Clinical Characteristics and Long-Term Outcomes of Patients with Acute Decompensated Heart Failure with Mid-Range Ejection Fraction

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Summary

According to recent guidelines, a new category of patients with heart failure (HF) with mid-range left ventricular ejection fraction (LVEF) (HFmrEF) (LVEF = 40%-49%) has been defined. The purpose of this study was to investigate the clinical characteristics and long-term outcomes of patients with HFmrEF. This was a single-center, retrospective, observational study in which we examined the clinical characteristics and outcomes of 494 consecutive patients with acute decompensated heart failure who were admitted to our institution between January 2014 and December 2016. Of this population, 282 (57.1%), 75 (15.2%), and 137 (48.6%) patients had heart failure with reduced ejection fraction (HFrEF), HFmrEF, and heart failure with preserved ejection fraction (HFpEF), respectively. Ischemic heart disease was the primary etiology in HFmrEF and HFrEF. At the time of discharge, β-blockers and renin-angiotensin system inhibitors were more frequently prescribed in HFmrEF than in HFpEF. The composite outcome of cardiovascular mortality and HF readmission was significantly lower in HFmrEF than in HFrEF. Further studies are needed to determine the effectiveness of the management of coronary artery disease and cardioprotective medications for HFmrEF.

Key words: Heart failure with borderline ejection fraction, Prognosis, Etiology, Cardioprotective medication

According to recent guidelines, patients with heart failure (HF) have been categorized into heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). There are distinct differences in the demography, etiology, comorbidities, and responses to therapies between HFrEF and HFpEF. In HFrEF, most of the previous studies included patients with a left ventricular ejection fraction (LVEF) value of < 35% to < 40%. However, in HFpEF, various cutoffs of LVEF were used in previous studies (LVEF: > 40% to > 50%). Consequently, patients with an LVEF value in the range of 40%-49% were considered in the “gray area.” Recent clinical guidelines categorized patients with LVEF in the range of 40%-49% as HF with “borderline” ejection fraction or HF with “mid-range” ejection fraction (HFmrEF) in order to stimulate research on the underlying characteristics, pathophysiology, and treatment of this group of patients.

Early studies that compared the prognoses of HFpEF, HFmrEF, and HFrEF reached various conclusions. The Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure, including 622 patients with Congestive Heart Failure, demonstrated that all-cause mortality and HF readmission were not significantly different among HFrEF, HFmrEF, and HFpEF, whereas the Chronic Heart Failure Analysis and Registry in the Tohoku District 2 (CHART-2) study, comprising 10,219 stable patients with HF, demonstrated that all-cause mortality and HF readmission were significantly higher in HFrEF followed by HFmrEF. Previous clinical trials have shown that some medications can possibly improve the prognosis of HFmrEF. The Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial, which enrolled patients with LVEF 45% or greater, demonstrated that the potential efficacy of spironolactone for the prognosis was greatest at the lower end of the LVEF spectrum. The Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity program, which enrolled patients with HF across the spectrum of EF, demonstrated that candesartan improved the outcomes in HFmrEF to a degree similar to that in HFrEF.

Although the above studies suggested that there are differences in the clinical characteristics and long-term prognoses among HFrEF, HFmrEF, and HFpEF, little is known about the clinical characteristics and long-term outcomes of HFmrEF, and the therapeutic strategy for HFmrEF has not been established yet. Further accumulation of real-world data is warranted in this territory. The purpose of this study was to investigate the clinical char-
acteristics and clinical outcomes of patients with HFmrEF who were hospitalized for acute decompensated heart failure (ADHF).

