Clinical Investigation

Heart Failure With Midrange Ejection Fraction in Patients Admitted for Acute Decompensation: A Report from the Japanese Multicenter Registry

MAKOTO TAKEI, MD,[1,2] SHUN KOHSAKA, MD,[1] YASUYUKI SHIRAISHI, MD,[1] AYUMI GODA, MD,[3] YUJI NAGATOMO, MD,[4] ATSUSHI MIZUNO, MD,[5] YASUMORI SUZINO, MD,[6] TAKASHI KOHNO, MD,[1] KEIICHI FUKUDA, MD,[1] AND TSUTOMU YOSHIKAWA, MD[7]

ABSTRACT

Background: Patients having heart failure with midrange ejection fraction (HFmrEF: 40% ≤ EF < 50%) are increasingly being considered a new subset of the population with heart failure. Despite recent advances in heart-failure treatment strategies, the prognosis of these patients has not improved substantially over time. In addition, the significance of this new phenotype in hospitalized patients with acute decompensated heart failure (ADHF), another population whose prognosis has not improved, also remains poorly understood. This study aimed to describe the clinical characteristics, prognosis and treatment responses of patients with HFmrEF hospitalized for ADHF.

Methods: On the basis of consecutive inpatient data from a multicenter ADHF registry, 651 of 3572 patients (17.1%) were classified as having HFmrEF. Prognostic factors predicting composite outcomes, defined as all-cause death and heart failure readmission, as well as all-cause death alone, were analyzed.

Results: In the median follow-up duration of 724 days, both composite endpoints and all-cause death alone were comparable in those with heart failure with preserved ejection fraction, HFmrEF and heart failure with reduced ejection fraction. Age, anemia, hyponatremia, elevated blood urea nitrogen, chronic kidney disease, and elevated plasma brain natriuretic peptide levels were significant predictors of composite outcomes in HFmrEF.

Conclusions: Roughly one-sixth of the patients with ADHF had HFmrEF. The long-term prognosis of patients with HFmrEF was not significantly different from that of patients with heart failure with preserved ejection fraction and heart failure with reduced ejection fraction in the population with ADHF. Risk factors for adverse outcomes in HFmrEF were also similar to those for heart failure with preserved ejection fraction and HFmrEF in the hospitalized population with ADHF. (*J Cardiac Fail 2019;25:666–673*)

Key Words: Heart failure with midrange ejection fraction, acute decompensated heart failure, East Asian.

From the [1]Department of Cardiology, Keio University School of Medicine, Tokyo, Japan; [2]Department of Cardiology, Saiseikai Central Hospital, Tokyo, Japan; [3]Department of Cardiology, Kyorin University School of Medicine, Tokyo, Japan; [4]Department of Cardiology, National Defense Medical College, Saitama, Japan; [5]Department of Cardiology, St. Luke's International Hospital, Tokyo, Japan; [6]Department of Cardiology, Saitama Medical University, International Medical Center, Saitama, Japan and [7]Department of Cardiology, Sakakibara Heart Institute, Tokyo, Japan.

Manuscript received January 31, 2019; revised manuscript received April 24, 2019; revised manuscript accepted May 16, 2019.

Reprint requests: Shun Kohsaka, MD, Department of Cardiology, Keio University School of Medicine, Shinanomachi 35, Shinjuku-ku, Tokyo, 160-8582, Japan, Tel.: +81 3 5363 3373; Fax: +81 3 5363 3875. E-mail: makoto_tk@hotmail.com

Funding: This work was supported by the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT) KAKENHI, grant number 26461088; a grant from the Japan Agency for Medical Research and Development (201439013C; S.K.); a Grant-in-Aid for Scientific Research (JPSS KAKENHI, 23591062, 26461088; T.Y.); a Grant-in-Aid for Young Scientists (JPSS KAKENHI, 18K15860 [Y.S.]); a Health Labour Sciences Research Grant (14528506; S. K.); and a Sakakibara Clinical Research Grant for Promotion of Sciences, 2012, 2013, 2014 (T.Y.); a Grant-in-Aid for Scientific Research (23591062, 26461088 [T.Y.] 17K09526 [T.K.]).

See page 673 for disclosure information.

1071-9164/$ - see front matter

https://doi.org/10.1016/j.cardfail.2019.05.010

Introduction

The treatment strategy and prognosis for patients having heart failure with reduced ejection fraction (HFrEF), defined as a left ventricular ejection fraction (LVEF) < 40%, have markedly improved over the past 2 decades.[1] However, there remain issues to overcome in the treatment of heart failure. One such issue is that despite recent advances in treatment strategies for heart failure overall, the prognosis of patients with LVEF > 40% has not improved significantly over the same time period. To elucidate the problem, the European Society of Cardiology announced a new classification for patients with LVEF > 40%—heart failure with preserved EF (HFpEF) (LVEF over 50%) and heart failure with midrange ejection fraction (HFmrEF) (LVEF between 40% and 49%).[1] This classification has revealed the differing clinical characteristics of HFmrEF compared to HFpEF and HFrEF. Furthermore, in contrast to the improved prognosis of HFrEF patients with stable chronic conditions, the prognosis of patients who required hospitalization for acute decompensated heart failure (ADHF) remains unclear, and its economic burden is reported to account more than half of the total costs of heart failure worldwide.[2–4]

Herein, our objective was to describe the clinical characteristics, prognosis and response to treatments in patients with HFmrEF who required hospitalization for ADHF.

