materials and Methods

Patients

We conducted a single-center, prospective observational study of hospitalized patients with decompensated HF who were admitted to the cardiology department of Tokyo Women's Medical University Hospital between September 2015 and December 2019. Decompensated HF was defined as new or progressive symptoms and signs of decompensated HF, such as significant weight gain, dyspnea, fatigue, pulmonary rales, hepatic congestion, lower extremity edema, unplanned addition of oral or intravenous loop diuretic drugs, dose increase of oral loop diuretics, addition of a thiazide diuretic drug to loop diuretics or the need for treatment with intravenous vasodilators, intravenous inotropes or intra-aortic balloon pumping. All patients underwent echocardiography when HF stabilized before hospital discharge.

After hospital discharge, all patients were followed in the HF clinic in our institution every year during the follow-up period. Follow-up electrocardiography (ECG), chest X-ray, and several laboratory tests, including plasma BNP and echocardiograms, were also performed at the one-year follow-up. Patients who failed to attend our HF clinic appointment were contacted by telephone or letter, and information about the patients' viability status, cause of death and cause of hospitalization was also obtained from family members, the patient's general practitioner and the admitting hospital. If available, ECG, chest X-ray, laboratory parameters and echocardiogram data were sent to our institution. This study has scheduled final follow-up visits through February 2021. The protocol was approved by the institutional review board of Tokyo Women's Medical University. All patients provided their written informed consent.

For the purposes of the present analysis, we studied 259 hospitalized patients with decompensated HF who met the criteria for HFmrEF during their hospitalization and were discharged alive between September 2015 and May 2019 as participants of this observational study. Among them, 202 (78%) patients who underwent a 1-year follow-up echocardiography examination were included in this study (Fig. 1).

Cardiovascular disease

Coronary artery disease was defined as positive stress test

findings, coronary angiography demonstrating at least 75% stenosis or coronary spastic angina documented by the acetylcholine provocation test, a history of prior myocardial infarction or ECG findings of Q-wave myocardial infarction or a history of revascularization procedures. Valvular and congenital heart diseases were diagnosed by angiographic, hemodynamic or echocardiographic tests or a history of valvular or congenital cardiac surgery. Aortic and mitral regurgitation were defined as valvular disease with at least moderate regurgitation by color-flow Doppler echocardiography. Nonischemic cardiomyopathy was defined as ventricular myocardial abnormalities in the absence of coronary artery disease or valvular, pericardial or congenital heart disease. Hypertensive heart disease was defined as a clinical history of hypertension and LV hypertrophy determined from echocardiographic or ECG findings but no diagnosis of hypertrophic cardiomyopathy. Hypertension was defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg or a history of treatment for hypertension.

Echocardiography

Experienced sonographers performed the echocardiographic studies with a SONOS 5500/iE33/EPIQ7 (Philips Healthcare, Andover, USA), an ARTIDA (Toshiba Medical Systems, Tochigi, Japan) or a GE Vivid E9 (GE Vingmed Ultrasound AS, Horten, Norway) ultrasound system during continuous electrocardiographic recording. Echocardiographic data were measured by independent investigators blinded to the patients' data.

The LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) were measured in apical two- and four-chamber views. From these results, the LVEF was calculated using the biplane method of disk summation. The left atrial diameter (LAD) in end-systole was determined using the standards of the American Society of Echocardiography (13). The LA volume (LAV) was measured in standard four- and two-chamber views. The end-systolic LAV was measured using the disk summation algorithm. The LV mass (LVM) was estimated from the LV cavity dimension and wall thickness at end-diastole on the M-mode echocardiogram: LV diastolic dimension (LVDd, cm), interventricular septum thickness (IVS, cm) and LV posterior wall thickness (LVPW, cm). The LVM was calculated using the cube formula (13): LVM (g) = $0.8\times1.04\times[(LVDd+IVS+LVPW)^3-(LVDd)^3]+0.6$.

