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ORIGINAL ARTICLE

Clinical characteristics and frailty status in heart failure with preserved vs. reduced ejection fraction

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Abstract

Aims The aim of this study was to elucidate the clinical characteristics, including frailty status, of patients with heart failure with preserved ejection fraction (HFpEF) in comparison with those in patients with heart failure with reduced ejection fraction (HFrEF) in a super-aged region of Japan.

Methods and results Of the 1061 Japanese patients enrolled in the Kochi YOSACOI study, a multicentre registry, we divided 645 patients (median age of 81 years [interquartile range, 72–87 years]; women, 49.1%) into two groups, HFpEF patients (61.2%) and HFrEF patients (38.8%). Physical frailty was diagnosed on the basis of the Japanese version of Cardiovascular Health (J-CHS) Study criteria. Patients for whom left ventricular ejection fraction data were not available (n = 19), patients with heart failure with mildly reduced ejection fraction (n = 172), and patients who were not assessed by the J-CHS criteria (n = 225) were excluded. The median ages of the HFpEF and HFrEF patients were 84 and 76 years, respectively. The proportion of patients with HFpEF gradually increased with advance of age. The proportion of patients with three or more comorbidities was larger in HFpEF patients than in HFrEF patients (77.9% vs. 65.6%, P = 0.003). Handgrip strength was significantly lower in HFpEF patients than in HFrEF patients for both men ($P < 0.001$) and women (P = 0.041). Comfortable 5 m walking speed was significantly slower in HFpEF patients than in HFrEF patients ($P < 0.001$). The proportions of patients with physical frailty were 55.2% in HFpEF patients and 46.8% in HFrEF patients, and the proportion was significantly higher in HFpEF patients (P = 0.043). In multivariate analysis, physical frailty was associated with advanced age [odds ratio (OR), 1.030; 95% confidence interval (CI), 1.010–1.050; P = 0.023] and low albumin level (OR, 0.334; 95% CI, 0.192–0.582; $P < 0.001$) in HFpEF patients, and physical frailty was associated with women (OR, 2.150; 95% CI, 1.030–4.500; P = 0.042) and anaemia (OR, 2.840; 95% CI, 1.300–6.230; P = 0.003) in HFrEF patients.

Conclusions In a super-aged population of HF patients in Japan, HFpEF patients are more likely to be frail/have a high frailty status compared with HFrEF patients. The results suggested that physical frailty is associated with extracardiac factors in both HFpEF patients and HFrEF patients.

Keywords Frailty; Physical function; Heart failure; Heat failure with preserved ejection fraction; Elderly

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Introduction

Heart failure (HF) has become a public health burden due to the increasing number of HF patients in ageing populations worldwide.[1,2] Several studies have shown that clinical outcomes in elderly patients with HF are poor.[3–5] Elderly patients often have adverse events caused by multiple comorbidities and non-medical factors such as self-management and medication adherence.[6–8] It has been reported that patients with HF frequently have multifaceted vulnerability including psychological and social aspects as well as the physical function domain.[9] These vulnerabilities are associated with poor

outcomes. For that reason, a multifaceted assessment of frailty is useful for understanding the status of elderly patients with HF and providing appropriate intervention. HF with preserved ejection fraction (HFpEF) is more common in elderly patients with HF, but drug therapy for HFpEF has not been well established compared with drug therapy for HF with reduced ejection fraction (HFrEF). Therefore, a multidisciplinary approach other than drug therapy for HF, including intervention for comorbidities and nutritional management and cardiac rehabilitation for maintenance of physical function, is very important for the management of HFpEF. It has been reported that patients with HFpEF and patients with HFrEF had similar impairments of physical and cognitive functions, while patients with HFpEF had a worse depressive status and poorer quality of life than those for patients with HFrEF.[10] However, there have been few reports on a comparison of clinical characteristics, including physical frailty and its related factors, in patients with HFpEF and patients with HFrEF in a Japanese population. The purpose of this study was to comprehensively investigate clinical characteristics, including frailty status, of patients with HFpEF by comparison with patients with HFrEF in a super-aged region of Japan.

Methods

Study design

In 2017, we established the Kochi Registry of Subjects with Acute Decompensated Heart Failure, named the Kochi YOSACOI study, to provide detailed information on the clinical characteristics of patients with HF in a contemporary, community-based unselected population in a super-aged region of Japan. Briefly, the YOSACOI Study is a multicentre, prospective observational study that enrolled 1061 patients with acute decompensated HF who were admitted to six hospitals serving as primary, secondary, and tertiary medical centres for patients with cardiovascular disease during the period from May 2017 to December 2019 in Kochi Prefecture, Japan. The clinical characteristics of the patients have been described in detail previously.[11] Data were collected by investigators at the participating hospitals during the registration period. We obtained information on clinical characteristics including patient demographics, aetiology of HF, medical history, social status (i.e. living environment, persons who live and eat with the patient, and long-term care insurance), multidimensional frailty status, HF symptoms and vital signs at admission and on discharge, discharge prescription, laboratory data, and echocardiography data. We used echocardiographic data at the time when HF status was stabilized during hospitalization. HF was classified according to the left ventricular ejection fraction (LVEF) including HFpEF (LVEF $\geq$ 50%), HF with mildly reduced ejection fraction (HFmrEF, LVEF of 40% to 49%), and HFrEF (LVEF $<$ 40%). We investigated 12 comorbidities: hypertension, diabetes mellitus, dyslipidaemia, chronic obstructive pulmonary disease, bronchial asthma, cerebrovascular accident, atrial fibrillation/flutter, peripheral arterial disease, malignant disease, anaemia, chronic kidney disease, and dementia.[11] We evaluated the pathophysiological status of HF on admission. The clinical scenario (CS) classification is an assessment tool to classify patients with acute HF according to pathophysiological status with reference to systolic blood pressure and to provide appropriate initial management for each type of patient.[12] The classification is as follows: CS1, acute pulmonary oedema; CS2, systemic fluid retention (congestion); and CS3, low cardiac output/hypoperfusion (including cardiogenic shock).

