Circulation Journal
Circ J 2019; 83: 347–356
doi:10.1253/circj.CJ-18-0543

ORIGINAL ARTICLE
Heart Failure

Comparison of Characteristics and 3-Year Outcomes in Patients With Acute Heart Failure With Preserved, Mid-Range, and Reduced Ejection Fraction

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Background: The clinical characteristics and outcomes of acute heart failure (AHF) according to left ventricular ejection fraction (LVEF) have not been fully elucidated, especially for patients with mid-range LVEF. We performed a comprehensive comparison of the epidemiology, patterns of in-hospital management, and clinical outcomes in AHF patients with different LVEF categories.

Methods and Results: The Korean Acute Heart Failure (KorAHF) registry is a prospective multicenter cohort of hospitalized AHF patients in Korea. A total of 5,374 patients enrolled in the KorAHF registry were classified according to LVEF based on the 2016 ESC guidelines. More than half of the HF patients (58%) had reduced EF (HFrEF), 16% had mid-range EF (HFmrEF), and 25% had preserved EF (HFpEF). The HFmrEF patients showed intermediate epidemiological profiles between HFrEF and HFpEF and had a propensity to present as de-novo HF with ischemic etiology. Patients with lower LVEF had worse short-term outcomes, and the all-cause in-hospital mortality, including urgent heart transplantation, of HFrEF, HFmrEF, and HFpEF was 7.1%, 3.6%, and 3.0%, respectively. Overall, discharged AHF patients showed poor 3-year all-cause death up to 38%, which was comparable between LVEF subgroups (P=0.623).

Conclusions: Each LVEF subgroup of AHF patients was a heterogeneous population with diverse characteristics, which have a significant effect on the clinical outcomes. This finding suggested that focused phenotyping of AHF patients could help identify the optimal management strategy and develop novel effective therapies.

Key Words: Acute heart failure; Left ventricular ejection fraction; Outcomes; Survival

Heart failure (HF) is a major public health problem affecting an estimated >23 million patients globally.[1] It remains the leading cause of hospitalization among adults >65 years of age,[1] and imposes a substantial socioeconomic burden through healthcare resource utilization.[2] Acute HF (AHF) refers to rapid onset or worsening of symptoms and/or signs of HF, which usually requires hospitalization and is associated with poor outcomes.[3] Despite recent advances in the treatment strategy and dramatic improvement in long-term outcomes of chronic HF,[4] patients with AHF continue to experience unacceptably high short-term mortality and re-hospitalization rates, which have not improved markedly over the past decades.[5]

Editorial p 274

HF is most commonly classified according to the severity

Received May 11, 2018; revised manuscript received October 1, 2018; accepted October 2, 2018; J-STAGE Advance Publication released online November 6, 2018 Time for primary review: 32 days

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ISSN-1346-9843

of left ventricular (LV) systolic dysfunction and is measured by LV ejection fraction (LVEF). Patients with LVEF <40% are categorized as having HF with reduced EF (HFrEF), and the majority of evidence supporting the beneficial effect of pharmacological- and device-based HF treatments has been generated within this group.[3,6] In contrast, patients with LVEF ≥50% are considered to have HF with preserved EF (HFpEF), a heterogeneous syndrome with different clinical characteristics and responses to therapeutic strategies compared with HFrEF.[7] The borderline population with LVEF between 40% and 50% have not been well represented in previous clinical trials and registries, and thus are a gray zone with scarce data requiring further characterization. Recently, the European Society of Cardiology (ESC) guideline defined this group as a distinct entity termed HF with mid-range EF (HFmrEF), with the intent of stimulating research into the characteristics and pathogenesis of, and effective therapies for, this group.[3]

The Korean Acute Heart Failure (KorAHF) registry is a nationwide prospective cohort of hospitalized AHF patients and has followed up 5,625 patients for at least 3 years after discharge. In this analysis, we performed a comprehensive comparison of the epidemiology, patterns of in-hospital management, and clinical outcomes with predictors in AHF patients with different LVEF categories.

Methods

Study Population and Data Collection

The rationale and detailed study design of the KorAHF registry have been presented in previous publications.[8,9] Briefly, the KorAHF registry is an ongoing, prospective nationwide multicenter cohort in Korea, which aims to describe the patient demographics, clinical characteristics, and outcomes of AHF. Patients hospitalized with signs or symptoms of AHF were consecutively enrolled from 10 representative university hospitals in Korea between March 2011 and February 2014. There were no specific exclusion criteria, but registration of the same patient from multiple institutions was screened and repeated data were merged to prevent duplication. Information about patient demographics, detailed medical history, symptoms and signs of HF, laboratory test results including electrocardiography and echocardiography, concurrent medications, hospital course, and clinical outcomes were collected at the index admission. Follow-up of the registered patients is planned until the end of 2018 with regular visits (at 1, 3, 6 and 12 months, then annually thereafter), and information about clinical outcomes and laboratory data are being collected.

