



TITLE:

Demographics, Management, and In-Hospital Outcome of Hospitalized Acute Heart Failure Syndrome Patients in Contemporary Real Clinical Practice in Japan --Observations From the Prospective, Multicenter Kyoto Congestive Heart Failure (KCHF) Registry--

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ORIGINAL ARTICLE

Heart Failure

Demographics, Management, and In-Hospital Outcome of Hospitalized Acute Heart Failure Syndrome Patients in Contemporary Real Clinical Practice in Japan

— Observations From the Prospective, Multicenter Kyoto Congestive Heart Failure (KCHF) Registry —

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Background: There is a scarcity of reports on the clinical characteristics and management practice in contemporary all-comer patients with acute decompensated heart failure (ADHF).

Methods and Results: The Kyoto Congestive Heart Failure (KCHF) registry is a prospective observational cohort study enrolling 4,056 consecutive patients who had hospital admission due to ADHF without any exclusion criteria between October 2014 and March 2016 in the 19 participating hospitals in Japan. Baseline characteristics, clinical presentations, management, and in-hospital outcomes were compared between heart failure (HF) with reduced left ventricular ejection fraction (LVEF; HFrEF, LVEF <40%), HF with mid-range LVEF (HFmrEF, LVEF 40–49%), and HF with preserved LVEF (HFpEF, LVEF ≥50%). Of the 4,041 patients with documented LVEF, 1,744 (43%) had HFpEF; 746 (19%), HFmrEF; and 1,551 (38%), HFrEF. The median age was 80 years (IQR, 72–86 years) in the entire population, and was higher with increasing LVEF ($P < 0.001$). The in-hospital mortality rate was higher in the HFrEF than in the HFmrEF and HFpEF groups (9.2%, 4.8%, and 5.1%, respectively, $P < 0.001$).

Conclusions: This registry elucidated the clinical features and clinically relevant in-hospital outcomes in contemporary consecutive patients with ADHF in real-world clinical practice in Japan. When classified by LVEF, significant differences in characteristics and in-hospital outcomes existed between patients with HFrEF, HFmrEF, and HFpEF.

Key Words: Cohort study; Heart failure; Hospitalization; Mid-range ejection fraction; Mortality

Hear failure (HF) is a major public health burden worldwide that is associated with high costs.^{1,2} The number of patients with acute decompensated heart failure (ADHF) continues to increase annually.^{3–5} Repeat hospitalization is a major issue in patients with ADHF, leading to high mortality rates² and a decline in quality of life (QOL). There are several previous large-scale registries evaluating the demographics, management, and

clinical outcomes of patients with ADHF in various geographical areas.^{6–12} Recently, however, the population in the developed countries, Japan in particular, has been aging rapidly, leading to a marked increase in new-onset HF.^{3,12–14} The demographics, management, and clinical outcomes of patients with ADHF in this rapidly aging society might be much different from those reported in the previous ADHF registries. Particularly, evaluation of social factors would

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be important in elderly patients with ADHF. Therefore, we established the multicenter Kyoto Congestive Heart Failure (KCHF) registry enrolling consecutive hospitalized ADHF patients and collecting comprehensive information including social factors, in order to explore the recent trends in the demographics, management and clinical outcomes of patients with ADHF. In this first report from the KCHF registry, we compared the baseline characteristics, clinical presentations, management, and in-hospital outcomes based on left ventricular ejection fraction (LVEF), because HF patients with borderline (mid-range) LVEF (HFmrEF) have not yet been adequately characterized as compared with HF patients with reduced LVEF (HFrEF) or with preserved LVEF (HFpEF).

Methods

Subjects

The KCHF registry is a physician-initiated, prospective, observational, multicenter cohort study enrolling the consecutive patients admitted to hospitals due to ADHF for the first time between October 2014 and March 2016 in the 19 secondary and tertiary hospitals, including rural and urban, large and small hospitals, in Tokai, Kinki, Chugoku, and Kyushu districts in Japan (**Appendix S1; Figure S1**). The overall design of the KCHF study has been previously described in detail.¹⁵ We enrolled all patients with ADHF as defined by the modified Framingham criteria, who were admitted to the participating centers,^{16,17} and those who underwent HF-specific treatment involving i.v. drugs ≤ 24 h after hospital presentation. In the present study, we compared the baseline characteristics, clinical presentation, management, and in-hospital clinical outcomes between patients with HFrEF, HFmrEF, or HFpEF in the KCHF registry. In addition, we compared the patients by dividing them into 4 quartiles of age, to clarify the impact of LVEF on their characteristics in each category of age.

Ethics

The study protocol was approved by the ethics committees at Kyoto University Hospital (local identifier: E2311) and at all participating hospitals (details given in **Supplementary File 1**). This study was registered with UMIN (UMIN identifier: UMIN000015238).

Data Collection and Definitions

The attending physicians or research assistants at each participating hospital collected comprehensive data on patient demographics, medical history, underlying heart disease, pre-hospital activities, socioeconomic status, signs, symptoms, medication, laboratory test, electrocardiogram, echocardiography, acute management during emergency room, status at discharge, and clinical events during the index hospitalization. The signs and symptoms were recorded at 4 time points: at hospital arrival; admission; 24 h after hospital arrival (data not shown); and discharge.

