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Fate of Acute Heart Failure Patients With Mid-Range Ejection Fraction

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Background: The outcomes of heart failure (HF) with mid-range ejection fraction (HFmrEF) have been rarely studied, and follow-up data on left ventricular ejection fraction (LVEF) are scarse.

Methods and Results: Patients were selected from a prospective multicenter registry of patients hospitalized for acute HF and then classified in the improved group if they exhibited %LVEF change ≥5 with follow-up LVEF ≥50%. Follow-up LVEF reported at least 90 days after discharge was used for classification. Of the 3,085 patients with acute HF, 454 were classified in the HFmrEF, and 276 had follow-up data. Of these 276 patients, 34.1% were classified in the improved group. Multivariate analysis revealed that hypertension, higher heart rate, lower serum sodium level, and maintenance therapy with β-blocker were associated with improved LVEF. The survival rate was significantly higher in the improved group than in the other groups. Young age and maintenance therapy with renin-angiotensin system blockers or aldosterone antagonists were significantly associated with better survival in HFmrEF.

Conclusions: One-third of HFmrEF patients showed improved LVEF; moreover, the survival rate in the improved group was higher than the other groups. Renin-angiotensin system blockers and aldosterone antagonists could improve the survival of HFmrEF patients.

Key Words: Acute heart failure; Heart failure with mid-range ejection fraction; Left ventricular ejection fraction

Heart failure with mid-range ejection fraction (HFmrEF) has been considered a gray zone of HF with reduced EF (HFrEF) or with preserved EF (HFpEF). Although patients with HFmrEF are often included in studies of HFpEF,[1–4] they are frequently treated with medical therapies similar to those used to treat patients with HFrEF.[5] Recent HF guidelines declared HFmrEF as a separate category that needs to be differentiated from HFrEF and HFpEF.[6] However, the outcomes of HFmrEF have been rarely studied, and the optimal medical treatments for these patients are not clearly defined. In particular, there are few follow-up data on the left ventricular EF (LVEF) in these patients. Therefore, we investigated mortality and improvement of LVEF in patients with acute HF showing mid-range EF.

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Methods

Study Design and Patients

The study population was selected from the Korean Acute Heart Failure (KorAHF) registry. Between March 2011

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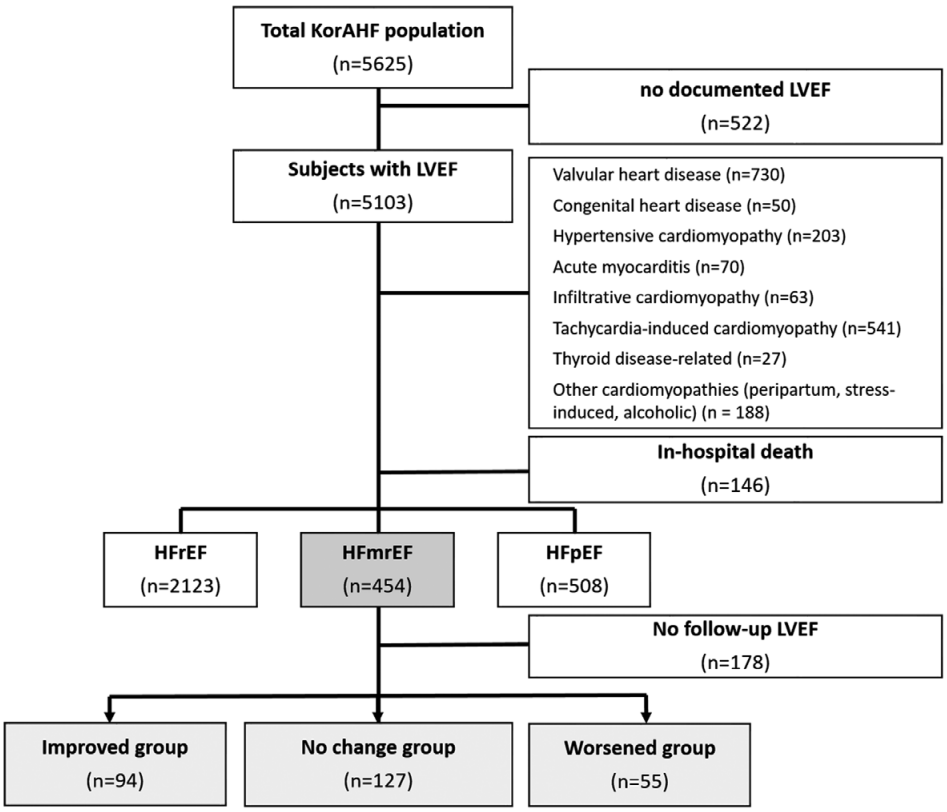