**Methods**

**Study design and participants:** This was a single-center, retrospective, observational study. 871 consecutive patients with ADHF who were admitted to our institution between January 2014 and December 2016 were screened. Patients who did not have available echocardiographic data examined by a sonographer within 30 days before and after the admission date were excluded. Patients who were not available of precise LVEF by modified Simpson’s method because of poor image were excluded. Then, the later admissions of duplicate patients who were admitted more than once during the study period were excluded. Finally, only patients who had precise echocardiographic data of LVEF were included in this study, and they were divided into three groups according to their LVEF: HFrEF (LVEF < 40%), HFmrEF (LVEF = 40%-49%), and HFpEF (LVEF ≥ 50%). Clinical events were traced via the patients’ medical records. The primary endpoint of this study was the composite of cardiovascular death and HF readmission. Event-free time was calculated from the date of index admission until the endpoint or the last follow-up day. This study was approved by the institutional review board. Written informed consent was waived because of the retrospective study design.

**LVEF measurement:** Echocardiographic images were obtained by three experienced sonographers. The echocardiographic equipment used was Epic 7G (Philips Electronics Industries, Amsterdam, the Netherlands) or Aplio 500 (Toshiba Medical Systems, Tochigi, Japan). LV images in each systolic and diastolic phase were acquired and recorded as four-chamber and two-chamber images from the transapical view. LVEF was calculated according to the modified Simpson method, with semiautomatic tracing of the inner border of the LV myocardium with online analysis (n = 144). If data of LVEF was recorded only using the Teichholz method and not the modified Simpson method, or if the semiautomatic tracing of the inner border of the LV myocardium with online analysis was not precise because of obesity or pulmonary emphysema (poor image from the transapical view), an experienced cardiologist (M.I.) recalculated the LVEF according to the modified Simpson method with offline analysis using offline software (CardioAgent™ Pro; Toshiba Medical Systems) (n = 350).

**Definition of characteristics:** We compared the clinical characteristics among these three groups from each different clinical aspect of HF, such as demographics, primary etiology of HF, medical history, laboratory data, treatment (including medications), and echocardiographic parameters. The diagnosis of ADHF was based on the criteria of the Framingham definitions and the guideline for acute HF of the Japanese Circulation Society. LVEF, left ventricular end-systolic volume, and left ventricular end-diastolic volume were measured according to the modified Simpson method by echocardiography. The left atrial diameter, interventricular septal thickness (IVST), posterior wall thickness (PWT), left ventricular end-diastolic dimension (LVDd), and left ventricular end-systolic dimension were measured by M-mode. The left ventricular mass (LVM) was estimated by LV cavity dimension and wall thickness at end diastole: LVM = 0.8 × 1.04 × ([LVDd + IVST + PWT] − LVDd) + 0.6. LVM was indexed to body surface area, and left ventricular hypertrophy was defined as the value of the LVM index (LVMI) (males: LVMI > 115 g/m²; females: LVMI > 95 g/m²). The relative wall thickness (RWT) was calculated as RWT = 2 × PWT/LVDd (normal: RWT ≤ 0.42; elevated: RWT > 0.42). LV geometries were classified into four patterns: normal (LVM and RWT normal), concentric remodeling (LVM normal but RWT elevated), concentric hypertrophy (LVM and RWT elevated), and eccentric hypertrophy (LVM elevated but RWT normal).

**Statistical analysis:** Continuous variables were expressed as the mean ± standard deviation, and categorical variables were expressed as frequency. Continuous variables were tested for normal distribution using the Shapiro-Wilk test and were compared among groups using one-way analysis of variance or the Kruskal-Wallis test, as appropriate. Categorical variables were compared using the chi-squared test. The survival curves of the three groups were drawn using the Kaplan-Meier method, and the log-rank test was used to calculate statistical differences. P < 0.05 was considered statistically significant. All statistical analyses were performed with SPSS software version 18.0.

**Results**

**Study flowchart and distribution of LVEF:** The number of patients who were finally included in this study was 494 (Figure 1). 282 patients (57.1%) had HFrEF, 75 patients (15.2%) had HFmrEF, and 137 patients (27.7%) had HFpEF. The mean LVEF of all patients, HFrEF, HFmrEF, and HFpEF were 39.6 ± 16.3%, 27.7 ± 7.4%, 44.6 ± 2.7%, and 61.6 ± 7.6%, respectively. The distribution of LVEF in this study is shown in Figure 2.