Methods

Study Design

Patient data were collected from the West Tokyo Heart Failure Registry (WET-HF). This registry is a multicenter, prospective registry that includes data about consecutive patients requiring hospitalization for ADHF from 5 high-volume hospital centers within the Tokyo metropolitan area (3 university hospitals and 2 tertiary referral community hospitals during this study period). ADHF was defined according to the Framingham acute heart failure criteria.[5] Exclusion criteria were refusal to participate in the study or presence of acute coronary syndrome at the initial presentation. For the present study, patients registered between January 2006 and March 2017 were analyzed. The patients were followed-up for a median duration of 724 days. The investigation conforms with the principles outlined in the Declaration of Helsinki and was approved by each center's ethics review committee. Informed consent was not required for this study; however, all patients had the opportunity to receive information regarding the study and to show their refusal to participate in the study.

Eligibility Criteria

For the present analysis, data from 3634 consecutive patients enrolled in the West Tokyo Heart Failure Registry from January 1, 2006, to March 31, 2017, were analyzed. For the analysis of the background characteristics in each LVEF stratum, those with LVEFs recorded via echocardiography during hospitalization were included (N = 3572). For the survival analysis, we excluded patients with in-hospital death (n = 117) and those lacking long-term follow-up data, including readmission because of heart failure and all-cause death (n = 503). As a result, 2952 patients were included in the survival analysis (Fig. 1). Patients were divided into HFpEF (LVEF ≥ 50%), HFmrEF (50% > LVEF ≥ 40%) and HFrEF (40% > LVEF) according to the guideline of the European Society of Cardiology.[1]

Data Collection

Data were collected at the time of enrollment, using a web-based form. Age, sex, comorbidities, body mass index, HF etiology, length of stay, and laboratory data were collected. Drugs prescribed at discharge and the New York Heart Association functional classification at admission were also included.

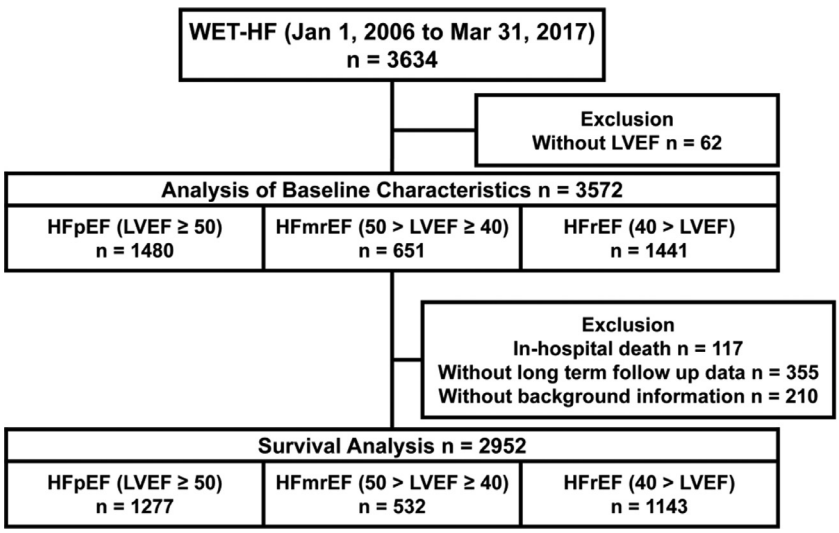

Fig. 1. Study outline.

Table 1. Baseline Clinical Characteristics, Treatment During Hospitalization and In-hospital Mortality in HFpEF, HFrEF and HFmrEF