The left ventricular mass index (LVMI, g/m^2) was defined as the LVM divided by the body surface area (m^2). The systolic velocities (s'), early diastolic velocities (e') and late diastolic velocities (a') (cm/s) were measured using tissue Doppler imaging (TDI) on the septal mitral annulus, lateral mitral annulus and right lateral tricuspid annulus as a peak modal velocity in early diastole at the leading edge of the spectral waveform. The E- and A-wave maximum velocities were measured using pulsed-wave Doppler of transmitral flow. The E/A ratio was calculated as the ratio of the E- and A-wave maximum velocities. The E/e' ratio was calculated using the E-wave maximum velocity and e' of the septal mitral annulus (14). The deceleration time of the E velocity (DT) was measured as the time interval from the E-wave peak to the decline in the velocity to baseline values. Tricuspid annular plane systolic excursion (TAPSE) was measured in the apical four-chamber view by placing the M-mode cursor optimally aligned along the direction of the tricuspid annulus. The peak excursion of the lateral annulus represented TAPSE (mm). The inferior vena cava (IVC) was measured during inspiration and expiration and imaged at the level just proximal to the entrance of hepatic veins by two-dimensional-guided M-mode echocardiography. Using the simplified Bernoulli formula [peak gradient=$4\times V^2$, where V is the peak tricuspid regurgitation (TR) jet velocity into the right atrium], the right ventricular systolic pressure (RVSP) was obtained by adding the peak TR gradient to the estimated right atrial (RA) pressure. The RA pressure was estimated at rest by the response of the IVC to deep inspiration (15).

Data analyses

The data are presented as numbers and as medians and interquartile ranges for continuous and categorical data, respectively. We specified 3 groups on the basis of the LVEF on follow-up echocardiography one year after the index hospitalization: the 1) improved (HFpEF, LVEF ≥50%), 2) unchanged (HFmrEF, LVEF 40-49%) and 3) worsened (HFrEF, LVEF<40%) groups. A one-way analysis of variance (ANOVA) was used to compare the groups with respect to normally distributed continuous variables, and the Kruskal-Wallis test was used for other variables. Categorical variables were subjected to a chi-squared analysis. The cumulative event-free rates were calculated using the Kaplan-Meier method. Differences in the event-free rates were compared using the log-rank test. To evaluate the influence of the LVEF groups on follow-up echocardiography with respect to subsequent death, adjusted Cox proportional hazards models were used.

For analyses, we considered adjusted models based on associations with clinical and therapeutic variables that are generally associated with outcomes of HF: age, body mass index, systolic blood pressure, hemoglobin level and serum sodium level as continuous variables; New York Heart Association functional class as a quadrichotomous variable; and sex, index hospitalization for *de novo* HF, presence of coronary artery disease, relevant comorbid conditions [atrial fibrillation, hypertension, diabetes mellitus, dyslipidemia, hyperuricemia, chronic obstructive pulmonary disease and chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 m^2)], the use of β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, mineralocorticoid receptor antagonists and cardiac dyssynchronization therapy as dichotomous variables. Univariate and multivariate analyses using the logistic regression model were performed to determine independent predictors of the worsened LVEF category. The forward stepwise method for

Table 1. Patients' Characteristics at Discharge.

