ORIGINAL RESEARCH ARTICLE

Clinical characteristics of hospitalized heart failure patients with preserved, mid-range, and reduced ejection fractions in Japan

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Abstract

Aims   There are regional differences in the patient characteristics, management, and outcomes of hospitalized patients with heart failure (HF). The aim of this study was to evaluate the clinical characteristics and outcomes of Japanese patients who are hospitalized with HF on the basis of the left ventricular ejection fraction (LVEF) stratum.

Methods and results   We retrospectively conducted a multicentre cohort study of 1245 hospitalized patients with decompensated HF between 2013 and 2014. Of these patients, 36% had an LVEF < 40% [HF with reduced ejection fraction (HFrEF), median age 72 years, 71% male], 21% had an LVEF 40–49% [HF with mid-range EF (HFmrEF), 77 years, 56% male], and 43% had an LVEF ≥ 50% [HF with preserved EF (HFpEF), 81 years, 44% male]. The primary outcome was death from any cause, and the secondary outcomes were cardiac death and re-hospitalization due to worsened HF after hospital discharge. There were high proportions of non-ischaemic cardiomyopathy (32%) in HFrEF patients, coronary artery disease (44%) in HFmrEF patients, and valvular disease (39%) in HFpEF patients. The frequencies of intravenous diuretic and natriuretic peptide administration during hospitalization were 66% and 30%, respectively. The median hospital stay for the overall population was 19 days, and the length of stay was >7 days for >90% of patients. In-hospital mortality was 7%, but was not different among the LVEF groups (HFrEF 7%, HFmrEF 6%, and HFpEF 8%). After a median follow-up of 19 months (range, 3–26 months), 192 (17%) of the 1156 patients who were discharged alive died, and 534 (46%) were re-hospitalized after hospital discharge. There were no significant differences in mortality after hospital discharge among the three LVEF groups (HFrEF 18%, HFmrEF 16%, and HFpEF 16%). There were no differences in cardiac death or re-hospitalization due to worsened HF after hospital discharge among the LVEF groups (cardiac death: HFrEF 8%, HFmrEF 7%, and HFpEF 7%; re-hospitalization due to worsened HF: HFrEF 19%, HFmrEF 16%, and HFpEF 17%). Multivariable-adjusted analyses showed that the HFmrEF and HFrEF groups, compared with the HFpEF group, were not associated with an increased risk for in-hospital death or death after hospital discharge. Non-cardiac causes of death and re-hospitalization after hospital discharge accounted for 35% and 38%, respectively.

Conclusions   Our results revealed different clinical characteristics but similar mortality rates in the HFrEF, HFmrEF, and HFpEF groups. The most common cause of death and re-hospitalization after hospital discharge was HF, but non-cardiac causes also contributed to their prognosis. Integrated management approaches will be required for HF patients.

Keywords   Heart failure; Hospitalization; Japanese; Left ventricular ejection fraction; Mortality

Introduction

Heart failure (HF) is a global public health problem that affects 26 million people worldwide.[1,2] In Japan, it is estimated that 1.0 million individuals have HF or left ventricular dysfunction.[3–5] The Japan Patient Survey 2014 of the Ministry of Health, Labour and Welfare reported that the estimated number of patients receiving medical treatment for HF was >300 000.[6] Data from the Japanese Registry of All Cardiac and Vascular Disease revealed that 215 548 patients were admitted to 1573 cardiovascular specialty hospitals for HF and that 17 543 (8.1%) patients experienced in-hospital death in 2016.[7] The number of patients hospitalized for HF increases by 10 000 per year as a result of the growing elderly population, and the economic burden has concomitantly increased.

HF is categorized on the basis of the left ventricular ejection fraction (LVEF). The outcomes of HF patients with a reduced EF (HFrEF), which is defined as a clinical diagnosis of HF and an LVEF ≤ 40%, have improved with advancements in evidence-based medical therapies and device therapies. However, half of patients hospitalized for HF have a preserved EF (HFpEF), and the proportion of hospitalizations for HFpEF is increasing. A meta-analysis reported that patients with HFpEF had a lower risk of death than had patients with HFrEF, but their absolute mortality was high.[8] There remains a lack of evidence regarding the management of HFpEF. Furthermore, the optimal cut-off for defining a preserved or reduced EF remains unclear (40% or 50%), and how to classify patients who are in the 'grey zone' (40–49%) remains controversial.[9,10] The European Society of Cardiology (ESC) has proposed mid-range EF (HFmrEF) as a new category of HF that includes patients with an LVEF of 40–49%.[11] However, the characteristics, management, and outcomes of these grey zone patients have yet to be established.

There are regional differences in the patient characteristics, management, and outcomes of hospitalized HF patients.[12] Japanese cohorts in the 2000s, compared with cohorts from the USA and Europe, revealed different clinical characteristics and medical treatments for hospitalized HF patients.[3,13–16] Over the past decade, the use of evidence-based pharmacotherapies and device therapies, including implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy, has increased in Japan. Therefore, we evaluated the clinical characteristics and outcomes of Japanese patients who were hospitalized for HF on the basis of their LVEF.

Methods

The Heart Institute of Japan Heart Failure II (HIJ-HF II) is a retrospective, multicentre cohort study using a Diagnosis Procedure Combination (DPC) database and including 10 participating DPC hospitals in Japan.

Patients

We retrospectively conducted a multicentre cohort study of consecutive hospitalized patients with decompensated HF from 10 DPC hospitals in six Japanese prefectures (Miyagi, Chiba, Saitama, Tokyo, Kanagawa, and Shizuoka) between 1 April 2013 and 31 March 2014. To identify patients, we first searched the DPC database of each hospital for all consecutive hospitalized patients whose highest medical cost diagnosis was HF. We then reviewed these patients using medical charts and enrolled consecutive patients who were admitted for decompensated HF. Decompensated HF included de novo HF (if there was no prior history of HF) and worsening HF (if previous decompensation or hospitalization for HF was documented). Decompensated HF was defined as (i) new or progressive symptoms and signs of decompensated HF, such as significant weight gain, dyspnoea, fatigue, pulmonary rales, hepatic congestion, and lower extremity oedema; (ii) a plasma brain natriuretic peptide (BNP) level ≥ 200 pg/mL at admission[17]; and (iii) unplanned addition of oral or intravenous loop diuretic drugs, dose-up of oral loop diuretics, addition of a thiazide diuretic drug to loop diuretics, or the need for treatment with intravenous vasodilators, intravenous inotropes, or intra-aortic balloon pumping.