Among the baseline characteristics, LVEF values were obtained by transthoracic echocardiography performed during the index hospitalization. Quantitative calculation using the modified Simpson's biplane method was recommended for LVEF measurement, but visually estimated

Table 1. Baseline Characteristics of Acute HF Patients According to Left Ventricular EF

	Total population (n=5,374)	HF category			P value
		HFrEF (n=3,140)	HFmrEF (n=880)	HFpEF (n=1,354)	
Demographics					
Age, years	68.4	66.2	70.8	72.0	<0.001
Male	53.4%	61.2%	48.1%	38.5%	<0.001
BMI, kg/m^2	23.3	23.1	23.4	23.7	<0.001
Current smoker	17.9%	21.6%	13.0%	12.3%	<0.001
Excessive alcohol use	6.8%	7.6%	5.7%	5.6%	<0.001
Comorbidities					
IHD	27.9%	30.0%	29.7%	21.9%	<0.001
Hypertension	59.1%	55.6%	63.5%	64.3%	<0.001
Diabetes mellitus	35.2%	37.3%	36.1%	29.8%	<0.001
AF	28.1%	23.4%	29.7%	37.7%	<0.001
Chronic kidney disease	14.1%	14.4%	16.1%	11.9%	0.013
Cerebrovascular disease	14.9%	14.3%	15.5%	15.8%	0.119
Chronic lung disease	11.3%	10.5%	11.0%	13.4%	0.010
Etiology of HF					
IHD	37.6%	42.4%	44.8%	21.7%	<0.001
Non-ischemic	62.4%	57.6%	55.2%	78.3%	
Cardiomyopathy	21.1%	30.5%	10.3%	6.4%	<0.001
Valvular heart disease	14.1%	7.1%	13.4%	30.7%	<0.001
Aortic stenosis#	26.9%	27.4%	21.1%	28.2%	0.306
Aortic regurgitation#	24.4%	34.1%	28.1%	18.1%	<0.001
Mitral stenosis#	20.8%	19.9%	25.4%	20.0%	0.415
Mitral regurgitation#	45.5%	41.2%	44.7%	48.1%	0.239
Tricuspid regurgitation#	31.5%	27.0%	27.2%	35.1%	0.061
Hypertension	4.0%	2.9%	4.3%	6.2%	<0.001
Tachycardia-induced (mainly AF)	10.6%	8.0%	14.6%	13.8%	<0.001

(**Table 1** continued the next page.)

	Total population (n=5,374)	HF category			P value
		HFrEF (n=3,140)	HFmrEF (n=880)	HFpEF (n=1,354)	
Initial presentation					
De novo HF	53.0%	51.3%	56.4%	54.8%	0.009
Admission via emergency department	75.5%	74.8%	78.8%	75.0%	0.047
Lung congestion	79.1%	78.9%	76.5%	81.0%	0.035
NYHA Fc III or IV	85.0%	86.9%	83.8%	81.4%	<0.001
Systolic BP, mmHg	131.4	128.0	137.1	135.6	<0.001
Diastolic BP, mmHg	78.8	79.3	79.4	77.2	0.002
Systolic BP <100 mmHg	11.9%	14.4%	9.0%	7.9%	<0.001
HR, beats/min	92.7	95.6	92.2	86.4	<0.001
HR >100 beats/min	36.3%	40.8%	35.4%	26.4%	<0.001
AF	34.7%	28.9%	39.3%	45.3%	<0.001
LBBB	5.3%	7.9%	2.7%	0.9%	<0.001
RBBB	6.9%	6.7%	5.4%	8.1%	0.044
Laboratory findings					
LVEF, %	37.8	26.6	44.3	59.4	<0.001
LVEDD, mm	57.4	61.8	53.9	49.6	<0.001
LVESD, mm	45.2	52.4	40.4	32.1	<0.001
LA dimension, mm	48.2	47.8	47.5	49.7	<0.001
WBC, /mcL	8,679.5	8,809.3	8,933.9	8,212.3	<0.001
Hemoglobin, g/dL	12.4	12.8	12.0	12.0	<0.001
Na, mmol/L	137.5	137.4	137.8	137.4	0.092
BUN, mg/dL	26.1	26.7	26.0	24.6	0.001
Creatinine, mg/dL	1.48	1.52	1.58	1.31	<0.001
Glucose, mg/dL	155.4	158.6	157.6	146.5	<0.001
BNP ≥500 pg/mL or NT-proBNP ≥1,000 pg/mL	83.2%	88.6%	82.0%	71.4%	<0.001
Concurrent medications					
ACE inhibitor	11.4%	13.7%	9.9%	7.1%	<0.001
ARB	27.7%	26.6%	29.1%	29.3%	0.109
β-blocker	28.1%	26.9%	29.6%	30.0%	0.064
Aldosterone antagonist	18.5%	19.8%	14.4%	18.1%	0.001

[#]n (%), among the patients with valvular heart disease as an etiology of HF. ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin-receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; EF, ejection fraction; HF, heart failure; HFmrEF, HF with mid-range ejection fraction; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; IHD, ischemic heart disease; LA, left atrium; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular endsystolic diameter; NT-proBNP, N-terminal pro-BNP; NYHA Fc, New York Heart Association functional class; RBBB, right bundle branch block; WBC, white blood cell.

LVEF, measured by specialist echocardiography cardiologists was also accepted as valid for HF categorization; visual LVEF estimation was used only if the biplane method might have been incorrect because of the poor echo window. There were 65 patients (total 1.2%) [36 HFrEF patients (1.1%), 19 HFmrEF patients (2.2%), 10 HFpEF patients (0.7%)] who had a visual estimation. According to the 2016 ESC HF guidelines, HFpEF was defined as LVEF ≥50% and HFrEF was defined as LVEF <40%. Patients with LVEF between 40–49% were considered to have HFmrEF.[3]

The main clinical outcomes of this study were death from any cause during the index hospitalization and during the minimum 3-year follow-up after discharge. For patients who survived to discharge but were lost to follow-up, the mortality data was collected from the National Insurance database or National Death Records of Korea. In-hospital deaths and the causes of death were adjudicated by an independent event committee. The definition of each category of death is described in Supplementary File 1. We also evaluated the relationship of LVEF with the in-hospital outcomes of AHF patients, including length of hospital stay, intensive care unit (ICU) admission, and need for urgent heart transplantation. The study protocol was approved by the ethics committee and local institutional review board of all participating centers.