	All (N = 3572)	HFpEF (n = 1480)	HFrEF (n = 1441)	HFmrEF (n = 651)	Missing Value
Patient characteristics					
Age, years	74.4 ± 13.3	77.8 ± 11.4	70.9 ± 14.3	74.7 ± 13.0	0
Sex, female %	40.3	52.6	28.8	37.5	0
BMI, kg/m^2	23.3 ± 4.6	23.4 ± 4.6	23.3 ± 4.6	23.1 ± 4.2	292 (8.2%)
Medical history					
Coronary artery disease, %	28.8	16.3	37.2	38.8	4 (0.1%)
Hypertension, %	67.2	67.9	64.2	72.1	19 (0.5%)
Diabetes mellitus, %	34.9	30.9	38.6	35.7	4 (0.1%)
Dyslipidemia, %	39.4	36.1	42.2	41.0	32 (0.9%)
COPD, %	5.3	6.0	4.9	4.5	20 (0.6%)
Smoking history, %	42.2	37.8	47.3	41.3	89 (2.5%)
Atrial fibrillation, %	48.0	56.7	40.4	45.1	10 (0.3%)
Dialysis, %	3.4	3.4	3.5	3.2	5 (0.1%)
CVD, %	13.9	14.1	14.7	11.7	14 (0.4%)
Laboratory data at admission					
Hb, mg/dL	12.0 ± 2.4	11.3 ± 3.2	12.7 ± 2.3	11.9 ± 2.4	6 (0.2%)
Na, mEq/L	139.2 ± 4.3	139.2 ± 4.2	138.9 ± 4.4	139.5 ± 4.1	7 (0.2%)
BUN, mg/dL	26.9 ± 16.0	26.1 ± 14.9	27.5 ± 16.3	27.6 ± 16.3	13 (0.4%)
BNP, pg/mL	622 (323−1219)	431 (234−804)	883 (485−1554)	709 (371−1318)	117 (3.3%)
Cr, mg/dL	1.03 (0.80−1.46)	0.96 (0.73−1.39)	1.1 (0.86−1.51)	1.08 (0.80−1.49)	6 (0.2%)
LVEF, %	44.5 ± 15.5	60.1 ± 6.4	28.5 ± 6.9	44.3 ± 2.8	0 (0%)
Medications at admission					
ACEI, %	12.2	9.9	15.3	10.4	31 (0.9%)
ARB, %	31.9	35.0	27.5	34.6	32 (0.9%)
β-blocker, %	43.2	41.9	45.8	40.6	36 (1.0%)
MRA, %	16.9	13.6	21.7	14.1	162 (4.5%)
Loop diuretics, %	44.5	43.2	48.0	39.7	30 (0.8%)
Medications at discharge (n = 3445)					
ACEI, %	28.9	20.8	38.9	25.6	4 (0.1%)
ARB, %	35.8	38.8	31.2	39.0	2 (0.1%)
β-blocker, %	76.4	64.7	86.8	80.1	2 (0.1%)
MRA, %	36.6	27.5	48.1	32.1	6 (0.2%)
Loop diuretics, %	74.8	73.2	78.3	70.9	3 (0.1%)
Treatment during hospitalization					
Median hospital stay, days	15 (10−24)	14 (9−22)	16 (11−26)	15 (10−23)	0 (0%)
Intravenous loop diuretics, %	67.6	67.0	67.0	70.0	139 (3.9%)
Intravenous nitrates, %	27.5	27.1	25.8	32.4	10 (0.3%)
Intravenous hANP, %	48.5	44.6	53.4	46.1	14 (0.4%)
Intravenous catecholamine, %	14.7	9.9	20.8	12.4	132 (3.7%)
In-hospital mortality, %	3.6	2.9	4.4	3.6	0 (0%)

ACEI, angiotensin converting enzyme inhibitor; ARB, aldosterone receptor blockade;BMI, body mass index; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; Cr, creatinine; CVD, cerebrovascular disease; hANP, human atrial natriuretic peptide; Hb, hemoglobin concentration; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; Na, serum sodium concentration.

Note: Values are expressed as mean ± SD, median (25th percentile value to 75th percentile value) for continuous variables, according to their distributions, and as percentages for categorical variables.

Within the first 48 hours of admission, blood samples were obtained to measure laboratory variables, including brain natriuretic peptide (BNP) levels. Given that some patients (n = 1716) had data concerning only N-terminal pro-brain natriuretic peptide, we used the formula to convert that value to the value of BNP.[6] The estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease equation. Chronic kidney disease was defined as an estimated glomerular filtration rate < 60 mL/min/1.73 m^2.

Endpoints

The primary endpoint was a composite of all-cause death and readmission due to worsening HF, and the secondary endpoint was all-cause death alone. Follow-up data were obtained from the hospital records or by contacting patients or referring physicians through mail or telephone. Cardiac mortality was defined as death due to a cardiac disease and sudden death without apparent cause. The study committee judged each clinical endpoint and cause of death.

Statistical Analysis

Continuous variables were represented as either mean ± standard deviations or median, 25th and 75th percentiles, according to their distribution. Categorical variables were represented as percentages. The clinical characteristics of HFpEF, HFmrEF and HFrEF were compared using the Student t, the Pearson χ^2, and the Mann-Whitney U tests, as appropriate. A univariable Cox proportional hazard analysis was performed to examine the association between the clinical characteristics and both composite endpoints, including heart failure readmission and all-cause death, and all-cause death alone, in each LVEF stratum. A multivariable Cox

proportional hazard analysis was also conducted using the variables significantly associated with composite endpoints or all-cause death ($P < 0.05$) in each cohort. For the survival analysis, we defined anemia as a hemoglobin concentration < 10 g/dL and hyponatremia as a serum sodium level < 135 mEq/L. Statistical power analysis was conducted for the survival analysis by assuming the event rate of 0.4 for composite outcomes and 0.3 for all-cause mortality. We defined the significant difference in these outcomes as a 30% decrease or increase in events. All statistical analyses were performed using SPSS v 24 (IBM, Armonk, New York). A P value of < 0.05 was considered statistically significant. Missing values are summarized in Table 1.

Results

Patients′ Characteristics

Patients' background characteristics are shown in Table 1. A total of 17.6% of patients were categorized as HFmrEF (n = 651). The characteristics of patients with HFmrEF were largely intermediate between those of patients with HFpEF and HFrEF in age, sex and prevalence of coronary artery disease (CAD). Regarding the laboratory data, hemoglobin and BNP concentrations were intermediate between those of patients with HFpEF and HFrEF. More than 80% of patients with HFmrEF were prescribed β-blockers at discharge, a rate that was comparable to that for patients with HFrEF.