Finally, we included a total of 1245 consecutive hospitalized patients with acute decompensated HF. The protocol was approved by the institutional review boards of Tokyo Women's Medical University and the other participating hospitals.

Cardiovascular disease

Coronary artery disease was defined as positive stress test findings, coronary angiography demonstrating at least 75% stenosis or coronary spastic angina documented by the acetylcholine provocation test, a history of prior myocardial infarction or electrocardiographic (ECG) findings of Q-wave myocardial infarction, or a history of revascularization procedures. Valvular and congenital heart diseases were diagnosed by angiographic, haemodynamic, or echocardiographic tests or a history of valvular or congenital cardiac surgery. Aortic and mitral regurgitation was defined as valvular disease with at least moderate regurgitation by colour-flow Doppler echocardiography. Non-ischaemic cardiomyopathies were defined as ventricular myocardial abnormalities in the absence of coronary artery disease or valvular, pericardial, or congenital heart disease. Hypertensive heart disease was defined as a clinical history of hypertension and LV hypertrophy determined from echocardiographic or ECG findings, but without

a diagnosis of hypertrophic cardiomyopathy. Aortic disease, peripheral artery disease, and other vascular diseases were diagnosed by angiographic or echocardiographic findings or by a history of vascular surgery or intervention. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, a diastolic blood pressure ≥ 90 mmHg, or a history of treatment for hypertension.

LVEF was obtained by echocardiography, left ventriculography, or radionuclide angiography during hospitalization. If the LVEF could not be obtained during the index administration, we accepted data concerning the LVEF from either a few months before admission or within 6 months after discharge.

A history of hypertension, dyslipidaemia, or diabetes mellitus was recorded if documented by the physician in the admitting notes or if the clinical diagnoses and criteria conformed to the World Health Organization standards. Impaired renal function was defined as a serum creatinine level ≥ 1.5 mg/dL. Anaemia was defined as a haemoglobin level < 12 g/dL.

Clinical outcomes

The primary outcome was death from any cause, and the secondary outcomes were cardiac death and re-hospitalization due to worsened HF after hospital discharge. Cardiac death was defined as death due to HF, myocardial infarction, cardiogenic shock, sudden cardiac death (SCD), or other cardiac causes. SCD was defined as a non-traumatic, unexpected death occurring within 1 h of the onset of symptoms or within 24 h after last having been seen alive if death is not witnessed.[18] Worsened HF was defined on the basis of symptoms and signs, such as dyspnoea, rales, and ankle oedema, and the need for treatment with diuretics, vasodilators, positive inotropic drugs, or an intra-aortic balloon pump. Patients were followed up until 31 January 2016.

Assessment of quality of life

We assessed quality of life (QOL) using the European Quality of Life-5 Dimensions scale (EQ-5D) at hospital discharge only for the patients who were discharged alive. In general, for patients who could not complete the self-reported QOL scale, alternative sources, such as proxy measures, were used.[19] The proxy EQ-5D measured by physicians or home care staff is likely to be an acceptable alternative to the self-reported EQ-5D for estimating the summary scores of the EQ index and quality-adjusted life year, although it does not have sufficient agreement at the domain level.[20,21] For acutely ill patients, retrospective proxy estimation patient QOL using the EQ-5D is also acceptable at a level that does not pose clinical problems.[22] In this study, physicians, nurses, and research associates retrospectively completed (as proxies) the EQ-5D

according to each patient's physical and psychological status when the patient was discharged.

Data analysis

Data are presented as numbers and as medians and inter-quartile ranges for continuous and categorical data, respectively. We specified three groups on the basis of LVEF: (i) HFrEF (LVEF < 40%), (ii) HFmrEF (LVEF 40–49%), and (iii) HFpEF (LVEF ≥ 50%). The baseline clinical data were compared between groups using analysis of variance. The cumulative event-free rates were calculated using the Kaplan–Meier method. Differences in event-free rates were compared using the log-rank test. The hazard ratios for outcomes, in-hospital death, and death after discharge were compared among the categories of LVEF, with LVEF ≥ 50% as the referent group. We estimated age-adjusted and sex-adjusted and multivariable-adjusted proportional hazards models for each outcome. A P value of <0.05 was considered significant. Data analyses were performed with SPSS statistical software (Version 11.01, SPSS Inc., Chicago, Illinois, USA).

Results

Baseline characteristics

The baseline patient characteristics are shown in *Table 1*. Of the 1245 hospitalized HF patients, 444 (36%) had HFrEF, 263 (21%) had HFmrEF, and 538 had HFpEF (43%). Age and the proportion of women were higher in patients with HFpEF than in those with HFrEF. Patients with HFpEF had higher systolic blood pressures on admission and higher incidence of anaemia. Regarding underlying heart disease, coronary artery disease had the highest incidence in patients with HFmrEF; non-ischaemic cardiomyopathy had the highest incidence in patients with HFrEF; and valvular heart disease had the highest incidence in patients with HFpEF. The highest rate of ICD implantation on admission was seen in patients with HFrEF. The highest proportions of hypertension and dyslipidaemia were seen in patients with HFmrEF. The QRS complex duration was the longest in patients with HFrEF, followed by that in HFmrEF and HFpEF patients. The plasma BNP levels were the highest in patients with HFrEF.

Regarding medications at admission, patients with HFrEF were more likely to be treated with angiotensin-converting enzyme inhibitors, beta-blockers, loop diuretics, mineralocorticoid receptor antagonists, digoxin, and amiodarone. Patients with HFmrEF and HFpEF were more likely to be treated with calcium antagonists. There were higher rates of statin use, antiplatelet use, and erythropoietin use in patients with HFmrEF than in those with HFrEF and HFpEF.