**Clinical characteristics:** The comparison of the clinical characteristics among these three groups is shown in Table I. The mean age of patients with HFrEF, HFmrEF, and HFpEF was 67.4 ± 14.0, 74.0 ± 11.3, and 75.8 ± 9.0 years, respectively. The prevalence of female sex in patients with HFrEF, HFmrEF, and HFrEF was 34.1%, 42.7%, and 51.8%, respectively. Patients with HFmrEF and HFrEF were more likely to have ischemic heart disease as an etiology compared to those with HFpEF (HFrEF: 43.3%; HFmrEF: 46.7%; HFpEF: 29.9%; P < 0.001). The prevalence of atrial fibrillation (HFrEF: 39.9%; HFmrEF: 42.7%; HFpEF: 65.0%; P < 0.001), the hemoglobin level (HFrEF: 12.9 ± 2.3 g/dL; HFmrEF: 12.4 ± 2.2 g/dL; HFpEF: 11.5 ± 2.4 g/dL; P < 0.001), and the serum brain natriuretic peptide (BNP) level of HFmrEF (HFrEF: 1,452 ± 1,295 pg/mL; HFmrEF: 1,044 ± 892 pg/mL; HFpEF: 707 ± 452 pg/mL; P < 0.001) were intermediate between HFrEF and HFpEF.

**Medications:** Medications at discharge are shown in Table I. At the time of admission, the prescription rates of cardioprotective medications, including β-blockers, renin-
angiotensin system inhibitors (RASIs), mineralocorticoid receptor antagonists (MRAs), and statins, were not significantly different among these three groups. At the time of discharge, β-blockers (HFrEF: 93.1%; HFmrEF: 82.2%; HFpEF: 71.9%; \( P < 0.001 \)) and RASIs (HFrEF: 84.7%; HFmrEF: 79.5%; HFpEF: 62.7%; \( P < 0.001 \)) were most frequently prescribed in HFrEF, followed by HFmrEF, and least frequently prescribed in HFpEF. Statins were most frequently prescribed in HFmrEF (HFrEF: 56.0%; HFmrEF: 57.5%; HFpEF: 40.7%; \( P = 0.009 \)), followed by HFrEF, and least frequently prescribed in HFpEF. **Echocardiography:** The echocardiographic data are

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**Figure 1.** Flowchart of the inclusion and exclusion of the patients. ADHF indicates acute decompensated heart failure; TTE, transthoracic echocardiography; and LVEF, left ventricular ejection fraction.

**Figure 2.** Distribution of LVEF of the study population. LVEF indicates left ventricular ejection fraction.
Table I. Clinical Characteristics of Patients with HF Stratified by the Ejection Fraction