Assessment of frailty status

We evaluated frailty status from multidimensional aspects in each of the HFpEF and HFrEF patients. Physical frailty was assessed on the basis of the Japanese version of the Cardiovascular Health Study (the J-CHS) criteria consisting of five physical components (walking speed, handgrip strength, shrinking, exhaustion, and physical inactivity) that were established by modifying the original CHS criteria.[13,14] Slow walking speed is defined using a cut-off ($<$1.0 m/s) for a comfortable 5 m walking speed.[13,15] Low handgrip strength of the dominant hand is defined using gender-specific cut-offs ($<$26 kg for men and $<$18 kg for women).[13,15] Shrinking is defined as having lost 2 kg or more in the past 6 months.[13] Exhaustion is present if patients answer 'yes' to the following question from the Kihon Checklist (KCL), a self-reported comprehensive health checklist: 'In the last two weeks, have you felt tired for no reason?'[13,16] Low physical activity is defined as when patients have a negative response to the following two questions: 'Do you engage in moderate levels of physical exercise or sports aimed at health?' and 'Do you engage in low levels of physical exercise aimed at health?'[13] Patients with none of these components were considered as patients with non-physical frailty, those with one or two components were considered as patients with physical pre-frailty, and those with three or more components were considered as patients with physical frailty. We evaluated nutritional status by Geriatric nutritional risk index (GNRI) on admission. GNRI was calculated as follows: 14.89 × serum albumin (g/dL) + 41.7 × body mass index (BMI)/22. GNRI $<$ 92 was defined as moderate or severe nutritional risk.[17] Cognitive aspects of frailty were assessed by the Hasegawa dementia rating scale-revised (HDS-R). Patients with a score of 20 or less were considered as patients with cognitive frailty. As social aspects of frailty, we assessed social engagement and social ties. Three components were assessed: (1) eating arrangement, (2) social ties of friends, and (3) social activity. Eating alone is defined as eating meals alone every time in

a week. Weakness of social ties of friends is defined as a negative response to the question 'Do you sometimes visit your friends?'[16] A low level of social activity is defined as a negative response to the question 'Do you go out less frequently compared to last year?'[16] Informed consent was given by all patients or their proxies in accordance with the guidelines of the Ethics Committee on Medical Research of Kochi Medical School. The present study was conducted in compliance with the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee on Medical Research of Kochi Medical School (approval No. 28-68) and at all participating hospitals.

Statistical analysis

Normally distributed data are expressed as means ± standard deviation, non-parametric data are expressed as medians [interquartile range (IQR)], and categorical data are expressed as numbers and percentages. Pearson's χ^2 test was used for comparisons between categorical variables, and Fisher's exact test was used when the expected frequency was lower than 5. The significance of differences between two groups was assessed using the unpaired *t*-test or Mann–Whitney *U*-test for continuous variables. Logistic regression analysis was performed to examine the determinants of physical frailty in HFpEF patients and HFrEF patients. Univariate logistic regression analysis was performed by considering the following independent variables: age, sex, BMI, living alone, HDS-R, prior HF admission, diabetes mellitus, ischaemic heart disease, hypertension, chronic kidney disease, anaemia, New York Heart Association class $\geq$ III, LVEF, number of multimorbidities ≥ 3, serum albumin level, and plasma brain natriuretic peptide (BNP) level at discharge. Independent variables with $P < 0.1$ in the univariate analysis were included in the multivariate logistic regression analysis. Statistical significance was defined by two-sided $P \leq 0.05$. All statistical analyses were performed using Microsoft R Open Version 4.0.2 (Microsoft, Redmond, Washington).

Results

Clinical presentation

Of the 1061 patients enrolled in our HF registry, a total of 645 patients (median age, 81 years [IQR, 72–87 years], women, 49.1%) were analysed in the present study. Patients whose LVEF was not measured (n = 19), patients with HFmrEF (n = 172), and patients not entirely assessed by the J-CHS criteria (n = 225) were excluded. There were 395 patients (61.2%) with HFpEF and 250 patients (38.8%) with HFrEF in the present study. The proportion of patients with HFpEF gradually increased with advance of age (*Figure 1*). The clinical characteristics of the patients with HFpEF and the patients with HFrEF are summarized in *Table 1*. The median ages of the HFpEF and HFrEF patients were 84 years (IQR,

Figure 1 Proportions of HFpEF patients and HFrEF patients according to age category. Cochran–Armitage trend test $P < 0.001$. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