Table 1 Patients' characteristics

Variable	Overall (*n* = 1245)	HFrEF (*n* = 444)	HFmrEF (*n* = 263)	HFpEF (*n* = 538)	*P* value
Age (years)	77 [65–85]	72 [60–81]	77 [65–84]	81 [72–87]	<0.001
Female gender	547 (44)	131 (30)	116 (44)	300 (56)	<0.001
Body mass index	22 [20–25]	22 [20–25]	22 [20–25]	22 [19–25]	0.028
Blood pressure (mmHg)					
Systolic	130 [110–152]	125 [106–145]	130 [110–150]	132 [114–157]	<0.001
Diastolic	71 [60–87]	72 [60–89]	73 [60–87]	70 [60–84]	0.187
Heart rate (b.p.m.)	84 [70–102]	90 [71–110]	82 [72–100]	81 [66–98]	<0.001
LVEF (%)	45 [34–58]	30 [23–35]	45 [41–46]	60 [54–64]	<0.001
NYHA class III/IV on admission	928 (75)	339 (76)	203 (77)	386 (72)	0.139
Underlying heart disease					<0.001
Coronary artery disease	425 (34)	171 (38)	117 (44)	137 (25)	
Cardiomyopathy	214 (17)	140 (32)	31 (12)	43 (8)	
Valvular disease	368 (30)	82 (18)	77 (29)	209 (39)	
Hypertensive heart disease	89 (7)	30 (7)	17 (6)	42 (8)	
Congenital heart disease	13 (1)	3 (1)	3 (1)	7 (1)	
Others	136 (11)	18 (4)	18 (7)	100 (19)	
Atrial fibrillation	318 (26)	105 (24)	73 (28)	140 (26)	0.454
Sustained VT/VF	62 (5)	41 (9)	12 (5)	9 (2)	<0.001
Hypertension	681 (55)	216 (49)	169 (64)	296 (55)	<0.001
Diabetes mellitus	383 (31)	154 (35)	79 (30)	150 (28)	0.068
Dyslipidaemia	375 (30)	148 (33)	93 (35)	134 (25)	0.002
Hyperuricaemia	175 (14)	87 (20)	38 (14)	50 (9)	<0.001
COPD	62 (5)	15 (3)	19 (7)	28 (5)	0.072
Impaired renal function[a]	675 (54)	230 (52)	146 (56)	299 (56)	0.444
Haemodialysis	69 (6)	27 (6)	19 (7)	23 (4)	0.190
Anaemia[b]	616 (50)	159 (36)	131 (50)	326 (61)	<0.001
ICD	94 (8)	68 (15)	12 (5)	14 (3)	<0.001
Laboratory data on admission					
White blood cell count (×10³/μL)	6.8 [5.2–9.0]	6.9 [5.3–8.8]	6.7 [5.2–9.2]	6.8 [5.1–9.1]	0.984
Haemoglobin (g/dL)	12 [10–14]	12.9 [11.2–14.6]	12.1 [10.4–13.8]	11.3 [9.7–12.9]	<0.001
Haematocrit (%)	36 [31–41]	39 [34–44]	36 [31–41]	34 [30–39]	<0.001
Platelet count (×10⁴/μL)	18 [14–22]	18 [14–22]	18 [14–23]	18 [14–22]	0.482
Albumin (g/dL)	3.7 [3.3–4.0]	3.7 [3.3–4.0]	3.7 [3.3–4.0]	3.6 [3.2–4.0]	0.215
Total bilirubin (mg/dL)	0.8 [0.5–1.1]	0.8 [0.6–1.2]	0.8 [0.5–1.0]	0.7 [0.5–1.0]	<0.001
BUN (mg/dL)	24 [17–36]	23 [17–35]	25 [18–38]	25 [17–36]	0.687
Creatinine (mg/dL)	1.2 [0.8–1.7]	1.2 [0.9–1.7]	1.2 [0.9–1.9]	1.1 [0.8–1.7]	0.218
Glucose (mg/dL)	121 [101–163]	123 [102–169]	120 [101–159]	119 [101–159]	0.295
Sodium (mEq/L)	140 [137–142]	139 [137–142]	140 [137–142]	140 [137–142]	0.294
Potassium (mEq/L)	4.3 [3.9–4.7]	4.3 [3.9–4.7]	4.2 [4.0–4.8]	4.3 [3.9–4.7]	0.819
C-reactive protein (mg/dL)	0.5 [0.2–1.7]	0.4 [0.2–1.5]	0.4 [0.2–1.3]	0.5 [0.2–2.1]	0.133
Plasma BNP (pg/mL)	567 [280–1098]	822 [400–1520]	512 [265–987]	450 [225–812]	<0.001
Electrocardiographic finding	(*n* = 1234)	(*n* = 439)	(*n* = 261)	(*n* = 534)	
Sinus rhythm	787 (64)	298 (68)	161 (62)	328 (61)	0.082
Atrial fibrillation	409 (33)	129 (29)	91 (35)	189 (35)	0.109
Other rhythm	38 (3)	12 (3)	9 (3)	17 (3)	
QRS complex duration (ms)	100 [80–122]	110 [90–140]	100 [80–125]	94 [80–110]	<0.001
<120	827 (67)	248 (56)	172 (66)	407 (76)	<0.001
120–149	241 (20)	94 (21)	62 (24)	85 (16)	0.014
≥150	166 (13)	97 (22)	27 (10)	42 (8)	<0.001
RBBB	137 (11)	37 (8)	33 (13)	67 (13)	0.081
LBBB	66 (5)	38 (9)	20 (8)	8 (1)	<0.001
Ventricular pacing	108 (9)	62 (14)	19 (7)	27 (5)	<0.001
Medications on admission					
ACE inhibitors	326 (26)	161 (36)	71 (27)	94 (17)	<0.001
ARBs	565 (45)	188 (42)	134 (51)	243 (45)	0.084
Beta-blockers	754 (61)	324 (73)	174 (66)	256 (48)	<0.001
Loop diuretics	894 (71)	339 (76)	194 (74)	361 (67)	0.004
Thiazide	219 (18)	74 (17)	54 (21)	91 (17)	0.368
MRAs	558 (45)	264 (59)	107 (41)	187 (35)	<0.001
Digoxin	168 (14)	85 (19)	34 (13)	49 (9)	<0.001
Nitrates	204 (16)	70 (16)	49 (19)	85 (16)	0.541
Calcium antagonists	443 (36)	100 (23)	107 (41)	236 (44)	<0.001
Statins	400 (32)	143 (32)	118 (45)	139 (26)	<0.001
Antiplatelets	481 (39)	179 (40)	131 (50)	171 (32)	<0.001
Oral anticoagulants	523 (42)	198 (45)	117 (44)	208 (39)	0.113