| Demographics | All (n = 494) | HFrEF (n = 282) | HFmrEF (n = 75) | HFrEF (n = 137) | P-value |
|--------------|--------------|----------------|----------------|----------------|---------|
| Age (years)  | 70.7 ± 13.0  | 67.4 ± 14.0    | 74.0 ± 11.3    | 75.8 ± 9.0     | < 0.001 |
| Female sex (%) | 35.0         | 23.4           | 48.0           | 51.8           | < 0.001 |
| Primary etiology |             |                |                |                | < 0.001 |
| Ischemic (%) | 40.1         | 43.3           | 46.7           | 29.9           |         |
| Hypertensive (%) | 24.9         | 23.0           | 21.3           | 30.7           |         |
| DCM (%) | 10.7         | 17.7           | 4.0            | 0.0            |         |
| Valvular (%) | 12.8         | 8.9            | 17.3           | 18.2           |         |
| Others (%) | 11.5         | 7.1            | 10.7           | 21.2           |         |
| Medical history |             |                |                |                |         |
| HF admission (%) | 29.8         | 35.1           | 24.0           | 21.9           | 0.011   |
| Hypertension (%) | 68.6         | 65.2           | 76.0           | 71.5           | 0.140   |
| Diabetes mellitus (%) | 44.1         | 44.7           | 52.0           | 38.7           | 0.168   |
| Dyslipidemia (%) | 70.6         | 74.5           | 69.3           | 63.5           | 0.067   |
| Hyperuricemia (%) | 61.3         | 70.9           | 42.7           | 51.8           | < 0.001 |
| Atrial fibrillation (%) | 47.3         | 39.9           | 42.7           | 65.0           | < 0.001 |
| COPD (%) | 7.9          | 5.0            | 10.7           | 12.4           | 0.019   |
| Stroke (%) | 12.8         | 14.2           | 10.8           | 10.9           | 0.557   |
| Smoking (%) | 62.7         | 69.9           | 52.7           | 53.3           | 0.001   |
| Data at admission |             |                |                |                |         |
| NYHA I (%) | 0.4          | 0.7            | 0.0            | 0.0            |         |
| NYHA II (%) | 5.5          | 5.0            | 5.3            | 6.6            |         |
| NYHA III (%) | 43.1         | 45.0           | 38.7           | 24.1           |         |
| NYHA IV (%) | 51.0         | 49.3           | 56.0           | 51.1           |         |
| BMI (kg/m²) | 23.6 ± 4.6   | 23.8 ± 4.8     | 23.5 ± 4.5     | 23.5 ± 4.2     | 0.949   |
| Laboratory data |             |                |                |                |         |
| Albumin (g/dL) | 3.6 ± 0.5    | 3.7 ± 0.5      | 3.6 ± 0.5      | 3.6 ± 0.6      | 0.917   |
| Uric acid (mg/dL) | 7.1 ± 2.4    | 7.5 ± 2.6      | 6.4 ± 1.9      | 6.4 ± 2.1      | < 0.001 |
| eGFR (mL/minute/1.73 m²) | 50.1 ± 25.3  | 49.2 ± 25.0    | 50.1 ± 23.0    | 52.1 ± 27.0    | 0.665   |
| Sodium (mEq/L) | 138.5 ± 4.5  | 138.2 ± 4.4    | 138.4 ± 5.4    | 139.2 ± 3.8    | 0.186   |
| Hemoglobin (g/dL) | 12.4 ± 2.4   | 12.9 ± 2.3     | 12.4 ± 2.2     | 11.5 ± 2.4     | < 0.001 |
| BNP (pg/mL) | 1182 ± 1166  | 1452 ± 1295    | 1044 ± 892     | 707 ± 452      | < 0.001 |

Continuous variables are expressed as the mean ± standard deviation, and categorical variables are expressed as %. HFrEF indicates heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with preserved ejection fraction; DCM, dilated cardiomyopathy; HF, heart failure; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; BMI, body mass index; eGFR, estimated glomerular filtration rate; and BNP, brain natriuretic peptide.

Table II. Medications at Discharge

| β-blocker (%) | All (n = 494) | HFrEF (n = 282) | HFmrEF (n = 75) | HFrEF (n = 137) | P-value |
|--------------|--------------|----------------|----------------|----------------|---------|
| RASI (%) | 77.8         | 84.7           | 79.5           | 62.7           | < 0.001 |
| MRA (%) | 49.6         | 54.0           | 47.9           | 41.5           | 0.056   |
| Loop diuretic (%) | 82.0         | 84.4           | 89.0           | 73.3           | 0.006   |
| Tolvaptan (%) | 9.3          | 11.3           | 5.5            | 7.4            | 0.212   |
| Thiazide (%) | 4.8          | 5.5            | 2.7            | 4.4            | 0.613   |
| Antiplatelet drug (%) | 49.9         | 50.2           | 58.9           | 44.4           | 0.136   |
| Anticoagulant (%) | 54.2         | 52.7           | 42.5           | 63.7           | 0.010   |
| CCB (%) | 24.0         | 16.7           | 34.2           | 33.3           | < 0.001 |
| Antihyperuricemic drug (%) | 42.0         | 48.0           | 27.4           | 37.8           | 0.003   |
| Statin (%) | 52.0         | 56.0           | 57.5           | 40.7           | 0.009   |
| Antidiabetic drug (%) | 25.7         | 25.5           | 32.9           | 22.2           | 0.243   |
| Insulin (%) | 8.7          | 8.0            | 11.0           | 8.9            | 0.730   |

Variables are expressed as %. RASI indicates renin-angiotensin system inhibitor; MRA, mineralocorticoid receptor antagonist; and CCB, calcium channel blocker.

shown in Table III. The left ventricular cavity dimensions, left ventricular cavity volume, and LVMI increased from HFrEF to HFmrEF, and HFmrEF had intermediate values. Regarding the classification of LV geometry patterns,
HFmrEF was likely to have eccentric hypertrophy, whereas HFrEF was likely to have concentric hypertrophy.