Variable	Overall (N=202)	Improved (N=87)	Unchanged (N=80)	Worsened (N=35)	p value
Age (years)	71 [59-78]	68 [59-77]	71 [57-78]	74 [63-77]	0.444
Male gender	137 (68)	53 (61)	60 (75)	24 (69)	0.150
Body mass index (kg/m^2)	22 [20-25]	23 [20-25]	23 [20-26]	21 [19-23]	0.054
Blood Pressure (mmHg)					
Systolic	116 [104-128]	120 [106-134]	114 [102-126]	111 [104-120]	0.159
Diastolic	64 [60-70]	64 [60-70]	65 [58-70]	62 [60-65]	0.765
Heart rate (bpm)	70 [61-78]	71 [61-80]	69 [61-76]	66 [54-76]	0.090
de novo HF	132 (65)	67 (77)	45 (56)	20 (57)	0.010
NYHA class I/II/III/IV	48/138/15/1 (24/68/7/1)	24/53/10/0 (28/61/11/0)	16/60/3/1 (20/75/4/1)	8/25/2/0 (23/71/6/0)	0.290
Underlying heart disease					0.165
Coronary artery disease	53 (26)	20 (23)	22 (28)	11 (31)	
Nonischemic Cardiomyopathy	58 (29)	18 (21)	28 (35)	12 (34)	
Valvular disease	49 (24)	23 (26)	18 (23)	8 (23)	
Hypertensive heart disease	14 (7)	11 (13)	3 (4)	0	
Congenital heart disease	9 (4)	4 (5)	3 (4)	2 (6)	
Others	19 (9)	11 (13)	6 (8)	2 (6)	
Atrial fibrillation	106 (53)	44 (51)	43 (54)	19 (54)	0.927
Sustained VT/VF	13 (6)	3 (3)	5 (6)	5 (14)	0.087
Hypertension	139 (69)	65 (75)	54 (68)	20 (57)	0.158
Diabetes mellitus	70 (35)	31 (36)	27 (34)	12 (34)	0.967
Dyslipidemia	97 (48)	41 (47)	40 (50)	16 (46)	0.892
Hyperuricemia	96 (48)	38 (44)	38 (48)	20 (57)	0.404
COPD	10 (5)	5 (6)	4 (5)	1 (3)	0.801
CKD (eGFR<60 mL/min/1.73 m^2)	139 (69)	58 (67)	54 (68)	27 (76)	0.669
Hemodialysis	22 (11)	10 (11)	8 (10)	4 (11)	0.947
Pacemaker	22 (11)	9 (10)	6 (8)	7 (20)	0.138
CRT-P/CRT-D	12 (6)	3 (3)	5 (6)	4 (11)	0.238
ICD	17 (8)	3 (3)	7 (9)	7 (20)	0.012
Laboratory data					
White blood cell count (×10^3/μL)	5.4 [4.4-6.7]	5.3 [4.4-7.2]	5.4 [4.4-6.6]	5.5 [4.5-6.7]	0.973
Hemoglobin (g/dL)	13 [11-14]	13 [11-14]	13 [11-14]	13 [11-14]	0.623
Albumin (g/dL)	3.8 [3.4-4.0]	3.7 [3.4-4.0]	3.8 [3.4-4.0]	3.8 [3.4-4.1]	0.990
Total bilirubin (mg/dL)	0.7 [0.5-1.0]	0.7 [0.5-0.9]	0.7 [0.4-1.0]	0.9 [0.6-1.2]	0.164
BUN (mg/dL)	21 [16-32]	21 [15-31]	22 [15-34]	24 [19-31]	0.831
Creatinine (mg/dL)	1.1 [0.9-1.5]	1.1 [0.9-1.4]	1.1 [0.9-1.5]	1.1 [0.9-1.6]	0.903
eGFR (mL/min/1.73 m^2)	48 [32-64]	46 [31-63]	49 [31-65]	49 [34-60]	0.755
Uric acid (mg/dL)	6.1 [4.9-7.2]	6.3 [5.0-7.4]	6.0 [4.8-7.2]	5.6 [4.2-7.5]	0.193
Sodium (mEq/L)	140 [138-141]	140 [139-142]	140 [138-142]	139 [137-141]	0.415
Potassium (mEq/L)	4.3 [4.0-4.7]	4.4 [4.0-4.7]	4.3 [4.1-4.6]	4.4 [4.1-4.8]	0.627
CRP (mg/dL)	0.2 [0.1-0.6]	0.3 [0.1-0.8]	0.2 [0.1-0.6]	0.2 [0.1-0.5]	0.905
Plasma BNP (pg/mL)	160 [52-304]	157 [43-308]	173 [75-293]	181 [49-317]	0.961
Electrocardiographic findings					
Sinus rhythm	130 (64)	62 (71)	46 (58)	22 (63)	0.268
Atrial fibrillation	61 (30)	23 (26)	27 (34)	11 (31)	
Others	11 (5)	2 (2)	7 (9)	2 (6)	
QRS complex duration (msec)					
<120 ms	141 (70)	67 (77)	54 (68)	20 (57)	0.248
120-149 ms	33 (16)	10 (11)	14 (18)	9 (26)	
≥150 ms	28 (14)	10 (11)	12 (15)	6 (17)	
RBBB	27 (13)	8 (9)	16 (20)	3 (9)	0.080
LBBB	8 (4)	4 (5)	1 (1)	3 (9)	0.054
Ventricular pacing	25 (12)	7 (8)	10 (13)	8 (23)	0.080

Table 1. Patients' Characteristics at Discharge. (Continued)