Laboratory tests were performed at hospital presentation and at the nearest time to discharge. LVEF was measured in a detailed assessment in the echocardiography department, hospital ward, and, in some cases, in the emergency department. We did not adopt LVEF data only with a quick survey. The timing was variable among the patients, but we adopted the data in the earliest echocardiography as possible after admission. LVEF was measured using the biplane modified Simpson's method. HF was classified according to LVEF, as HFrEF (LVEF $< 40\%$), HFmrEF (LVEF 40–49%), and HFpEF (LVEF $\geq 50\%$). Other definitions for the baseline factors were provided in **Supplementary File 1**. The clinical events included in-hospital mortality (death from any cause, cardiovascular death, and non-cardiovascular death), acute coronary events, arrhythmic events, stroke, and bleeding events during hospitalization. In addition, deterioration of HF during the index hospitalization and deteriorated renal function were adjudicated as clinical events. Worsening HF (WHF) during hospitalization was defined as additional i.v. drug treatment for HF, hemodialysis, or mechanical circulatory or respiratory support, occurring > 24 h after therapy initiation.¹⁸ Worsening renal function (WRF) was defined as > 0.3 mg/dL increase in serum creatinine during the index hospitalization.^{19–21} Definitions for other clinical events are provided in **Supplementary File 1**.

To ensure the quality of the data, a study management committee met every 2 months. For each meeting, a study management committee chose randomly 2 or 3 hospitals and evaluated the quality of the input.¹⁵

Statistical Analysis

Categorical variables are presented as n (%). Continuous variables are presented as mean \pm SD or median (IQR). Comparisons between patients with HFrEF, HFmrEF, or HFpEF, and comparisons between the 4 quartiles by age, were performed using chi-squared test for categorical variables and 1-way ANOVA or Kruskal-Wallis test for continuous variables. To determine the differences between HFrEF, HFmrEF, and HFpEF, we performed the Bonferroni post-hoc test in the entire cohort and in each quartile of age. All statistical analysis was conducted with JMP 13.0 (SAS Institute, Cary, NC, USA). Two-tailed $P < 0.05$ was considered statistically significant.

Results

Patient Background

A total of 4,056 patients were enrolled in this registry. There were 1,744 patients (43%) with HFpEF, 746 patients (19%) with HFmrEF, and 1,551 patients (38%) with HFrEF after excluding 15 patients with missing LVEF. Echocardiography was performed after a median of 1 day of admission (IQR, 0–6 hospital days), and 73% of the entire cohort were assessed for LVEF ≤ 5 days after admission. The median age was 80 years (IQR, 72–86 years; range,

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Table 1. Patient Characteristics

	Entire cohort (n=4,056)	HFREF (n=1,551)	HFmrEF (n=746)	HFpEF (n=1,744)	P-value			
					HFmrEF vs. HFREF	HFpEF vs. HFREF	HFmrEF vs. HFpEF	
Demographics								
Age (years)	80 (72–86)	77 (67–85)	80 (72–86)	82 (76–88)	<0.001	<0.001	<0.001	<0.001
Age ≥85 years	1,333 (33)	394 (25)	243 (33)	689 (40)	<0.001	<0.001	<0.001	0.003
Female	1,818 (45)	521 (34)	301 (40)	989 (57)	<0.001	0.005	<0.001	<0.001
BMI (kg/m ²)	22.8±4.5	22.8±4.6	22.7±4.3	22.9±4.4	0.57			
BMI <22 kg/m ²	1,787 (47)	705 (48)	326 (46)	753 (46)	0.62			
Medical history								
Prior hospitalization due to HF	1,442 (36)	597 (39)	248 (34)	593 (35)	0.004	0.03	0.01	1.00
AF/AFL	1,681 (41)	487 (31)	310 (42)	878 (50)	<0.001	<0.001	<0.001	<0.001
Hypertension	2,909 (72)	1,017 (66)	569 (76)	1,310 (75)	<0.001	<0.001	<0.001	1.00
Diabetes mellitus	1,510 (37)	626 (40)	300 (40)	578 (33)	<0.001	1.00	<0.001	0.002
Prior MI	908 (22)	492 (32)	223 (30)	190 (11)	<0.001	1.00	<0.001	<0.001
Current smoking	476 (12)	233 (15)	103 (14)	139 (8.1)	<0.001	1.00	<0.001	<0.001
Prior stroke/TIA	662 (16)	225 (15)	126 (17)	306 (18)	0.054			
VT/VF	165 (4.1)	123 (7.9)	18 (2.4)	23 (1.3)	<0.001	<0.001	<0.001	0.15
CKD	1,809 (45)	678 (44)	352 (47)	770 (44)	0.27			
Dementia	770 (19)	262 (17)	134 (18)	370 (21)	0.005	1.00	0.005	0.19
Social background								
Poor medical adherence	674 (17)	298 (19)	126 (17)	249 (14)	<0.001	0.54	<0.001	0.29
Employed	510 (13)	281 (18)	92 (12)	137 (7.9)	<0.001	0.001	<0.001	0.001
Public assistance	234 (5.8)	106 (6.8)	46 (6.2)	82 (4.7)	0.03	1.00	0.03	0.39
Lifestyle								
Single	866 (21)	348 (22)	161 (22)	355 (20)	0.34			
With a partner only	1,720 (42)	692 (45)	344 (46)	677 (39)	<0.001	1.00	0.002	0.002
Institution for aged or hospital	281 (7.0)	102 (6.6)	49 (6.6)	129 (7.4)	0.59			
Daily life activities								
Ambulatory	3,149 (78)	1,246 (81)	595 (80)	1,299 (75)	<0.001	1.00	<0.001	0.02
Use of wheelchair (outdoor only)	305 (7.6)	92 (6.0)	58 (7.8)	153 (8.9)	0.01	0.30	0.006	1.00
Use of wheelchair (outdoor and indoor)	388 (9.7)	126 (8.2)	62 (8.4)	198 (11)	0.003	1.00	0.006	0.07
Bedridden	172 (4.3)	69 (4.5)	25 (3.4)	77 (4.5)	0.41			