(*Continues*)

Table 1 (continued)

Variable	Overall (n = 1245)	HFrEF (n = 444)	HFmrEF (n = 263)	HFpEF (n = 538)	P value
Amiodarone	158 (13)	94 (21)	34 (13)	30 (6)	<0.001
Other antiarrhythmics	22 (2)	10 (2)	4 (2)	8 (1)	0.645
Erythropoietin	127 (10)	39 (9)	39 (15)	49 (9)	0.020

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; RBBB, right bundle branch block; VF, ventricular fibrillation; VT, ventricular tachycardia.
Values are n (%) or median [inter-quartile range].
[a]Impaired renal function was defined as a serum creatinine level ≥ 1.5 mg/dL.
[b]Anaemia was defined as a haemoglobin level < 12 g/dL.

In-hospital management and outcomes

During hospitalization, 66% of patients received intravenous diuretics; and 30% of patients, particularly those with HFrEF, received intravenous carperitide, a human atrial natriuretic peptide. There was a higher rate of intravenous inotrope use, especially dobutamine in patients with HFrEF. The incidence of percutaneous coronary intervention was the highest in patients with HFmrEF (*Table 2*).

The median hospital stay for the overall population was 19 days, and the length of stay was >7 days for >90% of patients. The hospital stay was the longest for HFrEF patients, followed by that for HFmrEF and HFpEF patients (*Table 3*).

In-hospital death was observed in 89 (7%) of the 1245 hospitalized HF patients, and its frequency did not differ among the groups (*Table 3*). HF was the most common cause of in-hospital death, followed by infection (*Table 3*).

Hospital discharge and subsequent prognosis

Of the 1245 hospitalized HF patients, 1156 (93%) patients were discharged alive from the cardiology department. The

age of these survivors at discharge was younger than that of all hospitalized patients upon admission, but it was the highest in the HFpEF group, followed by that in the HFmrEF and HFrEF groups. The blood pressure and heart rate of patients who were discharged alive were lower than those of patients upon admission in each group, and >85% of patients who were discharged alive were categorized as New York Heart Association function class I or II. The plasma BNP level was also lower at discharge than upon admission but was the highest in the HFrEF group, followed by that in the HFmrEF and HFpEF groups. Regarding medications at discharge, the frequencies of each medicine used did not change from those upon admission for any group. The discharge destination was home for 61% of patients and a nursing home for 13%; the other patients were transferred to other wards or hospitals. The EQ-5D score at discharge did not differ between groups (*Table 4*).

After a median follow-up of 19 months (range, 3–26 months), 192 (17%) patients died and 534 (46%) patients readmitted. Kaplan–Meier curves for all-cause mortality in the LVEF groups are shown in *Figure 1*. There were no significant differences in mortality among the three LVEF groups. Of the patients who died, cardiac causes of death accounted

Table 2 Treatment for decompensated heart failure during hospitalization

Variable	Overall (n = 1245)	HFrEF (n = 444)	HFmrEF (n = 263)	HFpEF (n = 538)	P value
Intravenous loop diuretics	823 (66)	305 (69)	156 (59)	362 (67)	0.031
Intravenous nitrates	352 (28)	114 (26)	91 (35)	147 (27)	0.034
Intravenous carperitide	371 (30)	164 (37)	78 (30)	129 (24)	<0.0001
Intravenous inotropes	213 (17)	102 (23)	47 (18)	64 (12)	<0.0001
Noradrenaline	91 (7)	39 (9)	23 (9)	29 (5)	0.068
Dobutamine	136 (11)	71 (16)	30 (11)	35 (7)	<0.0001
Dopamine	72 (6)	21 (5)	15 (6)	36 (7)	0.426
PDE III inhibitors	20 (2)	11 (2)	5 (2)	4 (1)	0.069
Intravenous amiodarone	36 (3)	18 (4)	8 (3)	10 (2)	0.122
Intravenous nifekalant	7 (1)	5 (1)	2 (1)	0 (0)	0.026
Intravenous heparin	136 (11)	42 (9)	23 (9)	71 (13)	0.058
Intravenous opioid	30 (2)	10 (2)	7 (3)	13 (2)	0.943
NPPV	6 (1)	5 (1)	0 (0)	1 (0.2)	0.070
Respirators	276 (22)	108 (24)	64 (24)	104 (19)	0.106
IABP	30 (2)	14 (3)	6 (2)	10 (2)	0.420
PCPS	4 (0.3)	2 (0.5)	1 (0.4)	1 (0.2)	0.688
PCI	80 (6)	33 (7)	26 (10)	21 (4)	0.002

IABP, intra-aortic balloon pumping; NPPV, non-invasive positive pressure ventilation; PCI, percutaneous coronary intervention; PCPS, percutaneous cardiopulmonary support; PDE, phosphodiesterase.
Values are n (%).