Variable	Overall (N=202)	Improved (N=87)	Unchanged (N=80)	Worsened (N=35)	p value
Medications					
ACE inhibitors	68 (34)	27 (31)	25 (31)	16 (46)	0.252
ARBs	87 (43)	40 (46)	36 (45)	11 (31)	0.308
Beta-blockers	146 (72)	64 (73)	59 (74)	23 (66)	0.634
Loop diuretics	113 (56)	49 (56)	40 (50)	24 (69)	0.181
Thiazide	7 (3)	3 (3)	4 (5)	0	0.403
Tolvaptan	14 (7)	6 (7)	7 (9)	1 (3)	0.519
MRAs	72 (36)	29 (33)	26 (33)	17 (49)	0.213
Digoxin	13 (6)	5 (6)	6 (8)	2 (6)	0.883
Nitrates	27 (13)	10 (11)	12 (15)	5 (14)	0.789
Calcium antagonists	59 (29)	32 (37)	20 (25)	7 (20)	0.104
Statins	74 (37)	25 (29)	35 (44)	14 (40)	0.119
Antiplatelets	28 (14)	11 (13)	11 (14)	6 (17)	0.809
Oral anticoagulants	109 (54)	48 (55)	40 (50)	21 (60)	0.586
Amiodarone	28 (14)	6 (7)	15 (19)	7 (20)	0.044
Other antiarrhythmics	9 (4)	5 (6)	3 (4)	1 (3)	0.725
Erythropoietin	10 (5)	5 (6)	3 (4)	2 (6)	0.816

Values are n (%) or median [interquartile range].

ACE: angiotensin-converting enzyme, ARB: angiotensin II receptor blocker, BNP: brain natriuretic peptide, BUN: blood urea nitrogen, CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease, CRT-D: cardiac resynchronization therapy with a defibrillator, CRT-P: cardiac resynchronization therapy with a pacemaker, CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, ICD: implantable cardioverter-defibrillator, LBBB: left bundle branch block, LVEF: left ventricular ejection fraction, MRA: mineralocorticoid receptor antagonist, NYHA: New York Heart Association, RBBB: right bundle branch block, VT: ventricular tachycardia, VF: ventricular fibrillation

confounding variables was used for the multivariate analyses with the entry or removal of demographic and echocardiographic variables associated with the worsened LVEF category based on p values set at 0.05.

A p value of <0.05 was considered significant. Data analyses were performed with SPSS statistical software (version 11.01, SPSS, Chicago, USA).

Results

Baseline characteristics

The LVEF of 202 patients with HFmrEF who were discharged after the index hospitalization had dramatically changed according to 1-year follow-up echocardiography: 87 (43%) had an LVEF ≥50% (HFpEF category, improved group), 80 (40%) maintained an LVEF of 40-49% (HFmrEF category, unchanged group), and 35 (17%) had an LVEF < 40% (HFrEF category, worsened group).

The patients' baseline characteristics at discharge from the index hospitalization according to these three groups are shown in Table 1. The proportion of *de novo* HF was highest in the patients in the improved group. The proportion of patients who received cardiac implantable electronic devices was highest in the worsened group. There was no significant difference in other demographic and electrocardiographic characteristics. Regarding the medications at discharge, there were no significant differences among groups except for the use of amiodarone being more frequent in the worsened group than in others.

The echocardiographic characteristics of the patients during the index hospitalization are shown in Table 2. The LV size was lowest in the improved group. The LVEF was lowest in the worsened group. The lateral s' determined by the TDI was lowest in the worsened group. There were no significant differences in the other echocardiographic parameters among the groups.

Outcomes

During a median follow-up of 33 (21-43) months, 27 (13%) patients died. The Kaplan-Meier curves for all-cause mortality in the LVEF groups are shown in Fig. 2. There were no marked differences in mortality between patients who maintained HFmrEF (unchanged group) and those who transitioned to HFpEF (improved group), while the mortality rate was significantly higher in patients whose condition worsened to HFrEF (worsened group) than in those who showed improvement. For treatments, the frequencies of standard medication use for HF did not change from discharge to one year after discharge in any group (Table 3). In multivariate Cox models, the hazard ratio for mortality was significantly higher in the worsened group (adjusted HR 7.02, 95% CI 1.13-43.48) than in the improved group (Table 4).

A multivariate analysis revealed that decreases in the baseline LVEF and TAPSE were independent predictors of

Table 2. Echocardiographic Characteristics during the Index Hospitalization.