Data given as n (%), mean ±SD, or median (IQR). AF/AFL, atrial fibrillation/flutter; BMI, body mass index; CKD, chronic kidney disease; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; MI, myocardial infarction; TIA, transient ischemic attack; VT/VF, ventricular tachycardia/fibrillation.

18–105 years) in the entire cohort, and trended to be higher with increasing LVEF (HFREF, 77 years; HFmrEF, 80 years; HFpEF, 82 years; **Table 1**; **Figure S2**). Women accounted for 45% of the patients, and the proportion of women was higher with increasing LVEF (HFREF, 33%; HFmrEF, 40%; and HFpEF, 57%; **Table 1**). In the entire cohort, the proportion of patients with body mass index <22 kg/m² was 47%. HFREF patients more often had a history of HF hospitalization than HFmrEF and HFpEF patients (**Figure A**). HFpEF patients less often had prior myocardial infarction than HFREF and HFmrEF patients (**Figure B**), and HFREF patients less often had hypertension than HFmrEF and HFpEF patients (**Figure C**). The prevalence of atrial fibrillation/flutter (AF/AFL; **Figure D**) was higher with increasing LVEF (**Table 1**). There were significant differences in social background, living status, and daily life activities between the 3 groups (**Table 1**). When we compared the patients by dividing them into 4 quartiles of age in each category of LVEF (**Tables S1,S2**), the trend in the prevalence of female sex and AF/AFL was generally

consistent with that in the entire cohort. Other background data are listed in **Table S3**.

The most common causes of HF were coronary artery disease (CAD; 33%), followed by hypertensive heart disease (24%), valvular heart disease (20%), and primary cardiomyopathy (15%; **Table 2**). CAD and cardiomyopathy were more prevalent in HFREF and HFmrEF patients than in HFpEF patients, while hypertensive heart disease and valvular heart disease were more prevalent in HFpEF and HFmrEF patients than in HFREF patients in the entire cohort (**Table 2**) and when stratified by age (**Tables S1,S2**).

Clinical Presentation

At presentation, heart rate was higher in HFREF and in HFmrEF patients than in HFpEF patients (**Figure E**), while systolic blood pressure (SBP) was higher in HFpEF and HFmrEF patients than in HFREF patients (**Table 3**; **Figure F**). C-reactive protein level was not significantly different between the 3 groups. A total of 67% had anemia and 13% had hyponatremia (**Table 3**). Anemia at presentation was