Statistical Analysis

Descriptive statistics of categorical variables are presented as proportions (%) and continuous variables are presented as mean±standard deviation (SD). Comparisons of baseline demographic and clinical characteristics of the AHF patients in each LVEF category were made with chi-square test for proportions and one-way ANOVA test or Kruskal-Wallis test for continuous variables according to the distribution of variables. We used a Cox proportional hazard regression model to identify the predictors associated with the risk of all-cause death during the index hospitalization for AHF. We also included interaction terms for each independent variable and LVEF in the Cox proportional hazard regression model to compare coefficients for the effect of each independent variable on mortality according to the LVEF status. Variables included in the regression

Table 2. In-Hospital Management of Acute HF According to HF Category

	Total population (n=5,374)	HF category			P value
		HFrEF (n=3,140)	HFmrEF (n=880)	HFpEF (n=1,354)	
Drug prescription during hospitalization					
ACE inhibitor	39.2%	47.5%	34.9%	22.8%	<0.001
ARB	45.7%	45.3%	46.5%	46.0%	0.774
ACE inhibitor and/or ARB	77.0%	83.7%	73.8%	63.8%	<0.001
β-blocker	58.4%	62.0%	61.9%	47.9%	<0.001
Aldosterone antagonist	56.4%	61.4%	48.2%	50.0%	<0.001
IV diuretics	89.0%	89.2%	86.8%	90.1%	0.071
IV inotropes	36.8%	43.0%	29.6%	26.2%	<0.001
IV vasodilators	49.0%	46.3%	54.9%	51.9%	<0.001
Drug prescription at discharge					
ACE inhibitor	29.0%	35.4%	25.9%	16.3%	<0.001
ARB	38.2%	38.1%	39.2%	37.9%	0.804
ACE inhibitor and/or ARB	66.8%	73.0%	64.7%	53.6%	<0.001
β-blocker	50.5%	54.0%	54.9%	39.3%	<0.001
Aldosterone antagonist	45.5%	50.5%	39.6%	37.7%	<0.001

Abbreviations as in Table 1.

Table 3. In-Hospital Clinical Outcomes According to LVEF

	Total population (n=5,374)	HF categories			P value
		HFrEF (n=3,140)	HFmrEF (n=880)	HFpEF (n=1,354)	
Total mortality, n (%) (including urgent heart transplant)	297 (5.5%)	224 (7.1%)	32 (3.6%)	41 (3.0%)	<0.001
Mortality, n (%)	234 (4.4%)	161 (5.1%)	32 (3.6%)	41 (3.0%)	0.004
Urgent heart transplant, n (%)	69 (1.3%)	67 (2.1%)	0 (0.0%)	2 (0.1%)	<0.001
Hospital stay, median (IQR)	9 (6–15)	9 (7–16)	9 (6–14)	8 (6–14)	<0.001
ICU/CCU admission, n (%)	2,621 (48.8%)	1,585 (50.5%)	462 (52.5%)	574 (42.4%)	<0.001

CCU, coronary care unit; ICU, intensive care unit; IQR, interquartile range. Other abbreviations as in Table 1.

model were chosen as potential confounding factors on the basis of their significance in the univariate regression analysis or on the basis of their biological plausibility. To elucidate the different patterns of risk factors in each HF category, the associations were assessed separately in the HFpEF, HFmrEF, and HFrEF groups with the same baseline variables. Post-discharge survival was assessed using Kaplan-Meier estimates, and the association between EF category and crude all-cause death was compared using log-rank test. A two-sided P-value less than 0.05 was considered to statistically significant, and all statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.5.1 (The R Foundation of Statistical Computing, Vienna, Austria).

Results

Demographics and Clinical Characteristics

From March 2011 and February 2014, a total of 5,625 consecutive patients with AHF were enrolled in the KorAHF registry. Reliable LVEF data were not available for 251 patients (4.5%), and thus the main analysis was based on 5,374 patients with quantitative LVEF data. Of these, 3,140 (58.4%) were classified as having HFrEF, 880 (16.4%) as having HFmrEF, and 1,354 (25.2%) as having HFpEF. The overall distribution of LVEF in the study population is shown in **Figure S1**.

Baseline characteristics at the index admission stratified by the 3 HF types according to the LVEF are presented in **Table 1**. Patients with HFmrEF were older and more often female than patients with HFrEF; however, they were younger and more commonly of the male sex in comparison with those with HFpEF. The proportion of ischemic etiology of HF was similar in the HFrEF (42.4%) and HFmrEF (44.8%) groups and those were higher than the HFpEF (21.7%) group.

At initial presentation, there was a higher prevalence of de novo HF in the HFmrEF (56.4%) and HFpEF (54.8%) groups than in the HFrEF (51.3%) group. Objective pulmonary congestion was documented in a similar proportion of HFrEF (78.9%) and HFpEF (81.0%) patients, although patients with lower LVEF more frequently experienced dyspnea that was New York Heart Association class III or IV. Patients with HFrEF showed lower mean systolic blood pressure and higher mean heart rate at admission compared with patients with HFpEF. The predominant aggravating factor of AHF in HFrEF and HFmrEF was acute coronary syndrome (ACS), whereas tachyarrhythmia, including atrial fibrillation, was the most prevalent aggravating factor in HFpEF (**Figure S2**).