Predictors for Composite Outcomes

Within the median follow-up period of 724 days, the incidences of composite outcomes (readmission due to heart failure and all-cause mortality) and all-cause mortality were not significantly different for HFpEF, HFrEF and HFmrEF (Fig. 2). In HFmrEF, age, anemia, hyponatremia, elevated blood urea nitrogen (BUN), CKD, and elevated plasm BNP levels were significant predictors of composite outcomes. These classic risk factors were also associated with composite outcomes both in HFpEF and HFrEF. Regarding medications, β-blockers and renin-angiotensin-aldosterone system inhibitors (RASIs) were protective against composite outcomes in HFrEF. In addition, the use of RASIs in HFpEF was also associated with better prognosis in this cohort (Table 2). These associations remained significant after multivariable adjustments. In HFmrEF, age (HR = 1.02, 95% CI 1.01−1.04 for every year, $P < 0.001$) and elevated BUN (HR = 1.02, 95% CI 1.01−1.02 for every 1 mg/dL unit increment, $P < 0.001$) remained significant predictors for composite endpoints after multivariable adjustments with these predictors. The use of β-blockers and RASIs was not associated with better outcomes in HFmrEF (Table 3).

Predictors of All-cause Death

Predictors of all-cause death in HFmrEF were similar to those for composite outcomes, except that the use of RASIs was protective against all-cause death in the univariate analysis (Table 4). After the multivariable analysis of these predictors, age (HR = 1.04, 95% CI 1.02−1.06 for every 1 year, $P < 0.001$); hyponatremia (HR = 2.20, 95% CI 2.41−3.42, $P < 0.001$); elevated BUN (HR = 1.01, 95% CI 1.01−1.02 for every 1 mg/dL unit increment, $P = 0.002$); and elevated BNP (HR = 1.01, 95% CI 1.00−1.01 for every 1 pg/dL unit increment, $P = 0.03$) remained significant in HFmrEF. Regarding HFpEF and HFrEF, age, hyponatremia, elevation of BUN, elevation of BNP, and use of RASIs in HFpEF, as well as age, history of CAD, anemia, CKD, use of β-blockers, and elevation of BUN in HFrEF remained significant after multivariable adjustments (Table 5). Although all-cause mortality did not differ significantly between each LVEF stratum, among these mortality events, the proportion of cardiac death was the highest in those with HFrEF (69 cardiac deaths in 271 total deaths; 74.5%) and the lowest in HFpEF (128 cardiac deaths in 287 total deaths; 55.4%). The proportion of cardiac deaths in

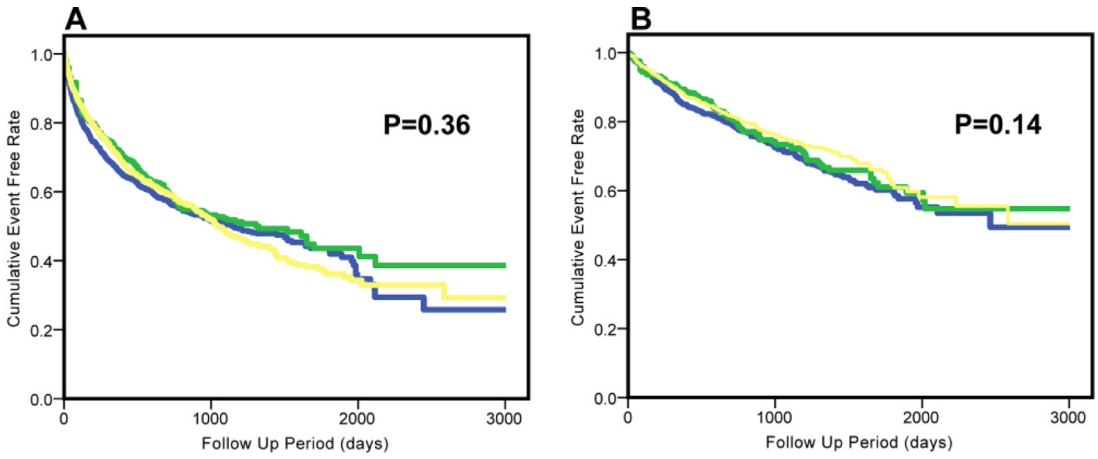

Fig. 2. Kaplan-Meier curves for survival analysis. (A) Composite endpoints, including both heart failure readmission and all-cause mortality. (B) All-cause mortality. Blue line, HFrEF; green line, HFmrEF; yellow line, HFpEF.