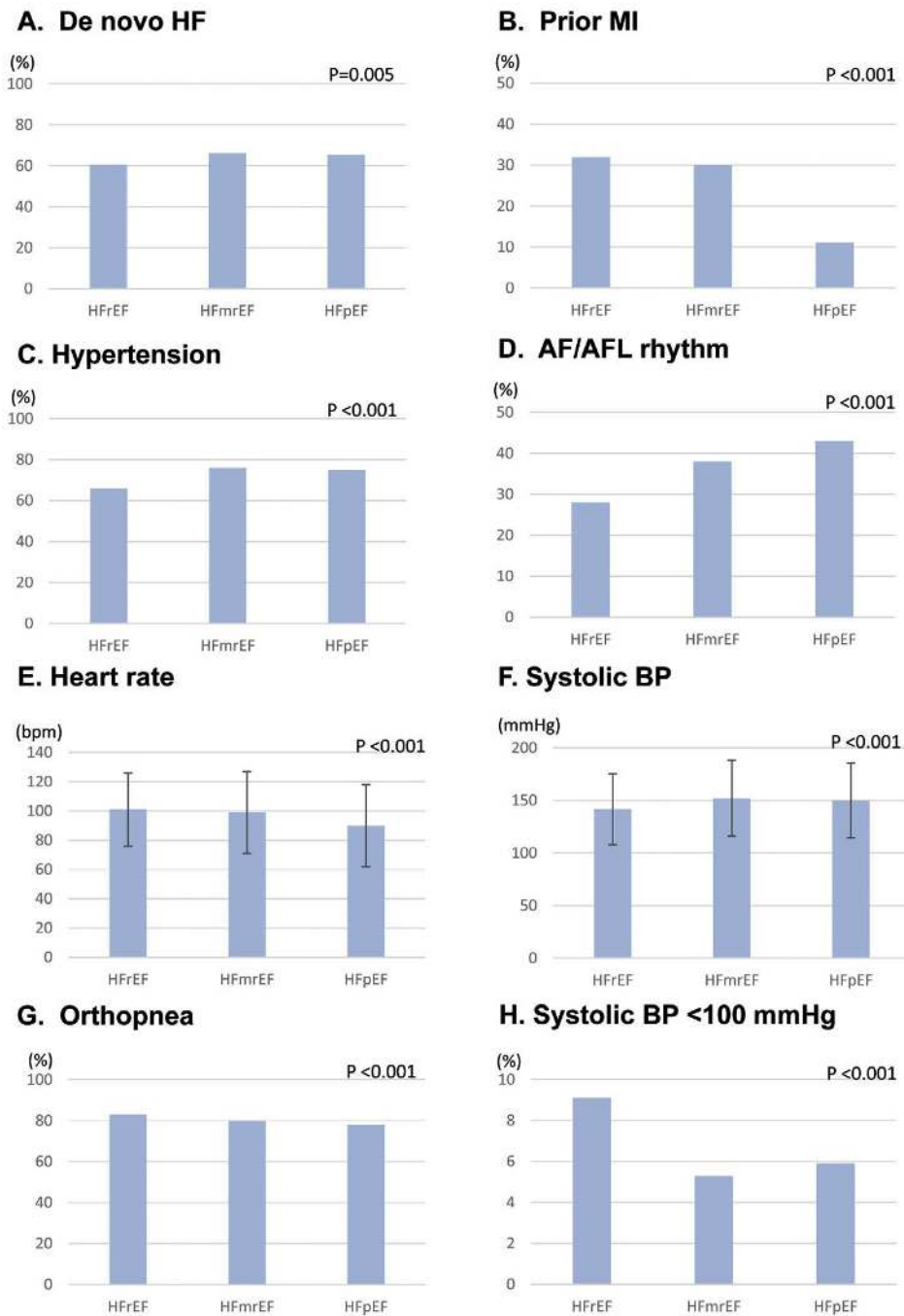


Figure. Rate of (A) de novo heart failure (HF), (B) prior myocardial infarction (MI), (C) hypertension, (D) atrial fibrillation/flutter (AF/AFL) at presentation, and (E) heart rate, (F) systolic blood pressure (SBP), (G) orthopnea, and (H) SBP <100 mmHg at presentation in HF patients with reduced left ventricular ejection fraction (LVEF; HFrEF), HF with mid-range LVEF (HFmrEF), and HF with preserved LVEF (HFpEF).

more prevalent with increasing LVEF, while brain natriuretic polypeptide (BNP) was higher with decreasing LVEF (Table 3). The trend in anemia and BNP, when stratified by age, was generally consistent with that in the entire cohort (Tables S1,S2). Renal function as evaluated with estimated glomerular filtration rate was not different between the 3 groups (Table 3).

Emergency Room and In-Hospital Management

Upon arrival at the emergency department, intubation and inotrope use were more prevalent with decreasing LVEF, while nitroglycerine was most often used in HFmrEF patients (Tables 3,S3). Although the prevalence of orthopnea at presentation was high in the 3 groups (Figure G), relief in orthopnea was observed in 32% of the patients following treatment in the emergency room. Coronary angiography

Table 2. Underlying Heart Disease

Subgroups	Entire cohort (n=4,056)	HF _r EF (n=1,551)	HEm _r EF (n=746)	HF _p EF (n=1,744)	P-value		
					HF _m rEF vs. HF _r EF	HF _p EF vs. HF _r EF	HF _m rEF vs. HF _p EF
CAD	1,327 (33)	708 (46)	301 (40)	312 (18)	<0.001	0.08	<0.001
Non-ACS	1,088 (27)	598 (39)	243 (33)	242 (14)	<0.001		
ACS	239 (5.9)	110 (7.1)	58 (7.8)	70 (4.0)	<0.001		
Hypertensive heart disease	985 (24)	196 (13)	189 (25)	597 (34)	<0.001	<0.001	<0.001
Cardiomyopathy	608 (15)	432 (28)	77 (10)	97 (2.4)	<0.001	<0.001	<0.001
DCM	434 (11)	363 (23)	48 (6.4)	26 (1.5)	<0.001		
HCM	59 (1.5)	6 (0.4)	10 (1.3)	42 (2.4)	<0.001		
DHCM	27 (0.7)	22 (1.4)	3 (0.4)	2 (0.1)	<0.001		
Others	88 (2.2)	45 (2.9)	16 (2.1)	27 (1.6)	0.03		
Valvular heart disease	819 (20)	161 (10)	146 (20)	510 (29)	<0.001	<0.001	<0.001
Aortic stenosis	297 (7.3)	63 (4.1)	58 (7.8)	176 (10)	<0.001		
Aortic regurgitation	104 (2.6)	32 (2.1)	29 (3.9)	41 (2.4)	0.03		
Mitral stenosis	36 (0.9)	4 (0.3)	4 (0.5)	28 (1.6)	<0.001		
Mitral regurgitation	250 (6.1)	35 (2.3)	36 (4.8)	179 (10)	<0.001		
Tricuspid regurgitation	41 (1.0)	3 (0.2)	5 (0.7)	33 (1.9)	<0.001		
Prosthetic valve dysfunction	91 (2.2)	24 (1.5)	14 (1.9)	53 (3.0)	0.01		
Other heart disease	297 (7.3)						
Arrhythmia	188 (4.6)	24 (1.5)	22 (3.0)	141 (8.1)	<0.001	0.07	<0.001
Bradycardia	64 (1.6)	4 (0.3)	3 (0.4)	56 (3.2)	<0.001		
Tachycardia	124 (3.1)	20 (1.3)	19 (2.6)	85 (4.9)	<0.001		
CHD	15 (0.4)	0	2 (0.3)	12 (0.7)	0.003		
Constrictive pericarditis	4 (0.1)	0	0	4 (0.2)	0.07		
Others	110 (2.7)	30 (1.9)	9 (1.2)	71 (4.1)	<0.001		