Table 3 Summary of hospital length and in-hospital outcomes

Variable	Overall (n = 1245)	HFrEF (n = 444)	HFmrEF (n = 263)	HFpEF (n = 538)	P value
Length of stay (days)					
Median	19	21	19	17	<0.001
Minimum	1	1	1	1	
Maximum	391	391	205	113	
Length of stay > 7 days	1148 (92)	416 (93)	244 (93)	488 (91)	0.209
In-hospital death	89 (7)	32 (7)	15 (6)	42 (8)	0.554
Cause of in-hospital death					0.193
Heart failure	67 (75)	22 (69)	11 (73)	34 (17)	
Myocardial infarction	2 (2)	0 (0)	1 (7)	1 (2)	
Pulmonary embolism	1 (1)	0 (0)	1 (7)	0 (0)	
Aortic dissection	2 (2)	2 (6)	0 (0)	0 (0)	
Infection	10 (11)	6 (19)	1 (7)	3 (7)	
Renal failure	1 (1)	0 (0)	0 (0)	1 (2)	
Malignancy	2 (2)	2 (6)	0 (0)	0 (0)	
Other non-cardiac causes	4 (4)	0 (0)	1 (7)	3 (7)	

Values are days and *n* (%).

for 56% of deaths and non-cardiac causes of death for 35%, and the cause of death remained unknown or undetermined in 8% of cases (*Table 5*). The most common reason for re-hospitalization was worsening HF (*Table 5*). Kaplan–Meier curves for cardiac death and re-hospitalization due to worsening HF are shown in *Figure 2*. There were no significant differences in cardiac death or re-hospitalization due to worsening HF among the three LVEF groups.

Risk of mortality according to the categorized left ventricular ejection fraction

In multivariable-adjusted analyses, the HFmrEF and HFrEF groups, compared with the HFpEF group, were not associated with an increase in the risk of in-hospital death. For all-cause death after discharge, the HFmrEF and HFrEF groups, compared with the HFpEF group, were also not associated with an increase in the risk of death after discharge (*Table 6*).

Discussion

Our results support the following conclusions. (i) Of the Japanese hospitalized HF patients, 36% had HFrEF, 21% had HFmrEF, and 43% had HFpEF. (ii) Age and the proportion of women were highest in HFpEF patients, followed by HFmrEF and HFrEF patients. (iii) Regarding underlying heart disease, there were high proportions of cardiomyopathy in HFrEF patients, coronary artery disease in HFmrEF patients, and valvular disease in HFpEF patients. (iv) The plasma BNP values upon admission were the highest and QRS widths were the longest in HFrEF patients, followed by HFmrEF and HFpEF patients. (v) During hospitalization, intravenous carperitide was commonly used. (vi) In-hospital mortality was recorded in 7% of patients, and there were no differences in in-hospital deaths among the LVEF groups. (vii) There were no

differences in mortality or re-hospitalization due to HF for patients discharged alive among the three groups.

Clinical characteristics of the different heart failure groups

Among hospitalized patients with worsening HF, the ratio of HFrEF, HFmrEF, and HFpEF was 2:1:2, comparable with the results of other cohorts of hospitalized HF patients in Japan.[23,24] Age and the proportion of women were the highest in the HFpEF group, followed by those in the HFmrEF and HFrEF groups; these results are comparable with reports from the USA and Europe.[25,26] Older age and female sex are risk factors for HFpEF,[27,28] and our results are consistent with previous reports. In general, coronary artery disease is a major type of underlying heart disease in HF patients in the USA and Europe (~50%).[2] However, our results showed that only 30% of HF patients had coronary artery disease. In recent Japanese cohorts, the proportion of coronary artery disease was ~30% among hospitalized HF patients.[23,24] However, the Chronic Heart Failure Analysis and Registry in the Tohoku District (CHART)-2 reported that coronary artery disease was found in nearly 50% of HF patients.[29] This difference may be due to patient characteristics: 80% of the subjects included in CHART-2 were outpatients, and >50% had coronary artery disease without HF or had stage B HF.[30] In our study, of the different HF groups, the HFmrEF group had the highest frequency of coronary artery disease. This result is consistent with other cohort studies from Japan.[23,24] Japanese patients with HFmrEF have a relatively high proportion of underlying coronary artery disease, and there is a possibility that the LVEF may improve with the subsequent treatment of ischaemia (including revascularization). Our findings may support that HFmrEF is a condition that represents a transition between HFrEF and HFpEF.[26]

Of our HFpEF patients, ~40% had valvular disease. In valvular disease, mechanistic variables, such as the capacity load,