Comorbidities exhibited different patterns of prevalence in relation to LVEF. There was more hypertension in

Table 4. Predictors of In-Hospital Death in Acute HF Patients

	Total population (n=5,374)		HF categories						
			HFrEF (n=3,140)		HFmrEF (n=880)		HFpEF (n=1,354)		P interaction
	HR	P value	HR	P value	HR	P value	HR	P value	
Age (per year)	1.023 (1.011–1.035)	<0.001	1.027 (1.013–1.041)	<0.001	0.992 (0.962–1.022)	0.589	1.047 (0.994–1.057)	0.005	0.030
BMI (per unit)	1.013 (0.976–1.052)	0.494	1.006 (0.957–1.057)	0.825	1.185 (1.017–1.308)	<0.001	1.025 (0.911–1.090)	0.574	0.334
Hypertension	1.381 (1.006–1.895)	0.046	1.710 (1.163–2.516)	0.006	0.383 (0.148–0.991)	0.048	1.098 (0.364–1.714)	0.822	0.058
Diabetes mellitus	0.675 (0.501–0.908)	0.009	0.737 (0.518–1.047)	0.089	0.704 (0.268–1.851)	0.477	0.356 (0.136–0.884)	0.025	0.429
Systolic BP <100 mmHg	1.566 (1.143–2.146)	0.005	1.471 (0.999–2.164)	0.050	0.994 (0.360–2.742)	0.991	1.583 (0.702–3.570)	0.268	0.469
WBC ≥10,000 /mcL	1.883 (1.422–2.493)	<0.001	1.864 (1.316–2.640)	<0.001	1.506 (0.657–3.673)	0.333	2.464 (1.201–5.053)	0.014	0.640
Na^+ <135 mmol/L	1.356 (1.025–1.793)	0.033	1.055 (0.740–1.504)	0.089	1.577 (0.681–3.652)	0.288	1.623 (0.806–3.271)	0.175	0.535
ACE inhibitor or ARB	0.350 (0.266–0.460)	<0.001	0.292 (0.209–0.409)	<0.001	0.760 (0.317–1.820)	0.538	0.374 (0.186–0.752)	0.006	0.330
β-blocker	0.284 (0.208–0.389)	<0.001	0.278 (0.189–0.409)	<0.001	0.086 (0.031–0.240)	<0.001	0.350 (0.156–0.782)	0.011	0.353
Aldosterone antagonist	0.609 (0.460–0.806)	<0.001	0.467 (0.330–0.661)	<0.001	0.780 (0.329–1.850)	0.573	0.988 (0.498–1.961)	0.973	0.048
Ischemic etiology	1.780 (1.323–2.396)	<0.001	1.367 (0.957–1.955)	0.086	5.860 (1.838–18.679)	0.003	2.039 (0.873–4.767)	0.100	0.784

HR, hazard ratio. Other abbreviations as in Table 1.

HFpEF and HFmrEF patients than in those with HFrEF. Diabetes mellitus and chronic kidney disease was more frequent in HFrEF and HFmrEF patients, while chronic lung disease was more prevalent in HFpEF patients. Previous or new-onset atrial fibrillation was documented more frequently in HF patients with higher LVEF.

In-Hospital Management and Outcomes

Detailed pharmacologic treatments during hospitalization and at discharge are described in **Table 2**. During the index admission, 83.7%, 62.0%, and 61.4% of HFrEF patients were treated with angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin-receptor blockers (ARBs), β-blockers, or mineralocorticoid-receptor antagonists, respectively. Compared with HFrEF patients, the use of guideline-directed medical therapy (GDMT) for HF was lower among patients with HFmrEF and HFpEF, except for a similar rate of β-blocker prescription in HFmrEF patients. Parenteral inotropes and diuretics were most frequently used in HFrEF, whereas vasodilators were most frequently prescribed in HFmrEF.

Table 3 presents the in-hospital clinical outcomes for the 3 HF types. All-cause in-hospital death including urgent heart transplantation was 7.1% in patients with HFrEF, 3.6% in patients with HFmrEF, and 3.0% in patients with HFpEF. In the post hoc analysis, HFrEF patients showed a significantly higher mortality than HFmrEF or HFpEF patients (P<0.001), whereas deaths of patients with HFmrEF or HFpEF did not differ significantly. Urgent heart transplantation was performed in 69 cases, mostly for patients with HFrEF, 6 of whom died during the index hospitalization. Overall, the most frequent cause of death in AHF was pump failure (HF progression, 51.5%), followed by ACS (24.7%). However, the proportion of patients who died of pump failure was less dominant in HFmrEF and HFpEF, and non-cardiovascular etiology accounted for most deaths in these groups (26.7% and 32.5%, respectively). Among patients with HFmrEF, death from ACS accounted for 30% of in-hospital deaths, which was comparable with the effect of pump failure in this group (**Figure S3**).

Predictors of In-Hospital Mortality

We analyzed 19 variables based on either the univariate analysis or their biological significance. We also examined interactions between LVEF subgroups. There were no significant interactions for most of the 19 variables. Only age and the use of aldosterone antagonists showed significant interactions with in-hospital death according to LVEF status.

Patients in each of the EF categories showed different patterns of baseline prognostic markers or potential risk factors associated with in-hospital death. **Table 4** presents the statistically significant predictors (all variables are presented in **Table S1**). In HFrEF patients, leukocytosis at initial presentation was most strongly associated with in-hospital death with an odds ratio (OR) of 1.86 (95% confidence interval [CI] 1.32–2.64). Older age, history of hypertension and low systolic blood pressure were also independently associated with a worse outcome in HFrEF patients. History of diabetes mellitus and leukocytosis maintained prognostic value in HFpEF patients and body mass index (BMI) and history of hypertension show significant association with in-hospital death in HFmrEF. Separately, ischemic etiology of HF was a strong predictive of in-hospital death in HFmrEF patients (OR 5.86, 95% CI 1.84–18.68).