Variable	Improved (N=87)	Unchanged (N=80)	Worsened (N=35)	p value
LVDd (cm)	5.1 [4.6-5.7]	5.4 [5.1-5.9]	5.4 [4.9-6.0]	0.019
LVDs (cm)	3.9 [3.4-4.3]	4.3 [3.9-4.7]	4.3 [3.8-4.8]	<0.001
IVST (cm)	0.9 [0.8-1.0]	0.9 [0.8-1.0]	0.8 [0.7-0.9]	0.185
LVPWT (cm)	0.9 [0.8-1.0]	0.9 [0.8-1.0]	0.8 [0.7-0.9]	0.135
LVEDV (mL)	146 [109-169]	149 [126-176]	150 [123-170]	0.364
LVESV (mL)	78 [61-92]	85 [73-100]	86 [66-97]	0.272
LVEF (%)	46 [44-48]	45 [42-47]	43 [41-45]	<0.001
LVMI (g/m^2)	97 [78-124]	104 [88-136]	100 [80-121]	0.050
LAD (cm)	4.4 [3.8-5.0]	4.4 [4.0-4.9]	4.3 [3.8-5.1]	0.851
LAVI (mL/m^2)	48 [36-67]	50 [35-68]	51 [42-75]	0.770
E/A*	1.2 [0.7-1.5]	0.9 [0.7-1.5]	1.5 [1.0-2.2]	0.066
DT (ms)	179 [150-222]	187 [153-227]	171 [144-196]	0.473
Septal s' (cm/s)	6.4 [5.6-6.4]	5.1 [4.3-6.7]	5.0 [4.0-5.6]	0.053
Septal e' (cm/s)	5.5 [4.5-6.8]	5.3 [4.1-7.1]	4.7 [4.0-6.1]	0.967
Septal a' (cm/s)*	7.3 [5.2-8.8]	7.0 [5.9-8.4]	5.2 [4.1-7.4]	0.147
Lateral s' (cm/s)	7.0 [5.6-7.9]	7.4 [6.0-9.0]	6.1 [5.0-7.7]	0.011
Lateral e' (cm/s)	7.3 [6.0-10.7]	9.1 [6.7-13.0]	7.1 [5.3-8.9]	0.473
Lateral a' (cm/s)*	8.0 [6.0-10.1]	7.8 [6.1-10.0]	7.0 [5.2-9.0]	0.881
RV s' (cm/s)	10.1 [8.6-12.9]	10.5 [9.2-12.8]	9.7 [7.1-13.2]	0.385
RV e' (cm/s)	9.7 [6.2-11.4]	9.6 [6.7-13.0]	9.3 [8.0-11.4]	0.896
RV a' (cm/s)*	11.2 [8.7-16.8]	11.7 [7.1-14.3]	9.7 [6.5-14.7]	0.256
TAPSE (mm)	17 [14-20]	18 [15-21]	16 [14-18]	0.269
E/e'	14 [10-18]	12 [9-17]	13 [9-17]	0.476
TRV max (m/s)	2.7 [2.2-3.0]	2.5 [2.1-2.8]	2.5 [2.2-3.0]	0.462
RVSP (mmHg)	38 [29-46]	35 [29-41]	35 [29-46]	0.490
IVC (cm)	1.2 [0.9-1.7]	1.3 [1.0-1.8]	1.4 [1.2-1.8]	0.300

Values are median [interquartile range].

*patients in suns rhythm: Improved (n=42), Unchanged (n=42) and Worsened (n=17).

a': peak late diastolic annular velocity, DT: deceleration time of early diastolic inflow, e': peak early diastolic annular velocity, E/A: ratio of peak transmitral early diastolic filling velocity to peak transmitral atrial filling velocity, E/e': ratio of peak transmitral early diastolic filling velocity to peak early diastolic mitral annular velocity, IVC: inferior vena cava, IVST: interventricular septum thickness, LAD: left atrial dimension, LAVI: left atrial volume index, LVDd: left ventricular end-diastolic dimension, LVDs: left ventricular end-systolic dimension, LVEDV: left ventricular end-diastolic volume: LVEF: left ventricular ejection fraction, LVESV: left ventricular end-systolic volume, LVMI: left ventricular mass index, LVPWT: left ventricular posterior wall thickness, RV: right ventricular, RVSP: right ventricular systolic pressure, s': lowest, TAPSE: tricuspid annular plane systolic excursion, TRV: tricuspid regurgitant velocity

the worsened LVEF category, and decreases in the heart rate and lateral s' also tended to be associated with a worsened LVEF category (Table 5, Supplementary material 1).