Table 4 Patient status at discharge

Variable	Overall (n = 1156)	HFrEF (n = 412)	HFmrEF (n = 248)	HFpEF (n = 496)	P value
Age (years)	76 [65–84]	70 [59–80]	76 [65–84]	80 [71–86]	<0.001
Female gender	503 (44)	120 (29)	107 (43)	276 (56)	<0.001
Blood pressure (mmHg)					
Systolic	112 [102–126]	108 [98–120]	112 [102–126]	118 [104–131]	<0.001
Diastolic	62 [55–70]	62 [54–71]	60 [54–68]	62 [56–71]	0.264
Heart rate (b.p.m.)	70 [61–78]	70 [63–78]	70 [62–76]	68 [60–77]	0.090
NYHA class I/II/III/IV	131/879/141/5 (11/76/12/1)	38/318/53/3 (9/77/13/1)	28/187/33/0 (11/75/13/0)	65/374/55/2 (13/75/11/1)	0.432
ICD	118 (10)	83 (20)	17 (7)	18 (4)	<0.001
Laboratory data					
White blood cell count (×10^3/μL)	5.6 [4.4–6.8]	5.6 [4.5–6.9]	5.5 [4.5–6.6]	5.5 [4.4–6.8]	0.544
Haemoglobin (g/dL)	12 [10–14]	13 [11–14]	12 [10–13]	11 [10–13]	<0.001
Haematocrit (%)	36 [32–40]	38 [33–42]	35 [32–40]	34 [31–38]	<0.001
Platelet count (×10^4/μL)	19 [15–24]	18 [15–23]	19 [15–24]	19 [15–25]	0.733
Albumin (g/dL)	3.6 [3.2–4.0]	3.6 [3.3–4.0]	3.6 [3.2–4.0]	3.5 [3.2–3.9]	0.066
Total bilirubin (mg/dL)	0.6 [0.5–0.9]	0.7 [0.5–0.9]	0.6 [0.4–0.9]	0.6 [0.4–0.9]	0.084
BUN (mg/dL)	25 [17–37]	24 [17–37]	26 [18–37]	25 [17–37]	0.601
Creatinine (mg/dL)	1.1 [0.8–1.7]	1.2 [0.9–1.6]	1.2 [0.9–1.9]	1.1 [0.8–1.7]	0.261
Glucose (mg/dL)	110 [93–137]	117 [97–141]	104 [93–125]	107 [92–140]	0.270
Sodium (mEq/L)	139 [136–141]	139 [136–141]	139 [137–141]	139 [136–141]	0.614
Potassium (mEq/L)	4.4 [4.1–4.7]	4.4 [4.1–4.7]	4.4 [4.0–4.7]	4.4 [4.0–4.7]	0.295
C-reactive protein (mg/dL)	0.3 [0.1–1.0]	0.3 [0.1–0.9]	0.3 [0.1–1.1]	0.3 [0.1–1.1]	0.654
Plasma BNP (pg/mL)	245 [114–496]	284 [153–566]	250 [117–517]	194 [83–392]	<0.001
Medications					
ACE inhibitors	312 (27)	154 (37)	66 (27)	92 (19)	<0.001
ARBs	545 (47)	181 (44)	128 (52)	236 (48)	0.145
Beta-blockers	724 (63)	308 (75)	166 (67)	250 (50)	<0.001
Loop diuretics	850 (73)	319 (77)	185 (75)	346 (70)	0.030
Thiazide	206 (18)	69 (17)	50 (20)	87 (18)	0.537
MRAs	528 (46)	245 (59)	102 (41)	181 (36)	<0.001
Digoxin	161 (14)	82 (20)	31 (13)	48 (10)	<0.001
Nitrates	183 (16)	61 (15)	46 (19)	76 (15)	0.409
Calcium antagonists	421 (36)	94 (23)	100 (40)	227 (46)	<0.001
Statins	386 (33)	137 (33)	114 (46)	135 (27)	<0.001
Antiplatelets	455 (39)	166 (40)	124 (50)	165 (33)	<0.001
Oral anticoagulants	499 (43)	186 (45)	111 (45)	202 (41)	0.365
Amiodarone	147 (13)	86 (21)	32 (13)	29 (6)	<0.001
Other antiarrhythmics	21 (2)	9 (2)	4 (2)	8 (2)	0.784
Erythropoietin	122 (11)	36 (9)	38 (15)	48 (11)	0.026
Discharge destination					
Home	703 (61)	279 (68)	135 (54)	289 (58)	0.001
Other ward	74 (6)	18 (4)	20 (8)	36 (7)	0.101
Other hospital	224 (19)	70 (17)	47 (19)	107 (22)	0.216
Nursing home	155 (13)	45 (11)	46 (19)	64 (13)	0.019
ED-5D score	79 [70–80]	80 [70–80]	77 [70–80]	78 [70–80]	0.304

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; ED-5D, European Quality of Life-5 Dimensions; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.
Values are n (%) or median [inter-quartile range].

Number at Risk

HFrEF	412	320	286	254	132
HFmrEF	248	170	148	130	72
HFpEF	496	351	298	251	154
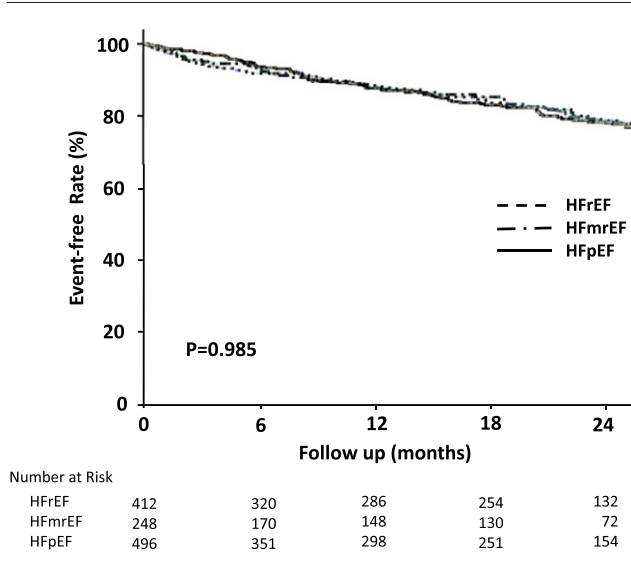
afterload, and mechanical obstruction of LV filling, lead to HF rather than impaired LV contraction. However, the increase in valvular disease in Japanese HF patients is interesting because the incidence of rheumatic valvular disease has diminished. The causes of valvular disease in our patients showed high frequencies of mitral valve regurgitation and tricuspid regurgitation (mitral valve regurgitation, 47%; tricuspid valve regurgitation, 35%; aortic valve regurgitation, 15%; aortic stenosis, 14%; and mitral stenosis, 3%). Valvular disorders were also common in the EuroHeart Failure Survey II (EHFS II), and mitral valve regurgitation occurred the most frequently, followed in prevalence by tricuspid valve regurgitation and aortic valve regurgitation.[31] Age-related changes in the mitral and aortic valves and an age-related increase in the pulmonary artery pressure, which is associated with an increased left heart diastolic pressure and systemic vascular stiffening, play roles in the increases in these valvular diseases.[32,33]

The difference between Japanese HF patients and Western HF patients is the considerably lower rate of ischaemic aetiology among Japanese patients with HFrEF than among Western patients with HFrEF.[25] In our study, the incidence of non-ischaemic cardiomyopathy, such as dilated cardiomyopathy, was relatively high. Race and ethnic variations might account for the differences in the causes of HF. Furthermore, the differences may be related to the lower frequency of surviving Japanese myocardial infarction patients than Western patients with a low LVEF in the primary percutaneous intervention era.[34] The overall plasma BNP values upon admission were higher for HFrEF patients, followed by those for HFmrEF and HFpEF patients, which were comparable with the results of previous reports.[35,36] Although the BNP level was a predictor of prognosis for individual HF patients despite the LVEF,[35,36] the differences in the contributing factors to the BNP values, such as age, renal function, and obesity, may be related to the distribution of the BNP values in the LVEF groups. The higher proportions of lethal arrhythmias and ICD implantation among patients with HFrEF were related to a low LVEF as a risk of SCD.