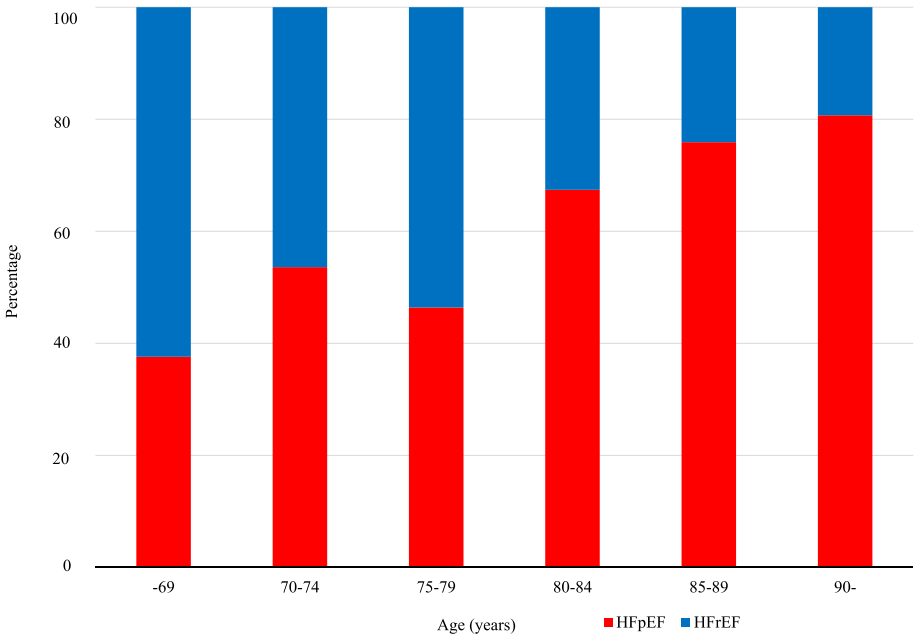


Table 1 Clinical characteristics in HFpEF patients and HFrEF patients

	HFpEF (n = 395)	HFrEF (n = 250)	P values
Demographics			
Age (years)	84 [77–89]	76 [67–82]	<0.001
≥80 years	265 (67.1)	92 (36.8)	<0.001
Women	241 (61.0)	87 (34.8)	<0.001
BMI (kg/m^2)	21.0 [18.9–23.6]	21.2 [18.7–23.7]	0.786
Underweight (BMI < 18.5 kg/m^2)	83 (21.2)	56 (22.6)	0.695
Normal (18.5 kg/m^2 ≤ BMI < 25.0 kg/m^2)	248 (63.4)	149 (60.1)	0.404
Overweight (25.0 kg/m^2 ≤ BMI < 30.0 kg/m^2)	53 (13.3)	34 (13.7)	0.906
Obese (BMI ≥ 30.0 kg/m^2)	8 (2.0)	9 (3.6)	0.313
GNRI	95.3 [88.5–101.7]	95.4 [88.3–102.5]	0.627
Moderate or severe nutritional risk (<92)	147 (38.2)	90 (36.7)	0.736
Prior admission due to HF	86 (25.7)	73 (33.6)	0.054
Clinical scenario			
CS1	174 (51.0)	73 (32.7)	<0.001
CS2	139 (40.8)	115 (51.6)	0.012
CS3	9 (2.6)	27 (12.1)	<0.001
Aetiology			
IHD	66 (16.7)	76 (30.4)	<0.001
VHD	91 (23.0)	15 (6.0)	<0.001
Cardiomyopathy	41 (10.4)	85 (34.0)	<0.001
Hypertensive	56 (14.2)	14 (5.6)	0.001
On admission			
Systolic BP (mmHg)	145 [126–167]	131 [115–152]	<0.001
Diastolic BP (mmHg)	79 [66–96]	86 [70–102]	0.001
Heart rate (/min)	83 [68–103]	100 [82–116]	<0.001
NYHA class III or IV on admission	297 (86.8)	197 (88.3)	0.627
At discharge			
Systolic BP (mmHg)	116 [104–129]	108 [97–119]	<0.001
Diastolic BP (mmHg)	64 [55–71]	64 [58–73]	0.038
Heart rate (/min)	70 [60–78]	71 [63–80]	0.136
NYHA class III or IV at discharge	5 (1.5)	5 (2.3)	0.526
Length of hospital stay (days)	18 [12–29]	19 [13–29]	0.202
Discharge to home	347 (88.0)	222 (89.5)	0.616
Laboratory parameters			
Albumin (g/dL)	3.7 [3.4–3.9]	3.7 [3.4–4.0]	0.494
Haemoglobin (g/dL)	11.1 [10.0–12.5]	12.7 [11.5–14.4]	<0.001
eGFR (mL/min/1.73 m^2)	44.2 [30.6–61.9]	47.4 [33.5–62.8]	0.349
Sodium (mEq/L)	139 [137–142]	139 [137–141]	0.550
BNP at discharge (pg/mL)	220.4 [110.2–428.5]	356.0 [194.6–582.0]	<0.001
Echocardiographic findings			
LV end-diastolic diameter (mm)	45.0 [41.0–48.6]	57.1 [53.0–62.0]	<0.001
LV end-systolic diameter (mm)	29.0 [26.0–33.0]	49.0 [44.0–55.0]	<0.001
Interventricular septum diameter (mm)	11.0 [10.0–12.0]	10.0 [9.0–11.0]	<0.001
Posterior wall diameter (mm)	10.2 [10.0–12.0]	10.0 [9.0–11.0]	<0.001
Left atrial diameter (mm)	43.0 [39.0–48.0]	45.0 [39.6–49.0]	0.083
LVEF (%)	62.0 [57.0–67.0]	30.0 [24.0–34.0]	<0.001
Comorbidities			
Hypertension	284 (71.9)	135 (54.0)	<0.001
Diabetes mellitus	100 (25.3)	76 (30.4)	0.174
Atrial fibrillation	180 (45.6)	99 (39.6)	0.143
Anaemia	297 (75.2)	127 (51.0)	<0.001
COPD	26 (6.6)	23 (9.2)	0.226
Chronic kidney disease	308 (78.0)	176 (70.7)	0.040
Malignant disease	35 (8.8)	26 (10.4)	0.581
Physical function domain			
J-CHS criteria			
Frailty, ≥3 of 5 domains met	218 (55.2)	117 (46.8)	0.043
Non-frailty	177 (44.8)	133 (53.2)	
Cognitive function domain			
HDS-R score	26.0 [21.0–29.0]	27.0 [22.0–30.0]	0.049
Cognitive impairment	81 (21.2)	51 (20.7)	0.920
Social relationship domain			
Eating alone	87 (22.7)	72 (29.0)	0.076
Not visiting the home of friends	205 (54.1)	111 (45.1)	0.033
Consult with family and friends	92 (24.1)	65 (26.4)	0.510
Going out less frequently	170 (44.6)	94 (38.4)	0.136