Figure 1. Flow diagram of the study population. KorAHF, Korean Acute Heart Failure [registry]; HF, heart failure; LVEF, left ventricular ejection fraction.

and February 2014, 5,625 consecutive patients admitted to 10 tertiary university hospitals for acute HF were enrolled in this prospective multicenter cohort registry. The rationale and design of the KorAHF registry have been published previously.[7] From the patients in the registry, patients with documented LVEF (n=5,103) were included in the present study. We excluded patients with HF that could only be corrected by surgical or interventional methods [valvular heart disease (n=730) or congenital heart disease (n=50)] and patients with HF routinely considered reversible [hypertensive cardiomyopathy (n=203), acute myocarditis (n=70), infiltrative cardiomyopathy (n=63), tachycardia-induced cardiomyopathy (n=541), thyroid disease-related cardiomyopathy (n=27), peripartum cardiomyopathy (n=22), stress-induced cardiomyopathy (n=92), or alcoholic cardiomyopathy (n=74)]. The final study population included 3,085 patients after excluding in-hospital cases of death during the first admission period (n=146). Patients were categorized into 3 groups according to baseline LVEF: HFrEF (LVEF <40%), HFmrEF (40%≤LVEF<50%), and HFpEF (LVEF ≥50%) (**Figure 1**). If a patient had been prescribed treatment or hospitalized for HF before the index admission to the KorAHF registry, the patient was considered to have decompensated HF.

The Institutional Review Board of Samsung Medical Center approved this study. Decisions regarding management of HF, including those related to medication, coronary revascularization, or mechanical support, were made by a healthcare professional with expertise in HF at the respective center. The registry protocol was registered at clinicaltrials.gov (NCT01389843).

Data Collection

To record baseline data, the attending physicians completed a web-based case report form in the Clinical Data Management System from the Korea National Institute of Health with the assistance of a clinical research coordinator. Follow-up data were collected at the first post-discharge visit (30 days after discharge) and again at 3, 6, 12, and 24 months post-discharge by the attending physicians using the web-based case report form. The variables collected were previously described in the interim study.[7] Clinical events included all-cause death. Maintenance of HF medication was evaluated at the time of echocardiographic follow-up.

Echocardiographic Examination

Two-dimensional transthoracic echocardiography was performed using commercially available equipment. All parameters were measured according to the European Association of Echocardiography/American Society of Echocardiography recommendations.[8] LVEF was derived by the volumetric method and the modified Simpson's method; the M-mode method was also allowed when LVEF was preserved without regional wall motion abnormality. LVEF was visually estimated if the previous 2 methods

Table 1. Baseline Characteristics of the Total Population According to Baseline LVEF