Patients' mortality at one year after discharge

In our study, 28 (11%) of 259 patients who were discharged alive from the index hospitalization died within 1 year of discharge and these patients were excluded from the analysis. The median age at discharge was older and the proportions of coronary artery disease and hemodialysis and frequency of antiplatelet use were higher than those of the analyzed patients. With regard to laboratory parameters, the hemoglobin levels, serum albumin levels and estimated glomerular filtration rate were lower, and the serum C-reactive protein levels and plasma brain natriuretic peptide level higher in patients who died within one year after discharge than in the analyzed patients (Supplementary material 2). There were no significant differences in other clinical characteristics at discharge or causes of death between patients who underwent a one-year follow-up echocardiography examination and those who died within one year of discharge (Supplementary material 2, 3).

Discussion

Our study revealed the following results. 1) Among hospitalized patients with HFmrEF, 43% transitioned to HFpEF (improved group), and 17% transitioned to HFrEF (worsened group) one year after discharge. 2) Patients in the worsened group had higher all-cause mortality rates than those in the other groups. 3) After multivariable adjustment, patients in the worsened group had an increased risk of all-

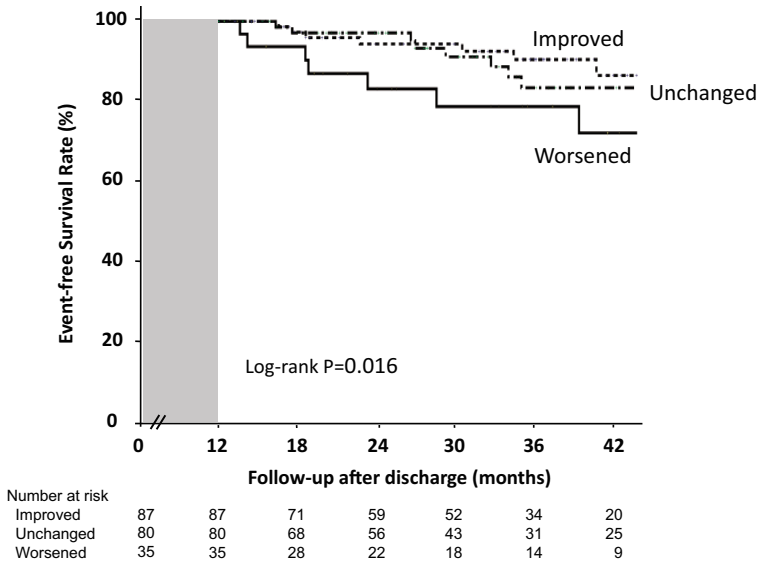

Figure 2. **Kaplan-Meier curves for all-cause death among the improved, unchanged and worsened groups according to the left ventricular ejection fraction one year after the index hospitalization.**

Table 3. **Frequencies of ACE Inhibitors/ARBs Use, Beta-blocker Use and MRA Use at Discharge and One Year after Discharge.**

Group	ACE inhibitors/ARBs			Beta-blockers			MRAs		
	At discharge	One year after discharge	p value	At discharge	One year after discharge	p value	At discharge	One year after discharge	p value
Improved	67 (77)	59 (68)	0.175	64 (73)	65 (75)	0.585	29 (33)	34 (39)	0.430
Unchanged	61 (76)	62 (78)	0.851	59 (74)	62 (78)	0.581	26 (33)	27 (34)	0.867
Worsened	27 (77)	26 (74)	0.781	23 (66)	25 (71)	0.607	17 (49)	16 (46)	0.811

Values are n (%).