Data were shown as the median [interquartile range] or n (%).
BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; COPD, chronic obstructive pulmonary disease; CS, clinical scenario; eGFR, estimated glomerular filtration rate; GNRI, geriatric nutritional risk index; HDS-R, Hasegawa dementia scale-revised; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IHD, ischaemic heart disease; J-CHS, Japanese version Cardiovascular Health Study; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; VHD, valvular heart disease.

77–89 years) and 76 years (IQR, 67–82 years), respectively. The proportion of women was significantly higher in HFpEF patients than in HFrEF patients (HFpEF patients, 61.0%; HFrEF patients, 34.8%). In the CS classification on admission, 51.0% of the HFpEF patients had CS1, and the proportion was significantly higher than the proportion in HFrEF patients. On the other hand, the proportions of patients with CS2 and CS3 in HFpEF patients were significantly lower than those in HFrEF patients. In HFpEF patients, the most common aetiologies of HF were valvular heart disease (23.0%) and ischaemic heart disease (16.7%). In HFrEF patients, cardiomyopathy (34.0%) and ischaemic heart disease (30.4%) were the main underlying heart diseases. The median BMI values were similar in HFpEF and HFrEF patients (21.0 kg/m^2 [IQR, 18.9–23.6 kg/m^2] and 21.2 kg/m^2 [IQR, 18.7–23.7 kg/m^2], respectively). The proportions of underweight patients (BMI $<$ 18.5 kg/m^2) and overweight patients (25 kg/m^2 $\leq$ BMI $<$ 30 kg/m^2) were similar in HFpEF patients (21.2% and 13.3%, respectively) and HFrEF patients (22.6% and 13.7%, respectively). The proportions of obese patients in both HFpEF patients and HFrEF patients were very low (2.0% and 3.6%, respectively, P = 0.313). Regarding nutritional status, the proportions of patients with moderate or severe nutritional risk were not significantly different between the two groups (HFpEF patients, 38.2%; HFrEF patients, 36.7%). The proportions of patients with severe symptoms (New York Heart Association class $\geq$ III) were not different in the two groups. There was no difference in length of hospital stay between the two groups. The frequency of prior hospitalization due to worsening HF was higher in HFrEF patients (HFpEF patients, 25.7%; HFrEF patients, 33.6%). In laboratory data, haemoglobin concentration and plasma BNP level were significantly lower in HFpEF patients than in HFrEF patients. There was no difference in renal function evaluated by estimated glomerular filtration rate between the two groups.

Comorbidities

The proportion of patients with three or more comorbidities was significantly larger in HFpEF patients than in HFrEF patients (HFpEF patients: 77.9%, HFrEF patients: 65.6%) (*Figure 2*). Hypertension and anaemia were more prevalent in HFpEF patients than in HFrEF, while myocardial infarction was more prevalent in HFrEF patients than in HFpEF patients (*Table 1*). The prevalences of atrial fibrillation were similar in the two groups. The proportion of patients with chronic kidney disease was significantly higher in HFpEF patients (78.0%) than in HFrEF patients (70.7%).

Frailty status

Heart failure with preserved ejection fraction patients scored higher than HFrEF patients when evaluated by the J-CHS criteria as an indicator of physical frailty (HFpEF patients vs. HFrEF patients, 3 [IQE, 2–3] vs. 2 [IQR, 2–3], P = 0.026) (*Figure 3*). The proportions of patients with physical frailty were 55.2% in HFpEF patients and 46.8% in HFrEF patients, and

Figure 2 Prevalences of comorbidities in HFpEF patients and HFrEF patients. P = 0.003. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