Data given as n (%). ACS, acute coronary syndrome; CAD, coronary artery disease; CHD, congenital heart disease; DCM, dilated cardiomyopathy; DHCM, dilated phase of hypertrophic cardiomyopathy; HCM, hypertrophic cardiomyopathy. Other abbreviations as in Table 1.

and percutaneous coronary intervention were more often performed in HF_rEF and in HF_mrEF patients than in HF_pEF patients, while pacemaker implantation was performed more frequently in HF_pEF patients than in HF_rEF and HF_mrEF patients (Table 3).

In-Hospital Outcome

Of the 4,056 hospitalized patients, 271 (6.7%) died in hospital. The in-hospital mortality rate was lower in the HF_mrEF and HF_pEF groups than in the HF_rEF group (4.8%, 5.1%, and 9.2%, respectively, $P < 0.001$; Table 4). The prevalence of WHF during hospitalization was higher with decreasing LVEF (25% in HF_rEF, 19% in HF_mrEF, and 15% in HF_pEF), while the prevalence of WRF was high in the HF_mrEF group (41%) as well as in the HF_pEF group (Table 4). The median length of hospital stay was 16 days (IQR, 11–25 days) without any significant difference across the 3 groups (Table 4).

Clinical Profile at Hospital Discharge

The signs and symptoms of congestion, such as dyspnea, rales, and jugular venous distention, improved at discharge in most of the patients (Tables 5, S4). The median change of body weight during hospitalization was -3.0 kg (IQR, -5.8 to -1.0 kg) without any significant difference across the 3 groups. The prevalence of hyponatremia was 13% at discharge without significant difference across the 3 groups, while the prevalence of anemia increased with increasing LVEF (Table 5).

The median number of prescribed drugs at discharge was 8 (IQR, 6–11) without any significant difference across

the 3 groups. Loop diuretics were prescribed in 81% of patients without significant difference across the 3 groups. Beta-blockers and renin-angiotensin-aldosterone system inhibitors were more frequently prescribed in patients with HF_rEF and HF_mrEF than in patients with HF_pEF, while calcium channel blockers were more often prescribed with increasing LVEF. Tolvaptan and amiodarone were more often prescribed in patients with HF_rEF than in patients with HF_mrEF and HF_pEF (Table 5). The prescription trend for β -blockers, calcium channel blockers, and amiodarone in the entire cohort was consistent with that when stratified by age (Table S1).

The proportion of patients discharged to their home was 82%, and the proportion of ambulatory patients decreased at discharge (Table 5). The proportion of ambulatory patients was greater in HF_rEF patients than in HF_mrEF and HF_pEF patients. The use of long-term care insurance included care required in 34% of patients, support required in 14% of patients, and plan to use it in 5.9% of patients (Table 5). The proportion of patients with care required was higher with increasing LVEF, but the trend in ambulatory patients and care planning was not observed when stratified by age (Table S1).

Discussion

Registry data on patients with ADHF in real clinical practice would have a great influence on the management for ADHF and clarify the unmet needs for the clinical trials evaluating new treatment. Most previous hospital-based registries in Japan, as well as in other countries, however,