ACE: angiotensin-converting enzyme, ARB: angiotensin II receptor blocker, MRA: mineralocorticoid receptor antagonist

Table 4. **All-cause Mortality among the Improved, Unchanged, and Worsened Groups according to LVEF One Year after the Index Hospitalization.**

Groups	Number of events/total	Incident rate (/100 patient-years)	Hazard ratio (95% CI)	
			Age and Sex Adjusted	Fully Adjusted*
Improved	7/87	3.0	(reference)	(reference)
Unchanged	10/80	4.6	1.73 (0.64-4.76)	2.45 (0.64-9.47)
Worsened	10/35	11.0	3.08 (1.15-8.24)	7.02 (1.13-43.48)

* Adjusted for age, sex, body mass index, *de novo* heart failure, presence of coronary artery disease, relevant comorbid conditions (atrial fibrillation, hypertension, diabetes mellitus, dyslipidemia, hyperuricemia, chronic obstructive pulmonary disease and chronic kidney disease [estimated glomerular filtration rate <60 mL/min/1.73 m^2], New York Heart Association functional class, cardiac resynchronizing therapy, systolic blood pressure, hemoglobin level, serum sodium level, and therapy with β-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and mineralocorticoid receptor antagonists.

CI: confidence interval, LVEF: left ventricular ejection fraction

cause mortality and HF hospitalization compared with those in the improved group. 4) A reduced baseline LVEF and TAPSE were independent predictors of the worsened LVEF category.

Changes in the LVEF

Among hospitalized patients with HFmrEF, the ratio of those with HFpEF (improved), HFmrEF (unchanged) and HFrEF (worsened) at 1 year after discharge was approximately 2:2:1. Previous cohorts from Europe (the Swedish

Table 5. Independent Predictors of Worsened LVEF Category among Patients with HFmrEF at the Index Hospitalization.

	OR	95% CI	p value
BMI (per 1 kg/m^2 decrease)	1.07	0.89-1.30	0.467
Heart rate (per 1 beat/min decrease)	1.08	0.99-1.18	0.056
LVEF (per 1% decrease)	2.13	1.25-3.63	0.006
Lateral s' (per 1 cm/s decrease)	2.07	0.95-4.50	0.066
Septal s' (per 1 cm/s decrease)	0.68	0.36-1.28	0.231
A wave (per 1 cm/s decrease)	1.03	0.97-1.07	0.540
E/A (per 1 unit decrease)	0.82	0.14-4.92	0.832
TAPSE (per 1 mm decrease)	1.31	1.01-1.70	0.039

HFmrEF: heart failure with mid-range ejection fraction, BMI: body mass index, CI: confidence interval, E/A: early to late diastolic transmitral flow velocity, LVEF: left ventricular ejection fraction, OR: odds ratio, s': systolic excursion velocity, TAPSE: tricuspid annular plane systolic excursion

Heart Failure Registry and a multicenter prospective observational study in Catalonia) reported that the transitioned percentages of patients with HFmrEF were approximately 25-33% (improved), 38-43% (unchanged) and 24-37% (worsened), showing that a higher number of patients transitioned to HFrEF than among our population (9, 10). However, a Japanese observational study (the Ibaraki Cardiac Assessment Study-Heart Failure registry) reported that the proportions of transitioning hospitalized patients with HFmrEF were 59% (improved), 29% (unchanged) and 11% (worsened) (11). This difference in LV transition might be due to differences in clinical settings, such as the inclusion of outpatients or hospitalized patients, those with existing or *de novo* HF and cases with ischemic or nonischemic causes. Among the hospitalized patients with decompensated HF, patients with *de novo* HF or those who had received inadequate HF treatment were included. Our study included 65% *de novo* HF patients, and the proportion of *de novo* HF patients was higher in the improved group than in the unchanged and worsened groups. Furthermore, the proportion of Japanese ischemic HF patients is approximately 30% (12, 16, 17), compared with a proportion of approximately 50% among HF patients in the United States and Europe (18). The Swedish Heart Failure Registry suggested that HF patients with coronary artery disease had a higher odds ratio (1.36) for a decrease in the LVEF than those without coronary artery disease (9).

Outcomes

The Ibaraki registry failed to show the relationship between changes in the LVEF and prognosis in hospitalized patients with HFmrEF (11). European cohorts indicated that the change in the LVEF was associated with the prognosis in patients with HFmrEF (9, 10). In our study, patients in the worsened group were significantly associated with worse outcomes than those in the improved or unchanged groups. The worsened group had high frequencies of ICD use and amiodarone use. This group included patients at high risk for sudden cardiac death and patients who transitioned from HFrEF to HFmrEF. Patients with HFmrEF included combined patients who transitioned into the midrange through either improvement or deterioration in their LVEF. In general, patients with HFmrEF whose LVEF had improved from the HFrEF category had better outcomes than those whose LVEF deteriorated into midrange levels (19, 20). However, some patients in this group might switch from the HFmrEF category back to the HFrEF category after HF hospitalization.