	HFrEF (n=2,123)	HFmrEF (n=454)	HFpEF (n=508)	P value
Age (years)	67.1±13.9*	71.2±12.4	72.7±12.6‡	<0.001
Male	1,315 (61.9)*	248 (54.6)†	231 (45.5)‡	<0.001
LVEF (%)	26.5±7.4*	44.3±2.8†	59.8±7.0‡	<0.001
Body mass index (kg/m²)	23.1±3.7	23.4±3.4†	24.1±3.9‡	<0.001
Decompensated HF	980 (46.2)*	172 (37.9)	158 (31.1)‡	<0.001
Ischemic cardiomyopathy	1,190 (56.1)*	348 (76.7)†	259 (51.0)	<0.001
Previous history				
Ischemic heart disease	774 (36.5)*	197 (43.4)†	185 (36.4)	0.02
Hypertension	1193 (56.2)*	322 (70.9)	345 (67.9)‡	<0.001
Diabetes mellitus	867 (40.8)	210 (46.3)	204 (40.2)	0.08
Atrial fibrillation	391 (18.4)	89 (19.6)	115 (22.7)	0.09
Chronic lung disease	217 (10.2)	45 (9.9)	69 (13.6)	0.07
Chronic kidney disease	329 (15.5)	91 (20.0)†	59 (11.6)	0.002
Cerebrovascular accident	303 (14.3)	67 (14.8)	90 (17.7)	0.15
Vital signs				
Systolic BP	127.4±29.8*	136.9±32.3	135.1±33.3‡	<0.001
Diastolic BP	78.8±17.6	78.6±18.3	77.0±16.7	0.10
Heart rate	93.3±23.2*	86.6±22.9†	82.4±22.8‡	<0.001
Laboratory data				
Hemoglobin (g/dL)	12.6±2.2*	11.7±2.5†	12.2±2.3‡	<0.001
Na (mmol/L)	137.5±4.7	138.0±4.4	137.4±4.9	0.13
Albumin (g/dL)	3.7±0.6	3.6±0.6	3.7±0.6	0.12
BUN (mg/dL)	26.8±16.2	26.7±16.7	25.2±15.7	0.16
Creatinine (mg/dL)	1.5±1.4	1.7±1.8†	1.4±1.2	0.003
NT-proBNP (pg/mL)	10,807.7±11,443.8	9,985.8±10,918.2†	5,069.1±7,037.8‡	<0.001
Medication at discharge				
RASB	1,637 (77.1)*	312 (68.7)†	287 (56.5)‡	<0.001
β-blocker	1,208 (56.9)*	298 (65.6)†	232 (45.7)‡	<0.001
Aldosterone antagonist	1,144 (53.9)*	164 (36.1)	172 (33.9)‡	<0.001

Values are expressed as mean±SD or n (%). P value refers to the difference among the 3 groups by the Kruskal-Wallis test. A P value <0.017 was considered statistically significant according to the Bonferroni correction. *P<0.017 for HFrEF vs. HFmrEF. †P<0.017 for HFmrEF vs. HFpEF. ‡P<0.017 for HFpEF vs. HFrEF. BP, blood pressure; BUN, blood urea nitrogen; EF, ejection fraction; HF, heart failure (mr, mid-range; p, preserved; r, reduced EF); LVEF, left ventricular EF; RASB, renin-angiotensin system blocker.

were inapplicable. The lowest LVEF measured during the first admission period was recorded as baseline LVEF. Follow-up echocardiography was encouraged at 12 months after discharge, although the final decision was left to each physician's discretion. LVEF reported at least 90 days after discharge was used to assess the improvement of LV systolic function in the HFmrEF group. The 'Improved group' was defined as percent%LVEF change ≥5 and follow-up LVEF ≥50%, and whereas the 'worsened group' was defined as percent%LVEF change ≥5 and follow-up LVEF <40%. Cases not classified into these 2 categories were assigned to the 'no change group'.