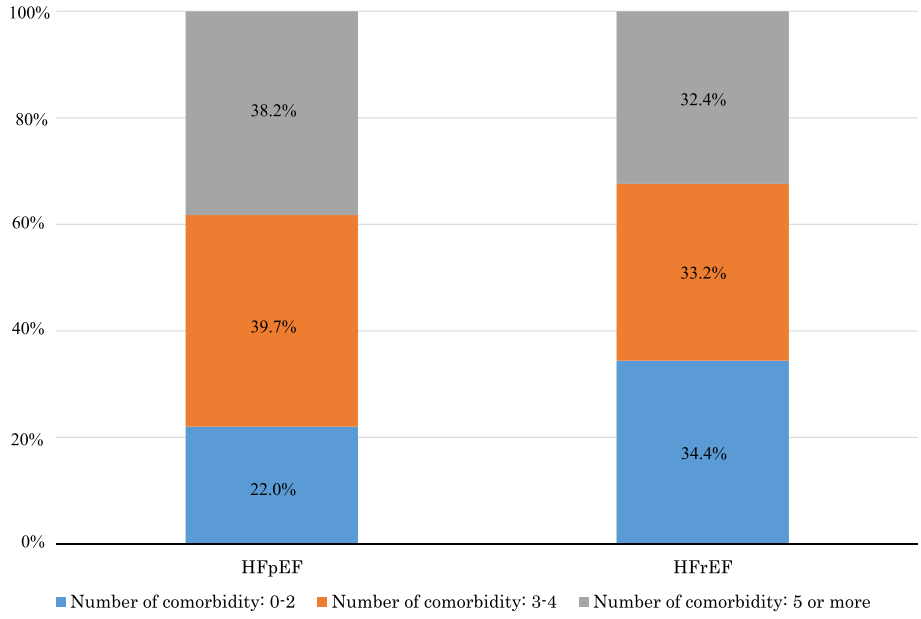
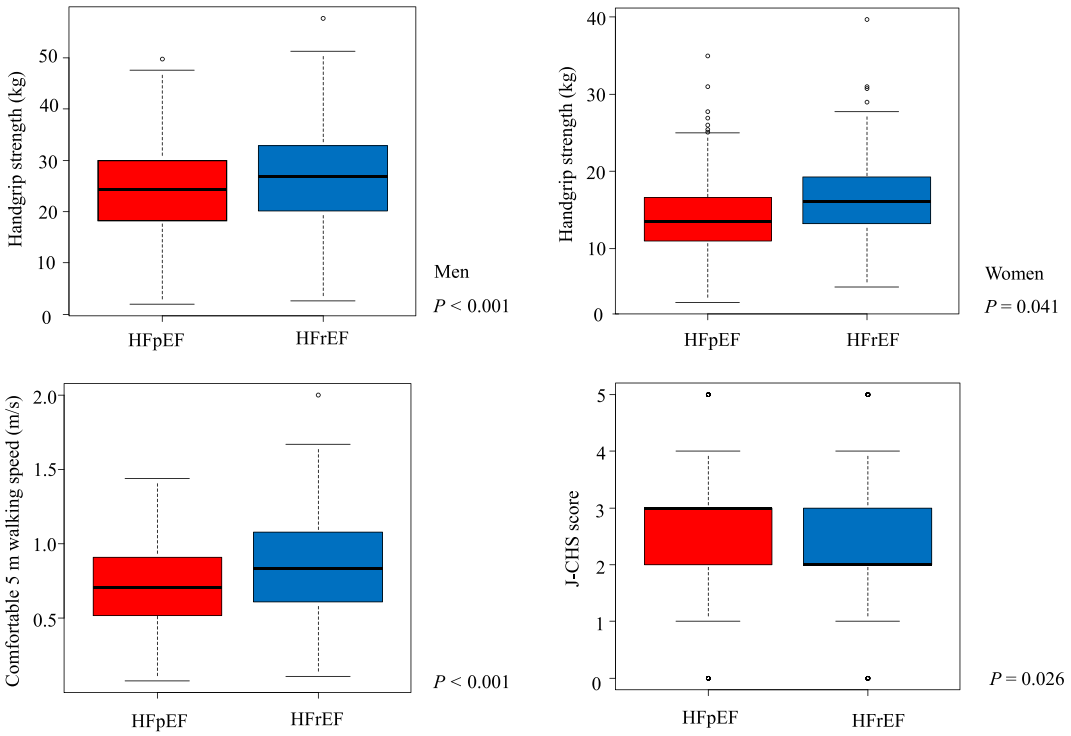


Figure 3 Comparison of physical function and frailty in HFpEF patients and HFrEF patients. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