	Entire cohort (n=4,056)	HFREF (n=1,551)	HFmrEF (n=746)	HFpEF (n=1,744)	P-value			
					HFmrEF vs. HFREF	HFpEF vs. HFREF	HFmrEF vs. HFpEF	
Vital signs at presentation								
Heart rate (beats/min)	96±28	101±25	99±28	90±28	<0.001	0.75	<0.001	<0.001
SBP (mmHg)	147±35	141±34	152±36	150±36	<0.001	<0.001	<0.001	0.54
>140	2,179 (54)	741 (48)	440 (59)	988 (57)	<0.001			
100–140	1,581 (39)	665 (43)	264 (36)	647 (37)	<0.001			
<100	282 (7.0)	141 (9.1)	39 (5.3)	102 (5.9)	<0.001			
BT ≥37.5°C	257 (6.6)	75 (5.1)	51 (7.2)	130 (7.7)	<0.001	0.15	0.008	1.00
Rhythms at presentation								
Sinus rhythm	2,274 (56)	1,006 (65)	414 (56)	845 (49)	<0.001	<0.001	<0.001	0.004
AF/AFL	1,453 (36)	427 (28)	280 (38)	743 (43)	<0.001	<0.001	<0.001	0.04
Admission laboratory data								
BNP (pg/mL)	721 (398–1,308)	994 (588–1,704)	780 (453–1,297)	499 (284–892)	<0.001	<0.001	<0.001	<0.001
NT-pro BNP (pg/mL)	5,830 (2,721–13,242)	7,384 (3,433–16,398)	6,270 (2,716–18,300)	4,890 (2,277–9,849)	<0.001	1.00	<0.001	0.03
Creatinine (mg/dL)	1.1 (0.8–1.6)	1.2 (0.9–1.7)	1.1 (0.8–1.7)	1.1 (0.8–1.6)	<0.001	1.00	<0.001	0.09
eGFR (mL/min/1.73 m ²)	44 (28–60)	44 (29–60)	45 (26–62)	43 (29–59)	0.30			
eGFR <30 mL/min/1.73 m ²	1,118 (28)	407 (26)	219 (29)	484 (28)	0.30			
Albumin (g/dL)	3.5±0.5	3.5±0.5	3.5±0.5	3.4±0.5	0.004	0.07	0.002	1.00
Sodium (mEq/L)	139±4.3	139±4.4	139±4.5	139±4.2	0.052			
Hyponatremia [†]	519 (13)	208 (14)	86 (12)	224 (13)	0.45			
Hemoglobin (g/dL)	11.5±2.3	12.2±2.4	11.5±2.2	10.9±2.2	<0.001	<0.001	<0.001	<0.001
Anemia [‡]	2,705 (67)	878 (57)	506 (68)	1,313 (75)	<0.001	<0.001	<0.001	<0.001
Management in the emergency room								
Respiratory management	2,986 (74)	1,114 (72)	552 (74)	1,307 (75)	0.12			
Oxygen inhalation	2,355 (58)	854 (55)	418 (56)	1,073 (62)	<0.001			
NPPV	556 (14)	221 (14)	119 (16)	213 (12)	0.03			
Intubation	75 (1.8)	39 (2.5)	15 (2.0)	21 (1.2)	0.02			
Nitroglycerin	741 (18)	255 (16)	172 (23)	312 (18)	<0.001	<0.001	0.81	0.008
Furosemide	2,052 (51)	783 (50)	353 (47)	906 (52)	0.11			
Inotropes	155 (3.8)	95 (6.1)	24 (3.2)	33 (1.9)	<0.001	0.01	<0.001	
I.v. drugs ≤24 h after hospital presentation								
Furosemide	3,400 (84)	1,276 (83)	616 (83)	1,495 (86)	0.02	1.00	0.02	0.14
Vasodilators								
Carperitide	1,487 (37)	588 (38)	286 (38)	605 (35)	0.09			
Nitrates	1,002 (25)	363 (23)	220 (30)	417 (24)	0.004	0.005	1.00	0.01
Nicardipine	251 (6.2)	82 (5.3)	53 (7.1)	115 (6.6)	0.15			
Inotropes	657 (16)	415 (27)	92 (12)	145 (8.3)	<0.001	<0.001	<0.001	0.005
Heparin	1,113 (27)	467 (30)	228 (31)	417 (24)	<0.001	1.00	<0.001	0.002
Landiolol	95 (2.3)	48 (3.1)	16 (2.1)	31 (1.8)	0.04	0.59	0.04	1.00
Procedural interventions								
Coronary angiography	1,262 (31)	588 (38)	284 (38)	390 (22)	<0.001	1.00	<0.001	<0.001
PCI	381 (9.4)	183 (12)	97 (13)	101 (5.8)	<0.001	1.00	<0.001	<0.001
CABG	50 (1.2)	22 (1.4)	12 (1.6)	16 (0.9)	0.26			

Data given as n (%), mean ± SD or median (IQR). [†]Sodium <135 mEq/dL. [‡]World Health Organization criteria (hemoglobin <12 g/dL for women and <13 g/dL for men). BNP, brain-type natriuretic peptide; BT, body temperature; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; NPPV, non-invasive positive pressure ventilation; NT-proBNP, N-terminal pro brain-type natriuretic peptide; PCI, percutaneous coronary intervention; SBP, systolic blood pressure. Other abbreviations as in Table 1.

Table 4. Clinical Outcomes and Length of Hospital Stay

	Entire cohort (n=4,056)	HFREF (n=1,551)	HFmrEF (n=746)	HFpEF (n=1,744)	P-value			
					HFmrEF vs. HFREF	HFpEF vs. HFREF	HFmrEF vs. HFpEF	
In-hospital mortality								
Death from any cause	271 (6.7)	142 (9.2)	36 (4.8)	89 (5.1)	<0.001	0.001	<0.001	1.00
Cardiovascular death	203 (5.0)	114 (7.4)	28 (3.8)	58 (3.3)	<0.001	0.002	<0.001	1.00
Cardiac death	190 (4.7)	107 (6.9)	26 (3.5)	54 (3.1)	<0.001	0.003	<0.001	1.00
Death from HF	165 (4.1)	90 (5.8)	24 (3.2)	48 (2.8)	<0.001			
Sudden death	16 (0.4)	13 (0.8)	2 (0.3)	1 (0.1)	0.002			
Other cardiac death	9 (0.2)	4 (0.3)	0	5 (0.3)	0.35			
Vascular death	13 (0.3)	7 (0.5)	2 (0.3)	4 (0.2)	0.51			
Death related to stroke	10 (0.2)	5 (0.3)	2 (0.3)	3 (0.2)	0.68			
Non-cardiovascular death	68 (1.7)	28 (1.8)	8 (1.1)	31 (1.8)	0.38			
In-hospital adverse events								
VT/VF	208 (5.5)	130 (9.0)	27 (3.9)	51 (3.1)	<0.001	<0.001	<0.001	1.00
Worsening HF	789 (19)	392 (25)	142 (19)	255 (15)	<0.001	0.003	<0.001	0.02
Worsening RF	1,307 (35)	417 (30)	291 (41)	597 (37)	<0.001	<0.001	0.001	0.08
Length of hospital stay (days)								
Median	16 (11–25)	16 (11–25)	16 (11–24)	16 (11–25)	0.20			
Mean	21±18	22±20	21±18	20±17	0.07			