**Prognosis:** The median (first quartile to third quartile) follow-up period was 268 (65-566) days. There was no significant difference in the follow-up period among these three groups ($P = 0.723$). During the follow-up period, there were 48 cardiac deaths, 27 noncardiac deaths, and 139 HF readmissions. The Kaplan-Meier curves for the primary endpoint of these three groups are shown in Figure 3. The primary endpoint was most frequently observed in HFrEF, followed by HFmrEF, and least frequently observed in HFpEF ($P = 0.012$). There was no significant difference between HFpEF and HFmrEF ($P = 0.562$). The incidences of all-cause death ($P = 0.852$), cardiovascular death ($P = 0.119$), and HF readmission ($P = 0.060$) were not different among these three groups.

**Discussion**

In the present study, we showed the clinical characteristics and prognoses of patients with HFmrEF who were admitted with symptomatic HF. Ischemic heart disease was the primary etiology in HFmrEF and HFrEF. At the time of discharge, β-blockers and RASIs were more frequently prescribed in HFmrEF than in HFrEF. The composite outcome of cardiovascular mortality and HF readmission was significantly lower in HFmrEF than in HFrEF.

**Distribution of LVEF:** The peak distribution of LVEF was unimodal and in the range of 20%-40%, indicating that patients with HFmrEF comprised a substantial proportion of this study population, with a relatively small proportion of patients with HFpEF. The prevalence of HFmrEF was comparable with some previous registries. However, a higher prevalence of patients with HFpEF was demonstrated in the CHART-2 study, in which 61.9% of the study population had HFpEF. These inconsistent results might be caused by the different populations. In the CHART-2 study, most of the study population had asymptomatic HF (stage B of AHA/ACC classification) or coronary heart disease without HF (53.7%), and the mean BNP level was 145.4 ± 249.3 pg/mL. On the other hand, the present study included hospitalized patients, many of whom had an advanced stage of HF (the mean BNP level was 1,182 ± 1,166 pg/mL at admission, stage C or stage D of AHA/ACC classification), so the proportion of patients with HFrEF might be higher than that in the CHART-2 study.

**Clinical characteristics:** In the present study, ischemic heart disease was the primary etiology in HFmrEF. Patients with HFpEF tend to be older, more often females, and to have a higher prevalence of atrial fibrillation and anemia compared with those with HFrEF, according to prior studies. LVM was an established risk factor for the cardiovascular events and prognosis in a patient with HF. A higher LVM might be related to the poor prognosis of HFrEF in the present study. In the classification of LV remodeling patterns in the present study, HFrEF was likely to have eccentric hypertrophy (concentric hypertrophy: 6.4%; eccentric hypertrophy: 77.7%), whereas HFpEF was likely to have concentric hypertrophy (concentric hypertrophy: 35.8%; eccentric hypertrophy: 25.5%), and HFmrEF had an intermediate proportion (concentric hypertrophy: 33.3%; eccentric hypertrophy: 49.3%).

**Treatment and prognosis:** In patients with HFmrEF, pharmacological and device therapies have been shown to improve their prognoses. However, in patients with HFpEF, there are few treatments that reduce their morbidity and mortality. In patients with HFpEF, the use of diuretics and the treatment of comorbidities are recommended in order to alleviate the symptoms and signs of HF. In patients with HFmrEF, prognostic and therapeutic evidence is still limited.