In the present study, only patients who were alive one year after discharge from the index hospitalization and underwent echocardiography at the one-year follow-up were analyzed in this study. For all 259 patients with HFmrEF who were discharged alive [median age 72 (60-79) years old, 68% men], their mortality rate was 21% during the median follow-up period of 843 (487-1,191) days (annual rate 9%), which was comparable to the value in previous studies among Japanese hospitalized patients with HFmrEF [HIJ-HF II: median age 76 years old, 16% mortality/median follow-up 608 days (12), Ibaraki registry: mean age 72 years old, 17% mortality/median follow-up 534 days (11), and WET-NaDEF: mean age 74 years old, 19% mortality/median follow-up 664 days (17)]. Half of our patients died within 1 year of hospital discharge because they were older (median 80 years old) and had more severe HF than the analyzed patients at the time of discharge. The KCHF registry included older patients with HFmrEF (median age 80 years old) (21) and showed that the mortality rate of the available patients (median age 78 years old) was 23% with a median of 470 days of follow-up (22). The prognosis of elderly patients with HFmrEF who are discharged alive is poor.

Predictors of a worsened LVEF

In our study, predictors of a worsened LVEF were a lower baseline LVEF within the range of 40-49% and a low TAPSE. Interestingly, TAPSE, which is a parameter for the RV systolic function (23), was a predictor of worsening LV contractility in patients with HFmrEF. RV systolic dysfunction may develop in association with LV systolic dysfunction by several mechanisms, such as pressure overload, septal dysfunction, restricted RV diastolic function and myocardial ischemia, and the RV systolic function is known to be an independent predictor of the survival in patients with HFrEF (24). López-Candales et al. reported that the TAPSE was lower in patients with a reduced LV systolic function than in those with a normal LV systolic function and indicated that TAPSE is determined not only by the RV systolic function but also by the LV systolic function (25). Gupta et al. reported that TAPSE was associated with LV dyssynchrony as well as LVEF (26). TAPSE plays a prognostic role in mortality for patients with HFrEF (27, 28).

Although TAPSE is limited as the index of the RV systolic function in patients with a severely reduced LVEF (29, 30), TAPSE may be a useful predictor of a worsening LV systolic function for patients with HFmrEF. Recently, Correale et al. reported that 12-month angiotensin receptor neprilysin inhibitor therapy improved TAPSE inde-

pendently of the LV systolic function improvements in HF patients (31). TAPSE may also be an indicator of therapeutic efficacy in HF patients with LV systolic dysfunction.

In our study, a decrease in the lateral s', which is a component of the LV systolic function (32), also tended to be associated with a worsened LVEF category, and this index might have a potential role in impaired LV contractility. Alam et al. reported that the s' value might have a role in predicting whether or not the global LV function will improve in patients with acute myocardial infarction (33).

The assessment of the RV function as well as the LV systolic function may be important for identifying high-risk patients in the HFmrEF group and for considering potential treatment strategies, including strategies for improving the RV function. Further studies regarding the role of RV function assessments in patients with HFmrEF are required.

Study limitations

Several limitations associated with the present study warrant mention. First, this study was an observational study performed at a single center. There was also treatment bias. The clinical characteristics of our patients might not reflect those of general HF patients because our institution is a university hospital in the metropolitan Tokyo area. In addition, only patients who were alive one year after discharge from the index hospitalization and underwent one-year follow-up echocardiography were analyzed in this study. Therefore, the findings could not be generalized to all Japanese patients with HF. Second, the patients with decompensated HF admitted to our hospital were not consecutively studied because patients for whom we obtained written informed consent were enrolled in our main study. Third, the number of patients included in our study was small. Therefore, a subgroup analysis was not feasible.

Conclusion

Our prospective observational study showed that a worsened LVEF category one year after discharge was associated with a poor prognosis after discharge in hospitalized patients with HFmrEF. A reduced baseline LVEF and TAPSE were independent predictors of a worsened LVEF.

The authors state that they have no Conflict of Interest (COI).

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