Data given as n (%), mean±SD, or median (IQR). *Moderate or severe bleeding according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) classification. RF, renal failure. Other abbreviations as in Table 1.

have non-consecutive enrollment of patients, due to the pre-defined inclusion/exclusion criteria.² In the present KCHF registry, we collected very comprehensive data in all consecutive patients hospitalized with ADHF including those with acute coronary syndrome, renal failure, anemia, or infectious diseases in multiple centers in a prospective manner.¹⁵ Consequently, this is the first “all-comer” registry and the most up-to-date registry collecting various outcomes after the recent guidelines for HF have been available. The median age of 80 years in this registry was notably higher than that in all the previous large registries on ADHF (Table S5).^{6–12} In addition, the information on physical, living, and socioeconomic status derived from the present registry would be important not only for health-care providers, but also for patients, their family members, and policy-makers.¹⁵

In the stable chronic condition, the features of HFmrEF were more similar to those of HFpEF.²² Data on HFmrEF, however, are scarce in patients with ADHF in Japan. Many features of the HFmrEF group fell between those of the HFREF and HFpEF groups. Of the previous representative HF studies examining the clinical characteristics of HFmrEF, 3 were acute HF registries (OPTIMIZE-HF,²³ GWTG-HF,^{24,25} ALARM-HF²⁶), 1 was a chronic HF registry in Japan (CHART-2)²⁷ and 1 was a randomized controlled trial for acute HF (PROTECT trial;²⁸ Table S6). Similar to these studies, the age of the HFmrEF patients was in between the ages of the HFREF and the HFpEF patients in the present study. The trend that ischemic etiology was less frequent in HFpEF compared with HFREF and HFmrEF, and the trend that hypertensive etiology was more frequent in HFmrEF and HFpEF compared with HFREF, were also observed in all of these studies. In the chronic HF registry, the HFmrEF patients mainly transitioned out of the HFREF category.^{27,29} In contrast, clinical presentations and in-hospital mortality of the HFmrEF patients were similar to those observed in the

HFpEF patients in the present study, consistent with other acute HF studies.^{21–23} The in-hospital management and medication at discharge in the HFmrEF patients were in between that in the HFREF group and that in the HFpEF group in the present study. Whether the present HFmrEF patients transitioned out of HFREF or HFpEF remains unknown. Whether they transitioned to HFREF or HFpEF in the course of treatment for acute HF is also currently unknown, because we and other researchers did not collect data on the changes in LVEF during hospitalization.^{6–12} Given that LVEF change was recognized at 3 months after medical intervention if LV reverse remodeling was achieved the early phase,³⁰ the present longitudinal cohort study describes the 6-month changes. In conjunction with these data, the information on the characteristics and management of HFmrEF patients in acute HF settings could provide insight into the chronic management of patients with HF.

Factors that characterized LVEF category across all 4 quartiles of age were as follows: prevalence of female sex; AF/AFL; anemia; underlying heart disease; SBP; and BNP level. SBP at presentation was high in HFmrEF as well as in HFpEF. According to the baseline presentations, in-hospital management and medication at discharge differed with LVEF category, even if stratified by age. The differences in social factors, cognitive function, and physical function observed in each LVEF category were not observed when stratified by age. To determine their phenotypes and what factors would influence the prognosis, there is a need for a longitudinal follow-up study of patient status including cardiac function and an investigation into the long-term prognosis of these patients.^{22,31}

There are several limitations in this study. First, this study presented comprehensive cross-sectional observational data of the KCHF registry without long-term follow-up data. We did not perform analysis on the predictors of morbidity and mortality. Clinical questions about care in the elderly will be addressed in future studies through analysis of

Table 5. Clinical Status, Medication at Hospital Discharge, and Living Status After Hospital Discharge