We also included the prescription of GDMT during hospitalization in the multivariable regression model. As expected, the administration of ACE inhibitors and/or ARBs, β-blockers, and mineralocorticoid-receptor antago-

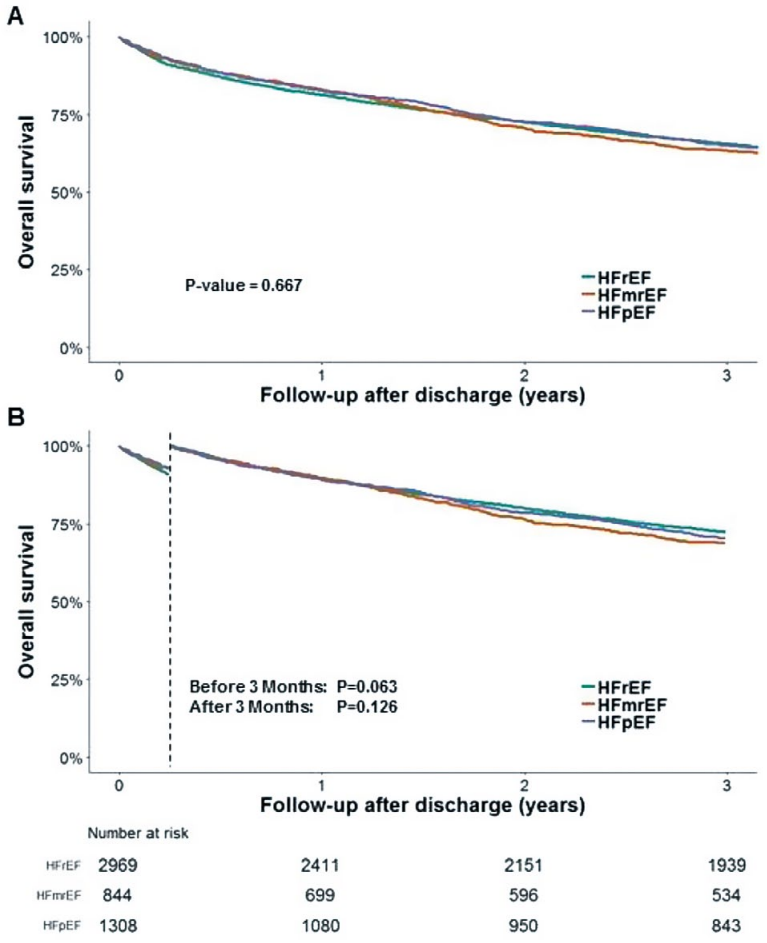

Figure 1. Overall survival of patients with acute heart failure and reduced (HFrEF), mid-range (HFmrEF), and preserved ejection fraction (HFpEF). Kaplan-Meier curves for (**A**) overall survival after discharge from index hospitalization and (**B**) stratified by cumulative survival on the basis of a landmark point at 3 months after discharge. The P values were calculated by means of the log-rank test on the basis of all available follow-up data.

nists significantly improved outcomes of AHF in HFrEF patients. However, these GDMTs for HFrEF did not influence the in-hospital mortality rate in other categories of HF patients, except for β-blockers, which were associated with lower in-hospital mortality in HFmrEF patients after multivariable adjustment.

Follow-up Mortality Rate at 3 Years

Of the initial 5,374 patients who were hospitalized with AHF, 5,140 (95.6%) survived to discharge. There were 20 subjects who were lost to follow-up, and the 3-year follow-up rate for mortality after discharge was 99.6%. Overall, 1,786 patients (34.7%) died during the 3-year follow-up period, resulting in a cumulative all-cause mortality, including death during index hospitalization, rate of 37.6% at 3 years. **Figure 1** presents the 3-year post-discharge all-cause mortality among the patients who survived the index hospitalization. Overall, all-cause mortality was not significantly different among the 3 different HF categories (**Figure 1A**). The Kaplan-Meier curves showed relatively high risk of death within the first 3 months after discharge, and overall the 3-month all-cause mortality among the 3 groups showed marginal significance (P=0.063). A landmark analysis demonstrated significantly higher 3-month all-cause mortality in HFrEF patients than HFpEF patients (P=0.032), whereas the incidence of all-cause death in HFmrEF patients did not differ significantly from that in patients with HFrEF (P=0.061) or HFpEF (P=0.930) during this period (**Figure 1B**). However, long-term follow-up over 3 years obscured these differences in short-term all-cause death among the HF categories. In addition, comparison of the long-term survival assessed from the day of the index admission consistently demonstrated comparable outcome of AHF patients with different LVEF categories (**Figure S4**).

There were significant differences in the incidence and pattern of all-cause death according to the etiology of HF. Overall, the all-cause post-discharge mortality rate was 39.4% in patients with ischemic HF and 30.1% in patients with non-ischemic HF (P<0.001) during the 3-year follow-up period. Among patients with ischemic HF, lower LVEF was associated with worse outcome, and 3-year all-cause mortality in the HFrEF, HFmrEF, and HFpEF groups was 41.8%, 35.1%, and 33.8%, respectively (**Figure 2A**). Pairwise comparison showed significant differences in mortality between patients with HFrEF and patients with HFpEF (P<0.001) or HFmrEF (P=0.025). HFrEF patients had a significant lower mortality rate than patients with HFpEF (P<0.001) or HFmrEF (P=0.001) in the non-ischemic HF group (**Figure 2B**). The mortality rates of HFpEF and HFmrEF did not differ significantly, regardless of the etiology of HF.