In the present study, the composite outcome of car-

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**Table III. Data of Echocardiography**

| Variable                      | All (n = 494) | HFrEF (n = 282) | HFmrEF (n = 75) | HFpEF (n = 137) | P-value |
|-------------------------------|---------------|-----------------|-----------------|-----------------|---------|
| LVEF (%)                      | 39.6 ± 16.3   | 27.7 ± 7.4      | 44.6 ± 2.7      | 61.6 ± 7.6      | <0.001  |
| LVEDV index (mL/m²)           | 86.1 ± 41.2   | 107.5 ± 38.3    | 72.8 ± 22.5     | 49.1 ± 20.5     | <0.001  |
| LVESV index (mL/m²)           | 56.9 ± 37.7   | 79.4 ± 33.8     | 40.4 ± 13.0     | 19.4 ± 9.6      | <0.001  |
| LVDD (mm)                     | 57.9 ± 10.9   | 63.4 ± 9.7      | 53.9 ± 7.1      | 48.7 ± 7.1      | <0.001  |
| LVDs (mm)                     | 45.4 ± 12.9   | 53.2 ± 10.3     | 40.3 ± 7.4      | 32.1 ± 5.8      | <0.001  |
| LV mass index (g/m²)          | 144.3 ± 44.4  | 153.4 ± 43.8    | 141.5 ± 36.4    | 127.1 ± 44.2    | <0.001  |
| LVH (%)                       | 77.5          | 84.0            | 82.7            | 61.3            | <0.001  |
| LVH classification            |               |                 |                 |                 | <0.001  |
| Normal (%)                    | 16.0          | 14.5            | 17.3            | 18.2            | 0.588   |
| Concentric remodeling (%)     | 6.5           | 1.4             | 0.0             | 20.4            | <0.001  |
| Concentric hypertrophy (%)    | 18.6          | 6.4             | 33.3            | 35.8            | <0.001  |
| Eccentric hypertrophy (%)     | 58.9          | 77.7            | 49.3            | 25.5            | <0.001  |

Continuous variables are expressed as the mean ± standard deviation, and categorical variables are expressed as %. EF indicates ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVDD, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; and LVH, left ventricular hypertrophy.
diovascular mortality and HF readmission was significantly better in HFmrEF compared to HFrEF. There was no significant difference in the all-cause mortality among these three groups.

In prior studies where the mortality and morbidity were compared, various conclusions were reported. The uncertainty of the results might be caused by the clinical settings (in-hospital or out-hospital) and the severity of HF. Furthermore, the proportion of patients with recovered LVEF in HFpEF or HFmrEF might influence the prognosis, because those patients had a lower mortality rate and fewer recurrent HF admissions.

The management of coronary artery disease also possibly influences the prognosis of HFmrEF. In the CHART-2 study, it was reported that the ischemic etiology is associated with the decrease of LVEF at one-year in HFmrEF and that the decrease of LVEF is related to increased mortality. The management of coronary artery disease may hold the key to improve the prognosis of HFmrEF, because ischemic heart disease was found to be the primary cause of HF in HFmrEF in the present study.

In the present study, the prescription rates of β-blockers and RASIs, and MRAs were significantly higher in HFmrEF compared to HFpEF at discharge. Although some studies reported the efficacy of cardioprotective medications for the prognosis of HFmrEF, further studies are needed to identify effective therapeutic strategies for HFmrEF.

**Limitations:** There are several limitations in the present study. First, as the present study was a single-center, retrospective, observational study, there is a risk of selection bias. Second, since the sample size was relatively small, there is a possibility of beta error. Third, we could not reach a conclusion regarding what the best approach is for ischemic heart disease because we did not evaluate the association between the treatments and prognosis of ischemic heart disease by a multivariable analysis in this study. Fourth, we did not analyze the proportion of patients with recovered LVEF in this study, those who might influence the prognosis.
Conclusion

The prevalence of ischemic etiology in HFmrEF is higher than in HFrEF. The cardiovascular prognosis of HFmrEF is better compared with HFrEF. Further studies are needed to determine the effectiveness of the management of coronary artery disease and cardioprotective medications for HFmrEF.

Disclosure

Conflicts of interest: The authors declare that there is no conflict of interest.

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