Table 2. Predictors for Composite Outcomes in HFpEF, HFrEF and HFmrEF (Univariate Analysis)

	HFpEF		HFrEF		HFmrEF	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age	1.03 (1.02−1.04)	<0.001	1.04 (1.03−1.05)	<0.001	1.02 (1.01−1.04)	<0.001
Coronary artery disease	1.00 (0.80−1.25)	1.00	1.65 (1.39−1.96)	<0.001	1.24 (0.95−1.61)	0.12
Hypertension	0.93 (0.78−1.11)	0.42	0.92 (0.77−1.10)	0.38	1.12 (0.83−1.51)	0.47
Diabetes mellitus	0.89 (0.74−1.07)	0.21	1.30 (1.09−1.55)	0.003	1.16 (0.89−1.52)	0.28
Chronic kidney disease	1.47 (1.23−1.76)	<0.001	2.24 (1.81−2.76)	<0.001	1.54 (1.14−2.09)	0.005
Atrial fibrillation	1.42 (1.19−1.68)	<0.001	1.17 (0.98−1.39)	0.08	1.21 (0.93−1.57)	0.16
Anemia	1.36 (1.14−1.62)	0.001	2.07 (1.64−2.61)	<0.001	1.53 (1.14−2.05)	0.01
Hyponatremia	1.23 (0.99−1.53)	0.06	1.37 (1.09−1.73)	0.007	1.63 (1.15−2.31)	0.01
BUN	1.01 (1.01−1.02)	<0.001	1.02 (1.02−1.03)	<0.001	1.02 (1.01−1.02)	<0.001
BNP at admission	1.01 (1.00−1.02)	0.01	1.01 (1.00−1.00)	0.003	1.01 (1.00−1.01)	0.002
RAS blockers at discharge	0.80 (0.67−0.94)	0.01	0.60 (0.50−0.72)	<0.001	0.91 (0.69−1.19)	0.49
β-blockers at discharge	0.96 (0.81−1.15)	0.67	0.58 (0.46−0.74)	<0.001	1.23 (0.87−1.75)	0.24
MRA at discharge	0.91 (0.76−1.10)	0.33	0.91 (0.77−1.09)	0.30	1.01 (0.77−1.34)	0.94

BNP, brain natriuretic peptide; BUN, blood urea nitrogen; Cr, creatinine; HFmrEF, heart failure with midrange ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; RAS, renin-angiotension system; MRA, mineralocorticoid receptor antagonist.

Table 3. Predictors of Composite Outcomes in HFpEF, HFrEF and HFmrEF (Multivariate Analysis)

	HFpEF		HFrEF		HFmrEF	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age	1.03 (1.02−1.04)	<0.001	1.03 (1.02−1.04)	<0.001	1.02 (1.01−1.04)	<0.001
Coronary artery disease			1.24 (1.03−1.48)	0.02		
Hypertension						
Diabetes mellitus						
Chronic kidney disease	1.07 (0.87−1.31)	0.55	1.39 (1.11−1.75)	0.01	1.05 (0.76−1.46)	0.77
Atrial fibrillation	1.37 (1.15−1.63)	0.001				
Anemia	1.16 (0.96−1.40)	0.12	1.34 (1.06−1.71)	0.02	1.14 (0.83−1.55)	0.43
Hyponatremia			1.09 (0.85−1.38)	0.50	1.34 (0.93−1.94)	0.12
BUN	1.01 (1.00−1.02)	0.003	1.02 (1.01−1.02)	<0.001	1.02 (1.01−1.02)	<0.001
BNP at admission	1.01 (1.00−1.01)	0.12	0.99 (0.99−1.00)	0.01	1.00 (1.00−1.01)	0.10
RAS blockers at discharge	0.80 (0.68−0.95)	0.01	0.79 (0.66−0.95)	0.01		
β-blockers at discharge			0.82 (0.64−1.04)	0.11		
MRA at discharge						

BNP, brain natriuretic peptide; BUN, blood urea nitrogen; Cr, creatinine; HFmrEF, heart failure with midrange ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; RAS, renin-angiotension system.

Table 4. Predictors of All-Cause Mortality in HFpEF, HFrEF and HFmrEF (Univariate Analysis)

	HFpEF		HFrEF		HFmrEF	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age	1.07 (1.05−1.08)	<0.001	1.05 (1.04−1.06)	<0.001	1.04 (1.03−1.06)	<0.001
Coronary artery disease	1.14 (0.84−1.55)	0.41	1.93 (1.54−2.44)	<0.001	1.06 (0.74−1.52)	0.77
Hypertension	0.91 (0.70−1.17)	0.45	1.05 (0.82−1.33)	0.72	0.97 (0.65−1.44)	0.88
Diabetes mellitus	0.97 (0.75−1.25)	0.79	1.27 (1.01−1.60)	0.05	1.03 (0.72−1.48)	0.88
Chronic kidney disease	1.62 (1.25−2.12)	<0.001	2.76 (2.03−3.75)	<0.001	1.92 (1.24−2.97)	0.004
Atrial fibrillation	1.04 (0.82−1.32)	0.76	0.98 (0.77−1.24)	0.85	1.09 (0.77−1.55)	0.63
Anemia	1.54 (1.20−1.98)	0.001	2.47 (1.84−3.30)	<0.001	2.02 (1.39−2.92)	<0.001
Hyponatremia	1.61 (1.20−2.16)	0.001	1.57 (1.16−2.12)	0.003	3.07 (2.06−4.57)	<0.001
BUN	1.03 (1.02−1.03)	<0.001	1.03 (1.02−1.03)	<0.001	1.02 (1.02−1.03)	<0.001
BNP at admission	1.02 (1.01−1.02)	<0.001	1.01 (1.01−1.02)	<0.001	1.01 (1.01−1.02)	<0.001
RAS blockers at discharge	0.65 (0.52−0.83)	<0.001	0.54 (0.43−0.69)	<0.001	0.63 (0.44−0.90)	0.01
β-blockers at discharge	0.86 (0.67−1.10)	0.22	0.41 (0.30−0.54)	<0.001	1.29 (0.80−2.09)	0.29
MRA at discharge	0.88 (0.67−1.15)	0.35	0.76 (0.60−0.96)	0.02	1.16 (0.80−1.66)	0.45