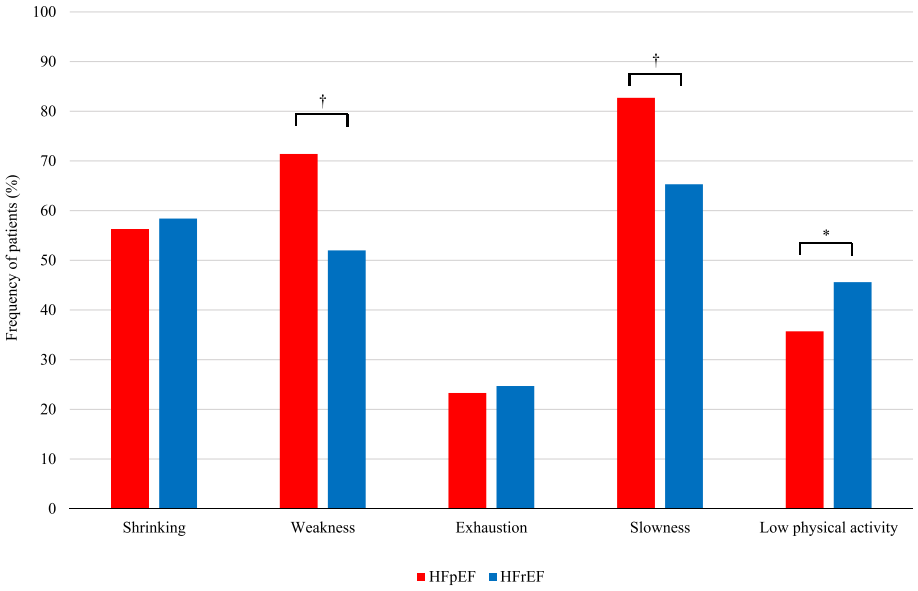


the proportion was significantly higher in HFpEF patients (P = 0.043) (*Table 1*). Handgrip strength was significantly lower in HFpEF patients than in HFrEF patients for both men (24.5 kg [IQR, 18.2–30.0 kg] vs. 26.8 kg [IQR, 20.2–32.9 kg], $P < 0.001$) and women (13.5 kg [IQR, 11.0–16.6 kg] vs. 16.0 kg [IQR, 13.0–19.3 kg], P = 0.041) (*Figure 3*). The proportion of patients with low handgrip strength (weakness) was higher in HFpEF patients than in HFrEF patients (71.4% vs. 52.1%, $P < 0.001$) (*Figure 4*). Walking speed was significantly slower in HFpEF patients than in HFrEF patients (0.71 m/s [IQR, 0.52–0.91 m/s] vs. 0.83 m/s [IQR, 0.61–1.08 m/s], $P < 0.001$). The proportion of patients with slow walking speed (slowness) was higher in HFpEF patients than in HFrEF patients (82.6% vs. 65.2%, $P < 0.001$) (*Figure 4*). The HDS-R scores were 26 (IQR, 21–29) in HFpEF patients and 27 (IQR, 22–30) in HFrEF patients. The HDS-R score was significantly lower in HFpEF patients, but the proportion of patients who met the criteria for cognitive impairment was not significantly different between the two groups (*Table 1*). In social relationships, HFpEF patients less frequently visited the homes of their friends (HFpEF patients: 54.1%, HFrEF patients: 45.1%, P = 0.033) (*Table 1*). Approximately 40% of the patients went out less frequently compared with last year. There was no difference between HFpEF and HFrEF patients.

Factors related to physical frailty

We investigated factors related to physical frailty in the HFpEF patients and HFrEF patients (*Table 2*). In HFpEF patients, univariate analysis showed that advanced age [odds ratio (OR), 1.040; 95% confidence interval (CI), 1.020–1.060; $P < 0.001$], women (OR, 1.680; 95% CI, 1.110–2.520; P = 0.013), cognitive impairment (OR, 2.300; 95% CI, 1.360–3.890; P = 0.002), low albumin level (OR, 0.303; 95% CI, 0.182–0.507; $P < 0.001$), anaemia (OR, 1.740; 95% CI, 1.100–2.750; P = 0.019), and three or more comorbidities (OR, 1.720, 95% CI, 1.050–2.800; P = 0.030) were associated with physical frailty. Cardiac factors were not associated with physical frailty in HFpEF patients. Multivariate analysis showed that advanced age (OR, 1.030; 95% CI, 1.010–1.050; P = 0.023) and low albumin level (OR, 0.334, 95% CI, 0.192–0.582; $P < 0.001$) were independent determinants of physical frailty in HFpEF patients. In HFrEF patients, univariate analysis showed that advanced age (OR, 1.060; 95% CI, 1.030–1.080; $P < 0.001$), women (OR, 1.800; 95% CI 1.060–3.050; P = 0.028), low BMI (OR, 2.330; 95% CI, 1.260–4.300, P = 0.007), living alone (OR, 2.240; 95% CI, 1.200–4.190; P = 0.011), cognitive impairment (OR, 4.050; 95% CI, 2.050–7.980; $P < 0.001$), prior HF admission (OR, 0.457; 95% CI, 0.258–0.811; P = 0.007), high BNP level at dis-

Figure 4 Percentage of patients who met the criteria for each component of the Japanese version of Cardiovascular Health Study criteria. *$P < 0.05$, †$P < 0.001$. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.



charge (OR, 1.000; 95% CI, 1.000–1.000; $P = 0.006$), low albumin level (OR, 0.431; 95% CI, 0.246–0.757; $P = 0.003$), and anaemia (OR, 2.850; 95% CI, 1.700–4.770; $P < 0.001$) were associated with physical frailty. Cardiac factors including plasma BNP level at discharge and prior HF admission were associated with physical frailty in HFrEF patients. Multivariate analysis showed that women (OR, 2.150; 95% CI, 1.030–4.500; $P = 0.042$) and anaemia (OR, 2.840; 95% CI, 1.300–6.230; $P = 0.003$) were independent determinants of physical frailty in HFrEF patients.

Discussion

In the present study, we examined the differences in comprehensive clinical characteristics including frailty status between HFpEF patients and HFrEF patients. HFpEF patients were older than HFrEF patients and included a larger percentage of women than that in HFrEF patients. HFpEF patients had a higher burden of comorbidities including hypertension, CKD, and anaemia than that in HFrEF patients. Although the proportions of patients with decreased social ties and cognitive impairment were similar in HFpEF patients and HFrEF patients, physical frailty defined using the J-CHS criteria was more common in HFpEF patients. Among the components of the J-CHS criteria, weakness and slowness were more common in HFpEF patients, while low physical activity was more common in HFrEF patients. Factors associated with physical frailty in HFpEF patients and HFrEF patients, rather than cardiac factors, reflected the vulnerability of the systematic condition.