Statistical Analysis

Categorical variables are summarized as frequencies with percentages and were compared using the chi-square test or Fisher's exact test. Continuous variables are shown as mean±standard deviation or median with interquartile range and were compared using Student's t-test, one-way analysis of variance, or the Kruskal-Wallis test, as appropriate. For outcome analysis, event-free survival was estimated by the Kaplan-Meier method and compared with the log-rank test. All tests were 2-sided, and P<0.05 was considered statistically significant. When multiple comparisons were performed between 2 groups according to the change in LVEF, P<0.017 was considered statistically significant based on the Bonferroni correction. A logistic regression model was used to determine the independent predictors of improved LVEF, and a Cox proportional hazards model was used to determine prognostic factors for mortality. Variables with P<0.2 in the univariate analysis were included in the multivariate analysis. Additionally, variables that were significantly associated with improved LVEF were included in the multivariate analysis to identify prognostic factors for death in HFmrEF. All statistical analyses were performed using IBM SPSS Statistics version 23 (IBM Corporation, Armonk, NY, USA).

Results

Baseline Population Characteristics According to Baseline LVEF

Of the 3,085 patients included in the present study, 2,123 (68.8%) had HFrEF, 454 (14.7%) had HFmrEF, and 508

Table 2. Baseline Characteristics of HFmrEF Patients According to Follow-up LVEF

	Improved (n=94)	No change (n=127)	Worsened (n=55)	P value
Follow-up LVEF (%)	57.6±5.8*	44.7±3.8†	31.2±5.6‡	<0.001
Age (years)	68.6±14.5	69.6±12.3	70.9±11.6	0.58
Male	47 (50.0)	80 (63.0)	29 (52.7)	0.13
Body mass index (kg/m²)	24.2±3.7	23.9±3.2	23.5±3.6	0.53
Decompensated HF	26 (27.7)*	58 (45.7)	30 (54.5)‡	0.002
Ischemic cardiomyopathy	67 (71.3)	100 (78.7)	40 (72.7)	0.40
Coronary revascularization	30 (31.9)	40 (31.5)	12 (21.8)	0.37
Baseline echocardiography§				
LVEF (%)	45.0±2.5	44.3±3.1	44.2±2.7	0.08
LVEDD (mm)	50.9±9.4*	54.3±12.8	54.1±14.8‡	<0.001
LVESD (mm)	37.8±6.9*	42.5±6.2	43.9±6.7‡	<0.001
LAVI (mL/m²)	45.6±8.9	47.4±9.5	46.8±9.3	0.46
Previous history				
Ischemic heart disease	32 (34.0)	59 (46.5)	26 (47.3)	0.13
Hypertension	54 (57.4)	89 (70.1)	46 (78.2)‡	0.023
Diabetes	50 (53.2)	52 (40.9)	26 (47.3)	0.20
Atrial fibrillation	18 (19.1)	29 (22.8)	9 (16.4)	0.60
Chronic lung disease	8 (8.5)	9 (7.1)	6 (10.9)	0.72
Chronic kidney disease	21 (22.3)	19 (15.0)	14 (25.5)	0.18
Cerebrovascular accident	14 (14.9)	17 (13.4)	5 (9.1)	0.59
Vital signs				
Systolic BP	136.4±27.4	135.4±33.4	137.3±32.1	0.93
Diastolic BP	77.6±14.7	78.1±19.9	80.0±18.3	0.72
Heart rate	90.3±23.5	83.7±24.4	83.9±23.4	0.09
Laboratory data				
Hemoglobin (g/dL)	11.9±2.6	12.0±2.7	11.7±2.3	0.87
Na (mmol/L)	137.5±4.2	138.6±4.1	138.8±3.8	0.08
Albumin (g/dL)	3.6±0.5	3.7±0.6	3.7±0.5	0.89
BUN (mg/dL)	26.1±17.0	24.8±12.4	31.1±18.6	0.08
Creatinine (mg/dL)	1.7±1.9	1.5±1.4	2.2±2.4	0.11
NT-proBNP (pg/mL)	8,204.1±9,639.7	8,431.5±10,399.0	13,391.2±11,932.6	0.11
Medication at discharge				
RASB	66 (70.2)	87 (68.5)	40 (72.7)	0.86
β-blocker	67 (71.3)	81 (63.8)	26 (47.3)‡	0.013
Aldosterone antagonist	37 (39.4)	52 (40.9)	14 (25.5)	0.13
Medication maintenance				
RASB	39 (41.5)	44 (34.6)	19 (34.5)	0.54
β-blocker	41 (43.6)	50 (39.4)	14 (25.5)	0.08
Aldosterone antagonist	22 (23.4)	29 (22.8)	4 (7.3)‡	0.035