BNP, brain natriuretic peptide; BUN, blood urea nitrogen; Cr, creatinine; HFmrEF, heart failure with midrange ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; RAS, renin-angiotension system.

Table 5. Predictors of All-Cause Mortality in HFpEF, HFrEF and HFmrEF (Multivariate Analysis)

	HFpEF		HFrEF		HFmrEF	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age	1.07 (1.05−1.08)	<0.001	1.04 (1.02−1.05)	<0.001	1.04 (1.02−1.06)	<0.001
Coronary artery disease			1.34 (1.05−1.71)	0.02		
Hypertension						
Diabetes mellitus			1.09 (0.86−1.40)	0.47		
Chronic kidney disease	0.87 (0.65−1.17)	0.34	1.45 (1.04−2.02)	0.03	1.06 (0.66−1.70)	0.80
Atrial fibrillation						
Anemia	1.07 (0.82−1.40)	0.62	1.42 (1.05−1.92)	0.03	1.33 (0.89−2.00)	0.17
Hyponatremia	1.41 (1.05−1.89)	0.02	1.08 (0.78−1.48)	0.65	2.20 (1.41−3.42)	<0.001
BUN	1.02 (1.01−1.03)	<0.001	1.02 (1.01−1.03)	<0.001	1.01 (1.01−1.02)	0.002
BNP at admission	1.01 (1.00−1.02)	0.01	0.99 (0.99−1.01)	0.70	1.01 (1.00−1.01)	0.03
RAS blockers at discharge	0.64 (0.51−0.82)	<0.001	0.78 (0.61−1.00)	0.05	0.74 (0.52−1.06)	0.10
β-blockers at discharge			0.61 (0.45−0.82)	0.001		
MRA at discharge			0.91 (0.72−1.16)	0.44		

BNP, brain natriuretic peptide; BUN, blood urea nitrogen; Cr, creatinine; HFmrEF, heart failure with midrange ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; RAS, renin-angiotension system.

HFmrEF was intermediate between these 2 cohorts (45 cardiac deaths in 123 total deaths; 63.4%).

Discussion

We have reported the incidence, clinical characteristics and prognostic predictors of patients with HFmrEF hospitalized for ADHF in the Japanese population. Our results suggest that in patients who experienced hospitalization for ADHF, the prognoses for those with HFmrEF were comparable to those of patients with HFrEF and HFpEF. The treatment strategies and prognoses for patients with hospitalization due to ADHF and patients with heart failure having LVEF > 40% have not improved substantially over the past 2 decades, much less so in cases involving the coexistence of these 2 pathologic conditions. Therefore, the value of our results lies on the provision of basic information, patient characteristics and prognostic factors related to HFmrEF in patients hospitalized for ADHF.

Clinical Characteristics of HFmrEF in ADHF

Consistent with previous reports focusing on chronic heart failure, which showed the prevalence of HFmrEF to be between 10% and 20%, the prevalence of HFmrEF was 17.6% in our cohort. Moreover, in accordance with previous studies, the clinical characteristics of HFmrEF in our cohort were largely intermediate between those of HFpEF and HFrEF in ADHF. The prevalence of ischemic etiology was lower in our cohort: 16.3% in HFpEF, 38.8% in HFmrEF and 37.2% in HFrEF; whereas the prevalence was 45% to 50% in HFpEF, 55% to 60% in HFmrEF and around 60% in HFrEF in a previous report.[7] Similarly, prevalence of the female population was lower in our cohorts: 28.8% in HFrEF, 37.5% in HFmrEF and 52.6% in HFpEF; whereas that in previous studies was around 40% in HFrEF, 50% in HFmrEF and 65% in HFpEF.[8,9]

Studies analyzing the clinical characteristics of HFmrEF in ADHF are scarce. However, Fonarow et al reported the differences in the clinical characteristics of patients with severely (LVEF < 25%), moderately (LVEF 25%−40%), mildly (LVEF 40%−55%) reduced and normal (LVEF > 55%) ejection fractions. Although the basic trend, such as female and elderly population predominance in HFpEF, was the same, our population included a greater prevalence of older patients but a lesser prevalence of females and those with CAD. These differences were consistent with the findings of the previous reports analyzing the difference between East Asians and Caucasians.[7,9]

Prognostic Predictors of HFmrEF in ADHF

The patients in our cohort who had HFmrEF seemed to have worse prognoses than indicated in previous reports targeting patients with chronic heart failure. The 1-year mortality in our cohorts was 10.0%, whereas that in reports targeting the ambulatory Japanese population was 6.8%.[10] Reported predictors of long-term prognosis in each cohort stratified with LVEF varied across studies. Within our cohorts, older age, anemia, hyponatremia, elevated BUN, BNP, and history of CKD were common predictors of adverse outcomes in HFpEF, HFrEF and HFmrEF. Although the prevalence of CAD was comparable in those with HFrEF and HFmrEF, the association between the history of CAD and worse prognosis was significant only in those with HFrEF. These results were different from the observation by Ola et al, who reported that the history of CAD was a common risk factor for adverse outcomes in all 3 LVEF categories.[11] This difference may reflect the pathologic difference between patients with ADHF and those with chronic heart failure. In addition, a relatively low prevalence of CAD in our cohorts may be responsible for this difference.