Goyal *et al*. reported that the proportion of HFpEF patients increased with advance of age, reaching 52% in HF patients over 75 years of age.[18] The proportion of HFpEF patients in this study also increased with advance of age. In the Japanese Cardiac Registry of Heart Failure in Cardiology, conducted in Japan between 2004 and 2005, the proportion of HFpEF patients was shown to be 30% (calculated by HFpEF patients and HFrEF patients excluding HFmrEF patients).[19] On the other hand, HFpEF patients accounted for 61% of the patients in the present study in which patients were enrolled from 2017 to 2019. The difference in the proportions of HFpEF patients was considered to be due to the age difference of participants. Disease management of HFpEF may be an important issue in elderly patients with HF in a super-aged society.

In the Japanese HF population, the proportion of overweight patients (BMI $\geq$ 25 kg/m^2) was reported to be 27%.[20] In the present study, however, the proportion of overweight or obese patients was only 16%. This difference in the proportion of overweight or obese patients was probably because the patients who participated in our study were more elderly. In Western countries, obesity is common, especially in patients with HFpEF. Overweight or obese patients account for more than 80% of patients with HFpEF.[21] On the other hand, the HFpEF patients in our study were older, and larger proportions of HFpEF patients were therefore lean and had weakness and slowness. In a previous study that showed differences of clinical characteristics and outcomes between elderly and young HFpEF patients, elderly patients with HFpEF were more likely than young patients with HFpEF to be women, had more comorbidities than those in young

Table 2 Predictors of physical frailty in HFrEF patients and HFpEF patients

	HFpEF patients						HFrEF patients					
	Univariate			Multivariate			Univariate			Multivariate		
	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Age	1.040	1.020–1.060	<0.001	1.030	1.010–1.050	0.023	1.060	1.030–1.080	<0.001	1.020	0.989–1.050	0.198
Women	1.680	1.110–2.520	0.013	1.440	0.924–2.250	0.107	1.800	1.060–3.050	0.028	2.150	1.030–4.500	0.042
BMI < 18.5 kg/m^2	1.450	0.878–2.380	0.147				2.330	1.260–4.300	0.007	1.850	0.787–4.330	0.158
Living alone	1.400	0.854–2.310	0.181				2.240	1.200–4.190	0.011	1.030	0.461–2.320	0.936
Cognitive impairment	2.300	1.360–3.890	0.002	1.410	0.792–2.500	0.245	4.050	2.050–7.980	<0.001	2.100	0.822–5.380	0.121
Albumin	0.303	0.182–0.507	<0.001	0.334	0.192–0.582	<0.001	0.431	0.246–0.757	0.003	0.709	0.332–1.510	0.374
BNP at discharge	1.000	1.000–1.000	0.478				1.000	1.000–1.000	0.006	1.000	1.000–1.000	0.185
DM	1.230	0.777–1.950	0.376				0.705	0.409–1.220	0.209			
IHD	0.969	0.570–1.650	0.908				0.958	0.558–1.640	0.876			
CKD	1.200	0.742–1.930	0.462				1.740	0.996–3.050	0.052	0.953	0.381–2.380	0.918
NYHA class III/IV at discharge	1.180	0.195–7.150	0.858				4.910	0.540–44.600	0.158			
Anaemia	1.740	1.100–2.750	0.019	1.200	0.717–2.010	0.486	2.850	1.700–4.770	<0.001	2.840	1.300–6.230	0.003
LVEF	1.000	0.972–1.030	0.993				0.995	0.957–1.030	0.781			
Number of comorbidities ≥ 3	1.720	1.050–2.800	0.030	1.320	0.769–2.270	0.314	1.570	0.911–2.690	0.105	1.320	0.483–3.620	0.586
Prior HF admission	1.170	0.717–1.920	0.525				0.457	0.258–0.811	0.007	0.889	0.417–1.890	0.760

BMI, body mass index; BNP, B-type natriuretic peptide; CI, confidence interval; CKD, chronic kidney disease; DM, diabetes mellitus; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IHD, ischaemic heart disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OR, odds ratio.

patients, and had a higher mortality rate due to non-cardiovascular causes than did young patients.[22] Therefore, it is thought that the clinical characteristics and outcomes of HFpEF patients differ depending on the region and age of patients. Given that HFpEF patients have a heterogeneous syndrome and it has been proposed that the clinical phenotype should be considered for the management of HFpEF, it is not appropriate to apply the results obtained in Western countries to Japanese HFpEF patients. Disease management of HFpEF should be carried out with consideration of the differences in clinical phenotype depending on the region.

Physical frailty was reported to be more common in elderly patients with ADHF, being present in approximately 50% of elderly patients.[10,23] In the present study, the prevalence of frailty in HFpEF patients was higher than that in HFrEF patients (55% and 47%, respectively). One of the reasons may be that HFpEF patients were older than HFrEF patients. In the present study, 71.4% of the HFpEF patients and 52.1% of the HFrEF patients had low handgrip strength, and 82.6% of the HFpEF patients and 65.2% of the HFrEF patients had slow gait speed. It was estimated that there were approximately 30% of HFpEF patients who did not met the criteria for physical frailty but had impaired physical function. Early cardiac rehabilitation for patients with pre-frailty is expected to be effective in improving outcomes. Konishi *et al*. reported that larger proportions of HFpEF patients had low handgrip strength and slow gait speed than did HFrEF patients (67.8% vs. 55.5% and 54.5% vs. 41.1%, respectively) and that the prevalences of sarcopenia were similar in the two groups.[24] In addition, in an age-matched comparison in that study, the prevalences of low handgrip strength and slow gait speed were similar in HFpEF patients and HFrEF patients.[24] It has been reported that the prevalences of physical dysfunction, frailty, and cognitive impairments were similar in HFpEF patients and HFrEF patients after adjusting for age, sex, BMI, and comorbidities.[10] Considering that HFpEF patients were older than HFrEF patients in the present study, the difference in the proportions of patients with low handgrip strength and slow gait speed may be partly due to age differences. In univariate and multivariate logistic regression analyses, only extracardiac factors including age, female gender, cognitive impairment, multicomorbidities, and serum albumin level were associated with physical frailty in HFpEF patients. On the other hand, in HFrEF patients, unlike HFpEF patients, univariate analysis showed that cardiac factors including BNP levels at discharge and prior HF admission were associated with physical frailty in addition to extracardiac factors. The results suggested that physical frailty in HFpEF patients was associated more with extracardiac factors than with cardiac factors such as severity of symptoms, plasma BNP level, and LVEF. In our previous study, we used the KCL (n = 949) as a method for evaluating multifaceted frailty,[11] and we found that older age, prior HF admission, plasma BNP at discharge,