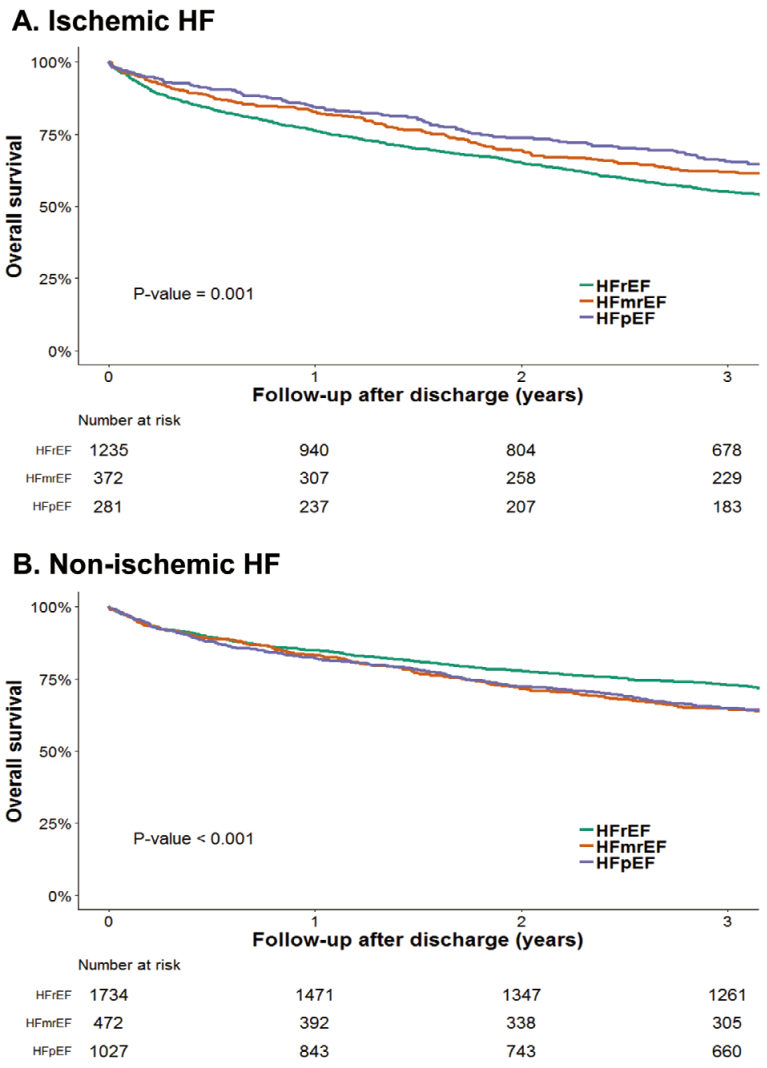

Figure 2. Overall survival of patients with acute heart failure and reduced (HFrEF), mid-range (HFmrEF), and preserved ejection fraction (HFpEF), according to the etiology of HF. Kaplan-Meier curves for overall survival of acute heart failure patients with (**A**) ischemic etiology and (**B**) non-ischemic etiology after discharge from index hospitalization. The P values were calculated separately for events that occurred within 3 months and those that occurred between 3 months and the end of follow-up at 3 years, by means of the log-rank test.

Predictors of Death at 3 Months and 3 Years After Discharge

In addition to predictors of in-hospital death, we investigated predictors of long-term outcomes. Predictors of death at 3 months after discharge in patients with AHF are shown in **Table S2**. Among these variables, age and low systolic blood pressure were independently associated with death at 3 months after discharge regardless of the strata of LVEF. An inverse association between BMI and death at 3 months was found in patients with HFrEF and HFpEF, and leukocytosis showed worse outcomes. In addition, male sex, chronic lung disease, anemia, hyponatremia, and renal failure were predictors of worse outcomes in patients with HFrEF. History of cerebrovascular disease and elevated B-type natriuretic peptide (BNP) or NT-proBNP in HFpEF patients and hyponatremia and renal failure in HFmrEF patients were significantly associated with worse outcomes. Among the GDMT prescribed during admission, only ACE inhibitors or ARBs in patients with HFrEF showed improved outcome.

Among predictors of death at 3 years after discharge in patients with AHF, male sex, age, BMI, anemia, hyponatremia, and elevated BNP or NT-proBNP were significantly associated with death in all 3 groups (**Table S3**). Additionally, a history of cerebrovascular, chronic lung disease, and renal failure were also predictive variables in patients with HFrEF.

Renal failure in patients with HFmrEF and a history of cerebrovascular disease, and leukocytosis in patients with HFpEF were also factors associated with 3-year mortality.

ACE inhibitors or ARBs, and β-blockers showed long-term protective effects in patients with HFrEF. Interestingly, use of ACE inhibitors or ARB during admission showed protective effects in patients with HFpEF in this study.

Discussion

The KorAHF registry provides comprehensive information on the clinical characteristics of AHF patients requiring hospitalization, and revealed heterogeneity of AHF within different categories of LVEF. We classified patients with AHF by LVEF according to contemporary ESC guidelines and demonstrated diverse demographics and clinical characteristics of 3 groups in a real-world database, as well

as different patterns of clinical practice and treatment response.