Values are expressed as mean±SD or n (%). P value refers to the difference among the 3 groups by the Kruskal-Wallis test. In this multiple comparison, P<0.017 was considered statistically significant according to the Bonferroni correction. *P<0.017 for Improved vs. No change. †P<0.017 for No change vs. Worsened. ‡P<0.017 for Improved vs. Worsened. §LVEDD, LVESD, and LA volume index values were not available in 9, 21, and 15 patients, respectively. HF, heart failure (mr, mid-range); LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVESD, left ventricular end-systolic dimension; LVESV, left ventricular end-systolic volume. Other abbreviations as in Table 1.

(16.5%) had HFpEF (**Figure 1**). Baseline characteristics are shown in **Table 1**. The mean baseline LVEF values were 26.5%, 44.3%, and 59.8% in the HFrEF, HFmrEF, and HFpEF groups, respectively. The mean age of patients with HFmrEF was similar to that of patients with HFpEF; however, patients in these 2 groups were older than patients with HFrEF. The mean systolic blood pressure and incidence of hypertension in HFmrEF patients were also similar to those in HFpEF patients, but were higher than those in HFrEF patients. The HFmrEF group had higher prevalences of previous ischemic heart disease (IHD) and ischemic HF etiology than the other 2 groups, and β-blockers were prescribed more frequently in the HFmrEF group than in the other groups. Patients in the HFmrEF group showed significantly lower hemoglobin levels than in the other 2 groups. The creatinine level and incidence of chronic kidney disease were higher in patients with HFmrEF than in patients with HFpEF, but there were no significant differences between the patients with HFmrEF and HFrEF. Likewise, the mean NT-proBNP

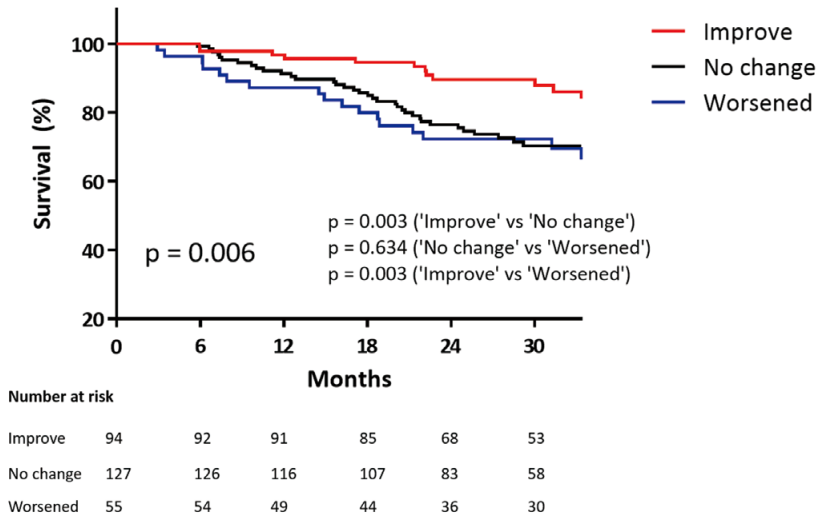

Figure 2. Kaplan-Meier survival curves according to left ventricular ejection fraction at follow-up.