	Entire cohort (n=3,785)	HFREF (n=1,409)	HFmrEF (n=710)	HFpEF (n=1,655)	P-value			
					HFmrEF vs. HFREF	HFpEF vs. HFREF	HFmrEF vs. HFpEF	
Discharge laboratory values								
eGFR (mL/min/1.73m ²)	43 (29–59)	45 (31–61)	43 (26–59)	41 (29–57)	<0.001	0.01	<0.001	1.00
eGFR <30 mL/min/1.73 m ²	964 (26)	327 (24)	207 (30)	425 (26)	0.01	0.01	0.36	0.25
Hyponatremia [†]	470 (13)	190 (14)	79 (11)	207 (13)	0.34			
Anemia [‡]	2,600 (70)	862 (63)	490 (71)	1,239 (76)	<0.001	<0.001	<0.001	0.02
Medication at discharge								
No. prescribed drugs	8 (6–11)	9 (6–11)	8 (7–11)	8 (6–11)	0.18			
RAAS inhibitors	2,806 (74)	1,116 (79)	529 (75)	1,156 (70)	<0.001	0.04	<0.001	0.06
ACEI/ARB	2,176 (57)	910 (65)	404 (57)	858 (52)	<0.001	0.002	<0.001	0.07
ACEI	928 (25)	490 (35)	160 (23)	276 (17)	<0.001	<0.001	<0.001	0.002
ARB	1,265 (33)	427 (30)	245 (35)	591 (36)	0.006	0.15	0.005	1.00
MRA	1,707 (45)	735 (52)	314 (44)	656 (40)	<0.001	0.002	<0.001	0.11
β-blockers	2,502 (66)	1,093 (78)	507 (71)	898 (54)	<0.001	0.005	<0.001	<0.001
Calcium channel blockers	1,298 (34)	311 (22)	267 (38)	714 (43)	<0.001	<0.001	<0.001	0.04
Loop diuretics	3,063 (81)	1,160 (82)	566 (80)	1,329 (80)	0.24			
Thiazide	222 (5.9)	64 (4.5)	36 (5.1)	121 (7.3)	0.003	1.00	0.004	0.13
Tolvaptan	402 (11)	173 (12)	58 (8.2)	169 (10)	0.01	0.01	0.21	0.36
Digoxin	215 (5.7)	90 (6.4)	30 (4.2)	95 (5.7)	0.13			
Amiodarone	251 (6.6)	154 (11)	43 (6.1)	50 (3.0)	<0.001	<0.001	<0.001	0.002
Living situation after discharge								
Home	3,079 (82)	1,201 (86)	571 (81)	1,304 (79)	<0.001	0.002	<0.001	1.00
Hospital	459 (12)	138 (10)	95 (13)	225 (14)	0.004	0.047	0.004	
Institution for the aged	183 (4.9)	45 (3.2)	37 (5.2)	100 (6.1)	0.001	0.08	<0.001	1.00
Other	25 (0.7)	7 (0.5)	5 (0.7)	13 (0.8)	0.62			
Daily life activities at discharge								
Ambulatory	2,738 (74)	1,077 (78)	516 (73)	1,137 (70)	<0.001	0.03	<0.001	0.37
Use of wheelchair (outdoor only)	356 (9.6)	117 (8.5)	62 (8.8)	177 (11)	0.06			
Use of wheelchair (outdoor and indoor)	488 (13)	149 (11)	90 (13)	247 (15)	0.002	0.57	0.001	0.37
Bedridden	138 (3.7)	34 (2.5)	38 (5.4)	65 (4.0)	0.003	0.002	0.06	0.40
Use of long-term care insurance at discharge								
Care required	859 (34)	252 (28)	166 (33)	459 (39)	<0.001	0.07	<0.001	0.06
Support required	355 (14)	108 (12)	80 (16)	175 (15)	0.03	0.07	0.11	1.00
Plan to use	150 (5.9)	60 (6.7)	29 (5.9)	61 (5.3)	0.39			

Data given as n (%) or median (IQR). [†]Sodium <135 mEq/dL. [‡]World Health Organization criteria (hemoglobin <12g/dL for women and <13g/dL for men). ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; MRA, mineralocorticoid receptor antagonists; RAAS, renin-angiotensin-aldosterone system. Other abbreviations as in Table 1.

background, in-hospital management, and improvement or worsening of patient status. Second, we did not perform statistical comparisons between the present data and data from other registries. Finally, there were no pre-specified criteria for hospital admission and the use of i.v. drugs for HF-specific treatment, which were left to the discretion of the attending physician.

Conclusions

This registry elucidated the contemporary clinical features and clinically relevant in-hospital outcomes of consecutive patients with ADHF in real-world clinical practice and presented the clinical features of HFREF, HFmrEF, and HFpEF populations in Japan. Significant differences in characteristics and in-hospital outcomes existed between

patients with HFREF, HFmrEF, and HFpEF.

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T. Kimura serves as an advisory board member for Abbott Vascular and Terumo Company. The other authors declare no conflicts of interest.

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Supplementary Files

Supplementary File 1

Supplementary Methods

Supplementary Discussion

Appendix S1. Kyoto Congestive Heart Failure Steering Committee Members

Figure S1. Kyoto Congestive Heart Failure Registry hospitals.

Figure S2. Distribution of age in (A) the entire cohort and patients with heart failure (HF) with (B) reduced ejection fraction (HFrEF), (C) mid-range ejection fraction (HFmrEF), or (D) preserved ejection fraction (HFpEF).

Table S1. Patient characteristics vs. age quartile and LVEF category

Table S2. Post-hoc analysis of patient characteristics vs. LVEF category and age quartile

Table S3. Patient characteristics, clinical presentation, and in-hospital management

Table S4. Clinical outcomes, clinical status, and medication at hospital discharge

Table S5. Previous representative ADHF registries and KCHF registry

Table S6. KCHF registry: comparison with other studies according to LVEF category

Please find supplementary file(s);
<http://dx.doi.org/10.1253/circj.CJ-17-1386>