In-Hospital Prognosis of AHF With Different LVEF Categories

In the current study, AHF patients with lower LVEF more frequently presented with worse initial hemodynamics. Although the proportion of patients who had pulmonary congestion was not significantly different among the LVEF groups, patients with HFrEF were more likely to be hypotensive and have increased heart rate, as well as worse functional capacity at initial presentation compared with HFpEF patients. The worse initial hemodynamics were reflected in the poor short-term outcomes, and AHF patients with lower LVEF showed incremental crude in-hospital mortality rates during the index hospitalization. Apart from death, HFrEF was associated with longer hospital stay, higher probability of admission to critical care units, and more need for urgent heart transplantation during the index hospitalization compared with HFpEF. Initial hemodynamic profiles and in-hospital outcomes of the HFmrEF patients were intermediate between the 2 other LVEF groups. Studies based on observational registries of AHF report worse in-hospital outcomes of HFrEF compared with HFpEF.[10,11] However, evidence regarding the comparative short-term outcomes of LVEF categories including HFmrEF in the AHF setting is limited. In the ASCEND-HF trial, AHF patients in each LVEF category, including HFmrEF, exhibited similar in-hospital and 30-day mortality rates in crude and age- and sex-matched analyses.[12] However, it should be appreciated that data from controlled clinical trials may not reflect phenotype and outcome of HF in real-world practice. High-risk populations including subjects with persistent hypotension or ACS were excluded from ASCEND-HF,[13] and the overall crude in-hospital mortality rate in ASCEND-HF (≈2%) was considerably lower compared with data from other AHF registries, as well as KorAHF.[10,11,14]

Considering the therapeutic aspect, the prescription of GDMT involving neurohormonal blocking agents was associated with improved all-cause in-hospital mortality of HFrEF patients but was not beneficial for HFpEF patients. Among the neurohormonal blocking agents, angiotensin antagonists (ACE inhibitors or ARBs) and mineralocorticoid-receptor antagonists did not reduce the mortality rate of HFmrEF patients. However, use of β-blockers was associated with lower in-hospital mortality in these patients after multivariable adjustment. The proportion of AHF with ischemic cause among HFmrEF patients was the largest, which was as high as that seen in patients with HFrEF (44.8%). Additionally, in the HFmrEF group, the ratio of ACS and sudden cardiac death was higher in comparison with the other 2 groups. Therefore, the use of β-blockers is considered to have a protective effect in HFmrEF patients. In contrast to previous randomized trials of angiotensin antagonists or mineralocorticoid-receptor antagonists, which did not show beneficial effects of these treatments on the endpoints of death or hospitalization in HFpEF patients,[15,16] trials of β-blockers in the treatment of HFpEF report conflicting results.[17,18] Consequently, conclusive evidence on the clinical efficacy of β-blockers in HFpEF is currently lacking, and use of β-blockers in HFpEF is limited to patients with alternative indications. Our data provided additional real-world evidence to support clinical decision making in HF treatment, by reducing heterogeneity with respect to LVEF criteria. Nevertheless, there is a need for well-founded evidence regarding the efficacy of HF treatments, including neurohormonal blocking agents, in patients with HFmrEF or HFpEF, and this remains to be addressed by future clinical trials.

Etiology of AHF and Implications for Outcomes: Ischemic vs. Non-Ischemic

Myocardial ischemia is a major component of cardiac remodeling, which leads to structural and functional abnormalities and HF.[19] It is well established that ischemic and non-ischemic HF represent distinct disease categories with different pathophysiology and clinical outcomes.[20,21] However, the effect of etiology on short-term clinical outcomes among different LVEF categories in the setting of AHF is not well established. In the KorAHF registry data, myocardial ischemia was the leading cause of AHF aggravation, and was also identified as one of the significant predictive risk factors for all-cause in-hospital death. However, the clinical implications for AHF outcome showed a clear distinction between patients with different LVEF categories. Among patients with HFmrEF, an ischemic etiology of HF was the strongest risk factor for in-hospital death with an OR of 5.86 (95% CI 1.84–18.68; P=0.003), whereas most of the other demographic profiles did not effectively predict short-term outcome of HFmrEF in the AHF setting. In addition, in-hospital death associated with ACS was the predominant cause of death in this group. Conversely, the etiology of HF was not significantly associated with the in-hospital outcome of HFrEF or HFpEF patients. Together with the demographic results, which showed abundantly the importance of ischemic heart disease as an etiologic and aggravating factor of HFmrEF, our data highlighted ischemic heart disease as a key component of the pathogenesis and prognosis in AHF with mid-range LVEF.

In our analysis, worse short-term mortality of AHF patients with reduced LVEF did not extend to long-term outcome, and long-term all-cause mortality at 3 years was similar across all LVEF strata. This result is concordant with data from previous studies that evaluated post-discharge outcomes of the patients hospitalized for AHF,[10,22] and mitigates the paucity of data with separate analysis of the mid-range LVEF group according to 2016 ESC guidelines. However, significant interactions were observed between LVEF and HF etiology in the long-term outcomes, and reduced LVEF was associated with higher long-term mortality among patients with ischemic HF, whereas non-ischemic AHF patients with different LVEF showed comparable long-term mortality. Among patients with HFrEF, ischemic etiology of HF was associated with higher long-term mortality than non-ischemic etiology (**Figure S5A**). In contrast, among patients with HFmrEF and HFpEF, the etiology of HF did not affect long-term mortality (**Figure S5B**,**C**). Taken together, compared with the other subgroups of AHF patients, patients with reduced EF and ischemic etiology showed the worst long-term prognosis, while patients with reduced EF and non-ischemic etiology had relatively favorable outcomes.