Hospital treatment and prognosis

In our study, the frequencies of intravenous diuretic use and intravenous vasodilator use were high during hospitalization. Because intravenous diuretics are the first-line therapy for acute decompensated HF,[11] the frequency of intravenous diuretic use is high among cohorts of hospitalized HF

Table 5 Summary of outcomes after discharge

Variable	Overall (*n* = 1156)	HFrEF (*n* = 412)	HFmrEF (*n* = 248)	HFpEF (*n* = 496)	*P* value
Death	192 (17)	73 (18)	40 (16)	79 (16)	0.740
Cause of death					
Cardiac cause	108 (56)	41 (56)	21 (53)	46 (58)	0.731
Heart failure	76 (40)	28 (38)	13 (33)	35 (44)	
Sudden cardiac death	30 (16)	13 (18)	7 (18)	10 (13)	
Myocardial infarction	2 (1)	0 (0)	1 (3)	1 (1)	
Non-cardiac cause	68 (35)	26 (36)	14 (35)	28 (35)	
Stroke	3 (2)	1 (1)	2 (5)	0 (0)	
Infection	31 (16)	14 (19)	8 (20)	9 (11)	
Malignancy	9 (5)	4 (5)	1 (3)	4 (5)	
Gastrointestinal disease (except malignancy)	7 (4)	1 (1)	1 (3)	5 (6)	
Renal failure	2 (1)	0 (0)	0 (0)	2 (3)	
Multiple organ failure	2 (1)	1 (1)	0 (0)	1 (1)	
Other non-cardiac causes	14 (7)	5 (7)	2 (5)	7 (9)	
Unknown/undetermined	16 (8)	6 (8)	5 (13)	5 (6)	
Re-hospitalization	534 (46)	196 (48)	108 (44)	230 (46)	0.740
Cause of hospitalization					0.646
Heart failure	205 (38)	79 (40)	40 (37)	86 (37)	
Other cardiac cause	124 (23)	50 (26)	27 (25)	47 (20)	
Non-cardiac cause	205 (38)	67 (34)	41 (38)	97 (42)	

Values are *n* (%).

Figure 2 Kaplan–Meier curves for cardiac death (A) and re-hospitalization due to worsening HF (B) in patients with HFrEF, HFmrEF, and HFpEF.
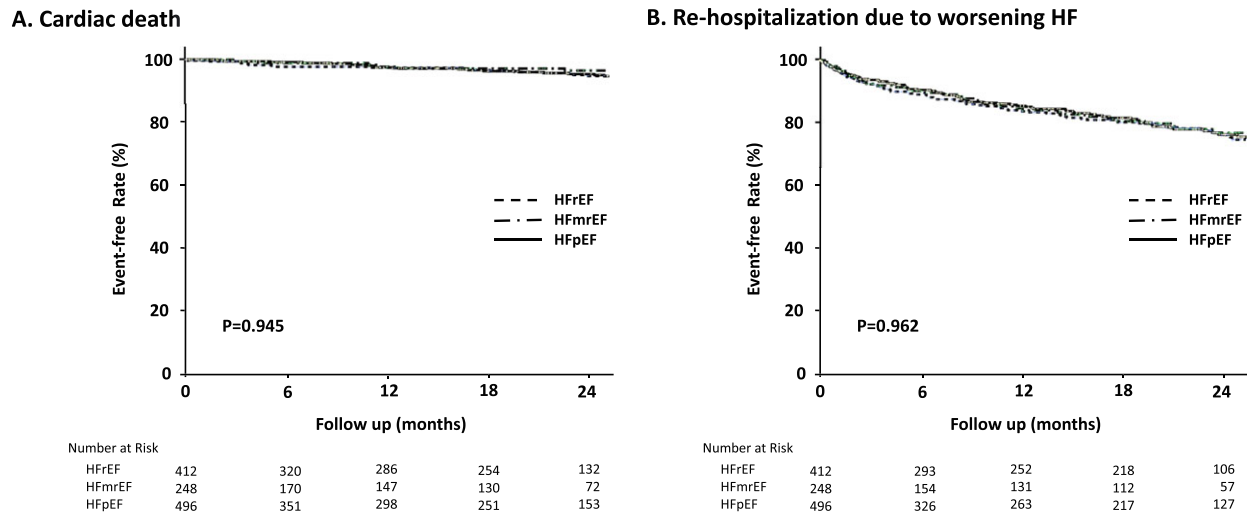
Table 6 Hazard ratios for all-cause death by categorical left ventricular ejection fraction

	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
In-hospital death								
HFpEF	Reference		Reference		Reference		Reference	
HFmrEF	0.73 (0.39–1.35)	0.314	0.97 (0.46–2.04)	0.935	0.92 (0.43–1.94)	0.823	0.80 (0.36–1.75)	0.570
HFrEF	1.08 (0.66–1.76)	0.765	1.49 (0.82–2.71)	0.194	1.41 (0.77–2.59)	0.262	1.10 (0.57–2.12)	0.768
Death after discharge								
HFpEF	Reference		Reference		Reference		Reference	
HFmrEF	1.20 (0.82–1.77)	0.348	1.09 (0.72–1.65)	0.683	1.11 (0.73–1.69)	0.611	1.17 (0.76–1.79)	0.476
HFrEF	1.25 (0.89–1.74)	0.202	1.12 (0.78–1.61)	0.551	1.11 (0.77–1.60)	0.573	1.12 (0.84–1.75)	0.307

CI, confidence interval; HR, hazard ratio.
Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, and body mass index. Model 3: adjusted for age, sex, body mass index, and baseline cardiovascular disease. Model 4: adjusted for age, baseline cardiovascular disease, hypertension, diabetes, dyslipidaemia, hyperuricaemia, chronic obstructive pulmonary disease, impaired renal function, anaemia, and systolic blood pressure.

patients.[14,31,37,38] The frequency of intravenous vasodilators, such as nitrates, in our study was similar to that reported by the EHFS II.[31] However, natriuretic peptides are used much more often in Japan than in Western countries.[37,38] The usage rates of natriuretic peptides were 30% in our study, 34% in the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD), and up to 69% in the Acute Decompensated Heart Failure Syndromes (ATTEND) registry.[14,38] Carperitide, a natriuretic peptide that is only approved in Japan, has been evaluated as a treatment for acute decompensated HF in only a few trials that have assessed mortality.[39] Furthermore, the superior cost-effectiveness of carperitide has not been demonstrated.[40] The use of carperitide for HF treatment may need to be reconsidered.