Table 3. Predictors for Improved LVEF in HFmrEF Patients

	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age (years)	0.992	0.973–1.011	0.40			
Male	0.670	0.406–1.106	0.12	0.569	0.299–1.082	0.09
Decompensated HF	0.408	0.239–0.699	0.001	1.640	0.779–3.453	0.193
Ischemic cardiomyopathy	0.744	0.423–1.309	0.31			
Baseline echocardiography						
LVEF (%)	1.101	1.007–1.203	0.034	1.022	0.907–1.150	0.73
LVEDD (mm)	0.899	0.863–0.936	<0.001	0.957	0.860–1.064	0.42
LVESD (mm)	0.887	0.848–0.928	<0.001	0.920	0.823–1.029	0.14
LAVI (mL/m^2)	0.981	0.954–1.009	0.18	1.022	0.983–1.604	0.27
Previous history						
Ischemic heart disease	0.589	0.351–0.987	0.045	1.859	0.842–4.105	0.13
Hypertension	0.511	0.303–0.862	0.012	2.107	1.008–4.402	0.047
Diabetes	1.515	0.919–2.499	0.10	0.552	0.278–1.096	0.09
Cerebrovascular accident	1.273	0.618–2.620	0.51			
Vital signs						
Systolic BP	1.000	0.992–1.008	0.92			
Diastolic BP	0.997	0.983–1.011	0.63			
Heart rate	1.012	1.001–1.023	0.031	1.016	1.002–1.031	0.027
Laboratory data						
Hemoglobin (g/dL)	0.994	0.902–1.096	0.91			
Na (mmol/L)	0.932	0.877–0.992	0.027	0.896	0.822–0.975	0.011
Creatinine (mg/dL)	0.996	0.870–1.141	0.96			
NT-proBNP (pg/mL)	1.000	1.000–1.000	0.38			
Medication maintenance						
RASB	1.339	0.803–2.234	0.26			
β-blocker	1.426	0.858–2.372	0.17	2.021	1.033–3.956	0.04
Aldosterone antagonist	1.380	0.751–2.535	0.30			

CI, confidence interval; HF, heart failure (mr, mid-range); HR, hazard ratio. Other abbreviations as in Tables 1,2.

levels were higher in patients with HFmrEF than in patients with HFpEF, but there was no difference between patients with HFmrEF vs. HFrEF.

Baseline Characteristics of the HFmrEF Group According to Follow-up LVEF

A total of 276 (60.8%) of the 454 HFmrEF patients underwent follow-up echocardiography at a median of 372 (245–530) days after discharge. Among these patients, 94 (34.1%)