Previous Studies: Similarities and Differences

In the current study, patients with HFmrEF were older and more likely female compared with the patients with HFrEF; however, they were younger and more likely to be of the male sex compared with those with HFpEF. These

trends are similar to those reported in other studies of patients with chronic HF (CHF).[23–26] In addition, the trends in the etiology of AHF were similar to those reported in other studies. In HFmrEF patients with AHF or CHF, myocardial ischemia was the leading cause of HF.[24,26,27] In our study, 44.8% of AHF in the HFmrEF group had an ischemic etiology and the proportion of ischemic etiology in the CHARM trial and CHART-2 study for patients with CHF was 66.9% and 52.9%, respectively, and was the most common cause in HFmrEF.[26,28] In all 3 studies, the proportion of ischemic etiology was higher for HFmrEF than for HFrEF and HFpEF. Moreover, in our study, ischemic etiology was the strongest predictor of in-hospital death and β-blockers had a protective effect on the in-hospital outcome, which is consistent with the results from the CHART-2 study.[26] These findings suggested that ischemic etiology is not only an important etiologic factor, but also a strong predictor of death in patients with HFmrEF with either AHF or CHF.

Although candesartan improved outcomes in HFmrEF patients with CHF in a subanalysis of the CHARM trial,[28] ACE inhibitor and/or ARB did not improve outcomes of AHF patients with HFmrEF in our study. Therefore further studies on the effects of ACE inhibitors and/or ARBs in AHF patients with HFmrEF are needed.

The predictors of 3-month post-discharge death in patients with AHF were influenced by variables that indicated the severity or condition at the time of hospitalization, such as low systolic blood pressure, leukocytosis, hyponatremia, and renal failure, regardless of LVEF. However, in the long-term follow-up, well-known risk predictors and comorbidities, such as male sex, age, BMI, anemia, and chronic kidney disease, influenced mortality in patients with AHF. These results are similar to those of studies involving patients with CHF. According to the study by Chioncel et al,[23] age, male sex and chronic kidney disease were predictors of death at 1-year follow-up in patients with CHF. In our study, higher BMI showed a protective effect in patients with AHF, a phenomenon known as the obesity paradox.[23,29]

Study Limitations

The results of the present study should be interpreted in the context of several limitations. First, because our study was based on observational data from the KorAHF registry, we could not establish causality between baseline characteristics or in-hospital treatments with clinical outcomes in our analysis. Second, laboratory and echocardiographic variables, including LVEF, were based on a single measurement during the acute stage of hospitalization. Systemic follow-up evaluation for LVEF was not performed, and patients' characteristics and outcomes associated with serial changes in LV function could not be assessed. Third, we included 65 patients whose EF were obtained by visual estimation because of a poor echo window. However, when we excluded the 65 patients and re-analyzed the data, the results were unchanged. Lastly, GDMT prescription during the index admission was not controlled, and the type, dose, and duration of each GDMT category were heterogeneous.

Conclusions

The present analysis of data from the KorAHF registry demonstrated substantial differences in the epidemiology, short- and long-term outcomes and prognostic value of clinical parameters among hospitalized AHF patients within different LVEF subgroups. Patients with HFrEF had worse initial hemodynamic profiles and experienced higher in-hospital mortality rates, predominantly from pump failure, whereas patients with HFpEF had better in-hospital outcomes with an increased proportion of non-cardiovascular causes of death. Regardless of LVEF strata, AHF was associated with poor long-term prognosis, and, notably, ischemic etiology had a significant detrimental effect on 3-year mortality in the HFrEF subgroup only.

The profiles of HF with preserved and reduced LVEF are relatively well established, but the characteristics and outcomes of HF with mid-range EF remain elusive. In the KorAHF registry, AHF patients with mid-range LVEF showed intermediate epidemiological profiles between HFrEF and HFpEF and tended to present as de novo HF with ischemic etiology. Ischemic etiology was associated with higher in-hospital mortality among patients with HFmrEF, whereas the long-term outcome was not affected by etiology in this subgroup.

These findings indicated that the clinical outcomes of AHF are influenced by multiple factors beyond LVEF and emphasized focused phenotyping of each patient to tailor the management strategy and develop novel effective therapies of AHF.

Conflict of Interest Statement

All authors declare they have no conflicts of interest relevant to the submitted work.

Funding

This work was supported by grants from Research of Korea Centers for Disease Control and Prevention (2010-E63003-00, 2011-E63002-00, 2012-E63005-00, 2013-E63003-00, 2014-E63003-01, 2015-E63003-02, 2016-ER6303-00, and 2017-ER6303-01). The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Supplementary Files

Supplementary File 1

Supplementary Methods

Table S1. Predictors of in-hospital mortality in acute heart failure

Table S2. Predictors of three months after discharge mortality in acute heart failure

Table S3. Predictors of three years after discharge mortality in acute heart failure

Figure S1. Distribution of left ventricular ejection fraction in the study population.

Figure S2. Distribution of the aggravating factors of acute heart failure in patients with acute heart failure and reduced, mid-range, and preserved ejection fraction.

Figure S3. Mechanism of in-hospital mortality in patients with acute heart failure and reduced, mid-range, and preserved ejection fraction.

Figure S4. Kaplan-Meier plots for overall survival of patients with acute heart failure and reduced, mid-range, and preserved ejection fraction from the day of index hospitalization.

Figure S5. Kaplan-Meier plots for post-discharge overall survival of patients with acute heart failure and reduced, mid-range, and preserved ejection fraction.

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-18-0543