In-hospital mortality did not differ among the HF groups, and HF was the most frequent cause of death; however, non-cardiac death was also not uncommon. These results may be due to the older age, many co-morbidities, and concomitant illnesses, such as infections, in HF patients in clinical settings.

The median length of in-hospital stays was 19 days in our study. This length was shorter than that in previous Japanese reports from the 2000s[14,38] but was longer than that in reports from the USA and Europe (4–9 days).[31,37] During hospitalization for a prolonged period, evaluation of the underlying disease, co-morbidities, and treatment, including cardiac rehabilitation, is available for patients with HF. However, whether the longer in-hospital stay improves their prognosis and re-hospitalization is not clear.

Prognosis after hospital discharge

For drug treatment at discharge, the frequency of beta-blocker use increased compared with that in the 2000s[13]; in the HFrEF group, 75% of patients received beta-blockers. The increased frequencies of statin, anticoagulant, amiodarone, and erythropoietin use compared with those in the 2000s[13] may be due to evidence-based treatment or guidelines.

In our study, there were no differences in QOL, later mortality, or re-hospitalization due to HF among the LVEF groups (for patients who were discharged alive), although in the only available follow-up echocardiographic data after hospital discharge (*n* = 363), 36% of patients with HFrEF showed an increased LVEF (21% in the HFmrEF category and 15% in the HFpEF category) and 38% of patients with HFmrEF showed an increased LVEF (the HFpEF category) during the follow-up period. However, 16% of patients with HFmrEF showed a decreased LVEF (the HFrEF category) and 22% of patients with HFpEF showed a decreased LVEF (3% in the HFrEF category and 19% in the HFmrEF category) during the follow-up period. These LVEF transitions might partially account for the lack of differences in the prognosis after discharge between LVEF groups at admission.

In our study, only 60% of discharged patients returned home. Older age, deterioration of living ability, and the many co-morbidities among HF patients might contribute more than LVEF to their prognosis. The most common cause of death was HF, followed by SCD and infection. SCD is an important cause of cardiac death in HF patients and accounted for 28% of the cardiac causes of death in our study. The ESC-HF Pilot survey reported that SCD accounted for 40% of the cardiac causes of death.[41] Infection including pneumonia was the leading cause of non-cardiac death, followed by malignancy in HF patients. Non-cardiac diseases such as respiratory and gastrointestinal disease and malignancy make a significant contribution to death and re-hospitalization in HF patients.[42] Several complications and co-morbid conditions in HF patients may have contributed to their prognosis. In the future, integrated management approaches will be required for HF patients.

Study limitations

There were some limitations to this study. First, this study was designed as a retrospective observational study to investigate all consecutive hospitalized HF patients. Therefore, patients with HF were ultimately identified from medical records. The LVEF could not be obtained for all patients from the data recorded during hospitalization. Furthermore, we could not collect detailed information about changes in medication and the LVEF after hospital discharge for all patients who were discharged alive. We could not exclude the influences of these factors, which might affect the prognosis, from our results. Some patients were lost to follow-up. The cause of death after discharge could not be determined in detail. The retrospective nature of this study also meant that we had to assess QOL using proxy EQ-5D measurements, not self-reported EQ-5D measurements. Second, data concerning the clinical conditions when clinical events occurred were not available. In addition, there was a treatment bias. Third, the

number of subjects was relatively small. Therefore, subgroup analyses were not feasible.

Conclusions

This study showed that the proportions of HFrEF, HFmrEF, and HFpEF occurrences among Japanese hospitalized HF patients were 36%, 21%, and 43%, respectively; the clinical characteristics of these patients were different, but their prognosis was not. The most common cause of death and re-hospitalization after hospital discharge was HF, but non-cardiac causes also contributed to their prognosis. Integrated management approaches will be required for HF patients.

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Conflict of Interest

Funding

Appendix A

The following investigators participated in the HIJ-HF II.

Cardiovascular Center of Sendai: Katsuhiro Yagi, Shinya Fujii, Kazuki Tanaka, Bun Yashiro, Mayui Nakazawa, Takahiro Yamada, and Masahiro Watarai

Saiseikai Kurihashi Hospital: Yoshimi Ota, Yusuke Inagaki, Eiji Shibahashi, and Tonre Ri

Tokyo Women's Medical University Yachiyo Medical Center: Shoji Haruta, Yuichiro Yamada, and Koichiro Miura

Shinmatsudo Central General Hospital: Joji Katoh

Tokyo Metropolitan Tama Medical Center: Hiroyuki Tanaka and Ayano Yoshida

Tama-Hokubu Medical Center: Satoshi Murasaki and Yuichiro Yamada

JCHO Sagamino Hospital: Takao Yamauchi

National Yokohama Medical Center: Kazunori Iwade, Fumiaki Mori, and Takashi Saito

Seirei Hamamatsu General Hospital: Toshiaki Oka and Naomi Kawakatsu

Tokyo Women's Medical University Hospital: Atsushi Suzuki, Tsuyoshi Suzuki, Erisa Watanabe, Noriko Kikuchi, Hidetoshi Hattori, Tomohito Kogure, Arata Nomura, Shintaro Haruki, Kensuke Shimazaki, Kimiko Nagara, Ryosuke Itani, Tasturo Iida, Naoki Iizuka, and Yuta Morioka

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