Table 4. Prognostic Factors for Mortality in HFmrEF Patients With Follow-up LVEF

	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age (years)	1.031	1.009–1.054	0.006	1.034	1.009–1.060	0.01
Male	1.168	0.726–1.878	0.52			
Baseline echocardiography						
LVEF (%)	1.039	0.955–1.130	0.37			
LVEDD (mm)	1.014	0.992–1.037	0.22			
LVESD (mm)	1.021	0.987–1.056	0.23			
LAVI (mL/m^2)	1.018	0.991–1.045	0.20			
Improved LVEF	0.391	0.215–0.713	0.002			
Follow-up LVEF (%)	0.962	0.941–0.984	0.001			
Body mass index (kg/m^2)	0.929	0.865–0.998	0.045	0.988	0.911–1.060	0.78
Decompensated HF	2.056	1.289–3.279	0.002	0.574	0.326–1.012	0.06
Ischemic cardiomyopathy	1.090	0.625–1.902	0.76			
Coronary revascularization	0.665	0.386–1.146	0.14	1.543	0.866–2.751	0.14
Previous history						
Ischemic heart disease	1.499	0.944–2.381	0.09	1.175	0.643–2.148	0.60
Hypertension	1.715	0.995–2.955	0.052	1.006	0.528–1.918	0.99
Diabetes	1.648	1.033–2.629	0.036	0.782	0.465–1.313	0.35
Atrial fibrillation	1.171	0.662–2.073	0.59			
Chronic lung disease	1.399	0.670–2.917	0.37			
Chronic kidney disease	1.684	1.005–2.821	0.048	1.365	0.646–2.885	0.42
Cerebrovascular accident	0.735	0.337–1.603	0.44			
Vital signs						
Systolic BP	1.005	0.997–1.012	0.22			
Diastolic BP	1.006	0.993–1.019	0.36			
Heart rate	1.005	0.996–1.014	0.24	1.002	0.991–1.012	0.77
Laboratory data						
Hemoglobin (g/dL)	0.845	0.774–0.923	<0.001	0.912	0.813–1.023	0.12
Na (mmol/L)	0.964	0.910–1.021	0.22	0.993	0.934–1.055	0.81
Albumin (g/dL)	0.892	0.640–1.244	0.50			
BUN (mg/dL)	1.021	1.009–1.033	<0.001	1.008	0.987–1.030	0.45
Creatinine (mg/dL)	1.102	1.010–1.202	0.029	1.031	0.876–1.213	0.72
NT-proBNP (pg/mL)	1.000	1.000–1.000	0.17			
Medication maintenance						
RASB	0.290	0.159–0.529	<0.001	0.309	0.162–0.588	<0.001
β-blocker	0.464	0.272–0.791	0.005	0.951	0.516–1.754	0.87
Aldosterone antagonist	0.208	0.076–0.569	0.002	0.240	0.085–0.673	0.01

HF, heart failure (mr, mid-range). Other abbreviations as in Tables 1–3.

showed improved LVEF, while 55 (19.9%) had worsened LVEF at follow-up echocardiography according to the criteria previously described. The baseline LVEFs of the 3 groups showed no statistically significant differences. LV dimensions were smallest and the prevalence of decompensated HF and hypertension were lowest in the improved group. The worsened group had the lowest prescription rate of β-blockers at discharge and had a tendency for low β-blocker maintenance therapy at follow-up. There were no significant differences in the prescription rates of renin-angiotensin system blockers (RASB) at discharge or follow-up among the 3 groups, although the improved group showed a higher rate of aldosterone antagonist maintenance therapy at follow-up than the worsened group (**Table 2**).

Mortality and Predictors of Improved LVEF in HFmrEF Patients According to Follow-up LVEF

Over a median follow-up duration of 30.1 months (21.8–38.5 months), a total of 160 (58.0%) all-cause deaths were identified. No significant difference in median follow-up duration was observed among the 3 groups (P=0.34). Patients with improved LVEF showed a significantly higher survival rate than patients in the other groups (P=0.006) (**Figure 2**). In the univariate logistic regression analysis, baseline LVEF, LV dimensions, presence of decompensated HF, previous history of IHD or hypertension, heart rate, and serum sodium level were all factors associated with the improved group. In a multivariate analysis including all variables with P<0.2 in the univariate analysis, we found that hypertension, higher heart rate, lower serum sodium level, and maintenance of β-blocker therapy were significantly associated with improved LVEF at follow-up (**Table 3**).

Predictors for Mortality of HFmrEF Patients With Follow-up LVEF

Cox regression analysis was performed to determine

prognostic factors for death in HFmrEF patients with follow-up LVEF. Multivariate analysis showed that young age and maintenance of RASB or aldosterone antagonist were significantly associated with better survival (**Table 4**).

Discussion

In the present study, we investigated mortality and follow-up LVEF in patients with acute HF with mid-range LVEF. The major findings of our study are as follows: (1) ischemic cardiomyopathy was more prevalent in patients with HFmrEF than in patients with HFrEF or HFpEF; (2) patients with HFmrEF in the improved group had significantly better survival compared with patients in the no change or worsened groups; (3) hypertension, higher heart rate, lower serum sodium level, and maintenance of β-blocker therapy were significantly associated with improved LVEF at follow-up in patients with HFmrEF; and (4) young age and maintenance of RASB or aldosterone antagonist therapy were significantly associated with better survival in patients with HFmrEF.