and a history of cerebrovascular accidents were factors related to frailty. On the other hand, in the current study, we focused on physical frailty and used the J-CHS criteria (n = 645). The factors related to physical frailty in HFpEF and HFrEF were partially different from those in our previous study. The reasons may be as follows. First, the KCL is a multifaceted method for evaluating frailty, and the J-CHS criteria are used for evaluating only physical frailty. Second, while frailty status is evaluated by 25 questions in the KCL, the J-CHS criteria include actual measurements of handgrip strength and walking speed. In this study, we might have excluded patients with more severely impaired physical function and those with severe symptoms of HF from the previous study. Third, this study was performed with analysis of a relatively small number of cases. Currently, there is no gold standard method for evaluating frailty status. Because HFpEF is a common disease in elderly patients with multiple comorbidities, appropriate treatment of comorbidities, nutritional management, and rehabilitation might be effective for the prevention and exacerbation of physical frailty. In the REHAB-HF trial, cardiac rehabilitation was performed in elderly patients with ADHF who were mostly pre-frail or frail. It has been reported that cardiac rehabilitation according to the individual domain of impaired physical function effectively improved physical function.[25] Guideline-directed medical therapy and non-pharmacotherapy such as cardiac resynchronization therapy have been established for treatment of HFrEF.[26] Recently, the Emperor-Preserved trial revealed that empagliflozin reduces the risk of a composite of cardiovascular death or hospitalization for HF in patients with HFpEF with or without diabetes.[27] In addition to the treatment of comorbidities, it is expected to be an effective medical therapy for patients with HFpEF. Greater frailty in HFpEF patients was reported to be associated with increased risk of all-cause mortality and HF rehospitalization.[28,29] Because HFpEF is a common disease in elderly patients with multiple comorbidities, deterioration of physical dysfunction needs to be addressed as a major issue in the disease management of HFpEF patients in clinical practice. Therefore, in addition to appropriate treatment for comorbidities, cardiac rehabilitation for physical frailty should be implemented in HFpEF patients. Moreover, caregivers and social services are needed for patients who need support in daily life. Palliative interventions need to be adequately introduced in very elderly patients and patients with stage D.

Study limitations

There are several limitations to be acknowledged. First, the study population was limited to Japanese patients. The number of patients was not large as an HF cohort study. However, HF patients were registered in our registry at major facilities in charge of cardiovascular medical care in Kochi Prefecture. Thus, the findings in this study were considered to reflect the real-world clinical practice for HF patients in our region. Second, this study showed that HFpEF patients had lower handgrip strength, slower gait speed, and more prevalent physical frailty than did HFrEF patients, but we did not perform age-matched analysis. Because physical frailty is associated with age, it is uncertain whether physical frailty is predominant in HFpEF patients regardless of age. However, because HFpEF is common in elderly HF patients and guideline-directed medical therapy for HFpEF has not been established, physical frailty could be an intervention target for improvement of quality of life and prognosis in HFpEF patients. Third, we excluded patients who were not entirely assessed by the J-CHS criteria and patients with HFmrEF from the total population. Patients who were excluded were older and had more severe symptom of HF, moderate to severe nutritional risk, a higher burden of comorbidities, and more often bedridden at discharge (data not shown). These findings indicate that there might have been selection bias. We consider that many of the patients who could not be assessed by the J-CHS criteria might have severely impaired physical function beyond frailty status. Finally, the clinical features of HFpEF patients and HFrEF patients were examined from clinical information obtained at the time of enrolment. We did not compare the prognosis of HFpEF patients and that of HFrEF patients, and we did not investigate the impact of physical frailty on the prognosis of HFpEF patients and HFrEF patients. We plan to investigate these clinical issues in future studies.

Future research

We need to investigate whether frailty status including physical, social, and cognitive frailty affects clinical outcomes in HFpEF and HFrEF patients and whether there is a difference in prognostic implication. Furthermore, it is necessary to investigate whether interventions for physical frailty will lead to improvements in clinical outcomes and quality of disease management and prognosis for HFpEF and HFrEF patients.

Conclusions

This study revealed the comprehensive clinical features of HFpEF patients and HFrEF patients in a super-aged society. HFpEF was the predominant disease type in the HF population mainly for the elderly and HFpEF patients had a higher burden of comorbidities than that in HFrEF patients. Physical frailty was more common in HFpEF patients, but decreased social ties and cognitive impairment were similar in HFpEF patients and HFrEF patients. Physical frailty was associated with extracardiac factors rather than cardiac factors and

might be an important intervention target in both HFpEF patients and HFrEF patients.

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Conflict of interest

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