Treatment Strategy

Based on our results, patients with HFmrEF were more likely to receive evidence-based therapy for HFrEF, including angiotensin converting enzyme inhibitors, aldosterone

receptor blockades and β-blockers. Some previous reports have suggested the favorable effects of these drugs for patients with HFmrEF in ambulatory settings. For example, a subanalysis from the TOPCAT and CHARM studies suggested the favorable effects of mineralocorticoid receptor antagonists and ARBs on the prognosis of patients with HFmrEF,[12] and Tsuji et al reported the association between the use of β-blockers and better prognosis in the Japanese population.[10] From these results, treating HFmrEF with an evidence-based therapy for HFrEF seems promising. Regretfully, however, our results cannot add further information on this interesting discussion due to the lack of statistical power. Our power analysis showed that the statistical power for analyzing the effects of these medications on mortality and composite outcomes in our HFmrEF cohort reached only 0.3 to 0.8, indicating that there was a possibility of beta error as high as 20% to 70% (Supplementary Table 1). Large prospective trials are warranted to resolve this problem.

Prognostic Implications of LVEF Strata in ADHF

Our results suggested that there was no association between the LVEF strata and the prognosis in patients with ADHF. This result was not consistent with previous observations in chronic heart failure.[13] Indeed, prognostic implications for LVEF stratification in patients with ADHF seem inconsistent.[14–16] For example, in a Korean acute heart-failure registry, the 3-year outcomes of patients with ADHF hospitalizations were not associated with the LVEF strata, and in-hospital mortality for ADHF in the ADHERE registry showed the same trend.[14,15] Several potential explanations for the differences between the population with ADHF and chronic heart failure exist. First, in the cases of hospitalization for ADHF, the LVEF changes dynamically as a result of correction of the underlying cardiac defects; thus, the effectiveness of the LVEF strata as the prognostic marker may be limited in this population. Second, in ADHF, many prognostic events occur during the vulnerable phase after hospital discharge. Events in this phase are largely the results of insufficient treatments during the index hospitalization or nonadherence to the treatment associated with socioeconomical status or lack of education.[17,18] In fact, from the WET-HF, 4.8% and 10.8% of patients experienced readmission due to heart failure within 30 days and 90 days after the index hospitalizations, respectively.[18] Considering these high event rates in the vulnerable phase, which is specific to the population with ADHF, and the fact that causal precipitating factors of the events during the vulnerable phase cannot be assessed through the LVEF strata, the existence of this vulnerable phase may be responsible for the difference between the populations with ADHF and congestive heart failure. Thus, simply trying to evaluate the long-term event rate in patients with ADHF according to the LVEF strata may be both difficult and inappropriate because the event rate for acute decompensation was greatly affected by the correction of underlying cardiac defects at index hospitalization and the event rate in the vulnerable phase, which is thought to be not associated with the LVEF strata.

Limitations

Our study has several limitations. First, because we collected the LVEF data during index hospitalizations, we cannot observe the changes in LVEF. A 3-year longitudinal observation of LVEF reported that 45% of patients with HFmrEF changed to HFpEF, and 21% transitioned to HFrEF.[10] These populations cannot be negligible; however, because we excluded the patients with acute coronary syndrome, the proportion of these patients "in transition" may be fewer in our cohorts. Second, the observational nature of the study design made it difficult to interpret the results. Unmeasured reasons for selection of medications may have existed and may have confounded the survival analysis. Third, lack of statistical power may have influenced the results. A much larger sample size may suggest a more reliable relationship between the baseline characteristics and treatment strategy and prognosis. However, because patients with HFmrEF were not the majority in the population with heart failure, it is difficult to conduct a prospective randomized controlled trial in this population. Therefore, it is worth revisiting the registry data. Finally, the prescription rates of RASIs and β-blockers left something to be desired. However, as shown in the Change the Management of Patients with Heart Failure (CHAMP-HF) study, a significant gap exists between the ideal state and the real-world implementation of the guideline-based medical treatments.[19] Among the factors associated with the low implementation rate of the guideline-based medical treatment discussed in the CHAMP-HF trial, older age may affect the prescription rate of RASIs and β-blockers in our study. In fact, currently, there are no definitive data regarding the effects of guideline-based medical treatments in those older than 75 years of age, even in cases of HFrEF, whereas the average age of the patients in the WET-HF is 74.4 years old. In fact, reflecting the advanced aging of the society, the prescription rate of β-blockers at discharge was only 38.1% and that for RASIs was 41% in a Japanese nationwide, claim-based analysis of hospitalizations for heart failure across all LVEF strata.[20] Considering these circumstances, we thought patients in the WET-HF were basically treated in a standard and guideline-based manner while compromising with the limitations in the real-world clinical settings.