The proportion of HFmrEF (15%) among patients with HF in our study was similar to that reported in recent papers (13–25%).[9–11] Generally, the characteristics of HFmrEF resemble those of HFpEF, with the exception of the high proportion of IHD.[12] Even though the prevalence of predominant comorbidities such as hypertension, IHD, or chronic kidney disease has been reported to differ among the HFrEF, HFmrEF, and HFpEF groups, the prevalence of these comorbidities in HFmrEF patients is quite consistent. Specifically, approximately 60–70% of all patients with HFmrEF have hypertension, 40–60% have IHD, and 20% have chronic kidney disease;[9–11] these findings are in good agreement with our data (70.9%, 43.4%, and 20.0%, respectively).

Regarding the prognosis of patients with HFmrEF, improved LV systolic function has been reported to be related to better survival. Savarese et al reported that patients with declining NT-proBNP level showed better survival than patients with elevating NT-pro BNP level.[13] Similarly, we found that patients who continued to have mid-range LVEF on follow-up echocardiography showed worse outcomes than patients with improved LVEF (above the lower normal range). A similar outcome was observed for the worsened LVEF group (**Figure 2**), even though the decreased LVEF was not as low as in the HFrEF group. Hence, efforts to improve LVEF are required to improve the survival of HFmrEF patients. When we corrected for confounding factors associated with LVEF improvement, RASBs and aldosterone antagonists were associated with better survival of HFmrEF patients. Although no study has yet focused on the effects of RASBs or aldosterone antagonists in HFmrEF patients alone, several studies of HFpEF patients (including some with HFmrEF) have observed beneficial effects of RASBs and aldosterone antagonists.[1,3,14,15] This finding can be partially explained by the high prevalence of ischemic cardiomyopathy in HFmrEF patients. Further studies are needed to confirm the beneficial effects of RASBs and aldosterone antagonists in HFmrEF patients.

Study Limitations

First, unmeasured confounding factors may not have been adequately controlled for because this study included an observational cohort, even though we corrected for measured confounding factors with multivariable analysis. Second, less than half of all the HFmrEF patients were excluded for a lack of follow-up echocardiography data. Third, we could not differentiate HFmrEF patients from patients recovering from HFrEF. However, in reality, it is not possible to discriminate whether patients who initially manifest HFmrEF are recovering from low LVEF or are developing HFmrEF as is. Therefore, the identified prognostic factors for improved LVEF and overall mortality in our study reflect relevant data of patients who display HFmrEF at the first manifestation. Fourth, LV mass data could not be investigated in this study. Fifth, the precise reason that HFmrEF patients with worsened LVEF showed relatively lower maintenance of HF medications could not be assessed because the information was not available in our registry. Because there is no established guideline for the treatment of HFmrEF, we suggest that physicians' preference is a possible reason for the maintenance of HF medication. Lastly, cause-specific mortality could not be assessed because most survival data were confirmed using the National Insurance data or National Death Records. However, the quality of 1-year mortality analysis was much improved after adopting these data, because many cases of death that were lost to follow-up in each center could be incorporated in the final analysis. Therefore, we believe that the high follow-up rate regarding all-cause death is the strength of our registry, even though cardiovascular death could not be assessed.

Conclusions

In our multicenter prospective cohort study, approximately one-third of all patients with HFmrEF had improved follow-up echocardiography results. The HFmrEF patients in the improved group had a better survival rate than those in the no change or worsened group. Maintenance of RASB or aldosterone antagonist therapy was an independent prognostic factor for death in patients with acute HF with mid-range EF. The role of RASB and aldosterone antagonists merits future investigation because of their potential to improve the prognosis of HFmrEF patients.

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Conflicts of Interest / Disclosures

None.

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