Conclusions

In the population of patients hospitalized for ADHF, HFmrEF accounts for roughly one-sixth of these patients. The long-term prognoses for patients with HFmrEF were not significantly different from those for patients with HFpEF and HFrEF in the hospitalized population. Risk factors for adverse outcomes in HFmrEF were also similar to those for HFpEF and HFrEF in the hospitalized population with ADHF.

Disclosures

This work was supported by the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT) KAKENHI grant 26461088; a grant from the Japan Agency for Medical Research and Development (201439013C; S.K.); a Grant-in-Aid for Scientific Research (JPSS KAKENHI, 23591062, 26461088; T.Y.); a Grant-in-Aid for Young Scientists (JPSS KAKENHI, 18K15860 [Y. S.]); Health Labour Sciences Research Grant (14528506; S. K.); and a Sakakibara Clinical Research Grant for Promotion of Sciences, 2012, 2013, 2014 (T.Y.). Dr. Kohsaka received an unrestricted research grant for the Department of Cardiology, Keio University School of Medicine from Bayer Pharmaceutical and Daiichi Sankyo. The other authors have no conflicts of interest to disclose. There are no patents, products in development or marketed products to declare.

Acknowledgments

The authors are grateful to the members of the WET-HF investigators.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2019.05.010.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:891–975.
2. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, et al. The global health and economic burden of hospitalizations for heart failure. J Am Coll Cardiol 2014;63:1123–33.
3. Shafie AA, Tan YP, Ng CH. Systematic review of economic burden of heart failure. Heart Fail Rev 2018;23:131–45.
4. Tavazzi L, Senni M, Metra M, Gorini M, Cacciatore G, Chinaglia A, et al. Multicenter prospective observational study on acute and chronic heart failure: one-year follow-up results of IN-HF (Italian Network on Heart Failure) outcome registry. Circ Heart Fail 2013;6:473–81.
5. McKee P, McNamara P, Kannel W. The natural history of congestive heart failure: the Framingham Study. N Engl J Med 1971;285:1441–6.
6. Alibay Y, Schmitt C, Beauchet A, Dubourg O, Alexandre JA, Boileau C, et al. Non-radioimmunometric NT-ProBNP and BNP assays: impact of diluent, age, gender, BMI. Ann Biol Clin (Paris) 2005;63:43–9.
7. Akiyama E, Van Aelst LNL, Arrigo M, Lassus J, Miro O, Celutkiene J, et al. East Asia may have a better 1-year survival following an acute heart failure episode compared with Europe: results from an international observational cohort. Eur J Heart Fail 2018;20:1071–5.
8. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail 2017;19:1574–85.
9. Koh AS, Tay WT, Teng THK, Vedin O, Benson L, Dahlstrom U, et al. A comprehensive population-based characterization of heart failure with mid-range ejection fraction. Eur J Heart Fail 2017;19:1624–34.
10. Tsuji K, Sakata Y, Nochioka K, Miura M, Yamauchi T, Onose T, et al. Characterization of heart failure patients with mid-range left ventricular ejection fraction: a report from the CHART-2 Study. Eur J Heart Fail 2017;19:1258–69.
11. Vedin O, Lam CSP, Koh AS, Benson L, Teng THK, Tay WT, et al. Significance of ischemic heart disease in patients with heart failure and preserved, midrange, and reduced ejection fraction: a nationwide cohort study. Circ Heart Fail 2017;10. pii: e003875.
12. Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, et al. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. Eur Heart J 2016;37:455–62.
13. Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. Eur Heart J 2012;33:1750–7.
14. Cho JH, Choe WS, Cho HJ, Lee HY, Jang J, Lee SE, et al. Comparison of characteristics and 3-year outcomes in patients with acute heart failure with preserved, mid-range, and reduced ejection fraction. Circ J 2019;83:347–56.
15. Sweitzer NK, Lopatin M, Yancy CW, Mills RM, Stevenson LW. Comparison of clinical features and outcomes of patients hospitalized with heart failure and normal ejection fraction (>or =55%) versus those with mildly reduced (40% to 55%) and moderately to severely reduced (<40%) fractions. Am J Cardiol 2008;101:1151–6.
16. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251–9.
17. Cheema B, Ambrosy AP, Kaplan RM, Senni M, Fonarow GC, Chioncel O, et al. Lessons learned in acute heart failure. Eur J Heart Fail 2018;20:630–41.
18. Kimura M, Kohno T, Yoshikawa T. Early versus late readmission during the vulnerable phase following hospitalization for heart failure. Eur J Heart Fail 2018;20:1165–6.
19. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, et al. Medical therapy for heart failure with reduced ejection fraction: The CHAMP-HF registry. J Am Coll Cardiol 2018;72:351–66.
20. Yasuda S, Miyamoto Y, Ogawa H. Current status of cardiovascular medicine in the aging society of Japan. Circulation 2018;138:965–7.