


Frailty in patients with acute decompensated heart failure in a super-aged regional Japanese cohort

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Abstract

Aims The aim of this study was to investigate clinical characteristics of frail patients based on a comprehensive frailty assessment in patients hospitalized for acute decompensated heart failure (HF) (ADHF) in super-aged regional Japanese cohort.

Methods and results We established the Kochi Registry of Subjects with Acute Decompensated Heart Failure (Kochi YOSACOI) study, which was a prospective multicentre community-based cohort study in six participating hospitals in Kochi Prefecture, Japan. We enrolled 1061 patients (median age, 81 years; 50.0% men) hospitalized for ADHF between June 2017 and December 2019 in this registry. Patients were classified into the three groups by the severity of frailty using the Kihon Checklist: we identified frailty in 510 patients (53.7%), prefrailty in 293 patients (30.9%), and non-frailty in 146 patients (15.4%). Compared with prefrail and non-frail patients, frail patients were older (84 years interquartile range [IQR, 77–88] vs. 79 years [IQR, 69–86] and 72 years [IQR 65–81], $P < 0.001$) and more often had prior HF hospitalization (29.6% vs. 21.8% and 16.4%, $P < 0.05$), chronic kidney disease (81.6% vs. 71.7% and 61.0%, $P < 0.01$), anaemia (75.3% vs. 61.4% and 50.0%, $P < 0.001$), cerebrovascular accident (19.0% vs. 9.9% and 4.1%, $P < 0.01$). The proportion of patients with three or more comorbidities was larger in the frailty group than in the other groups (78.0% vs. 67.2% and 63.0%, $P < 0.01$). The frequency of functional decline in all domains increased with frailty status. Approximately 70% of frail patients were identified as functional decline in physical function and socialization domains. Fifty to sixty per cent of frail patients had functional decline in instrumental activities of daily living, cognitive function, and depression domains. The percentage of worsening walking ability during hospitalization was increasing with the frailty status (frailty, 27.5%; prefrailty, 21.8%; non-frailty, 8.9%). In multivariate logistic regression analysis, frailty was associated with age [odds ratio (OR) 1.031, 95% confidence interval (CI) 1.011–1.052, $P = 0.003$], prior HF hospitalization (OR 1.789, 95% CI 1.165–2.764, $P = 0.008$), brain natriuretic peptide level at discharge (OR 1.001, 95% CI 1.000–1.001, $P = 0.020$) and prior cerebrovascular accident (OR 2.549, 95% CI 1.484–4.501, $P < 0.001$).

Conclusions More than half of patients with ADHF were frail and had functional decline across multiple domains, not only physical function domain. The Kihon Checklist provided useful and valuable information for easily identifying frail patients and comprehensive management of HF.

Keywords Frailty; Acute decompensated heart failure; Elderly; Functional decline; Kihon Checklist

Received: 9 December 2020; Revised: 27 February 2021; Accepted: 31 March 2021

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Introduction

Heart failure (HF) is one of the leading causes of hospitalization and death, and the number of patients with HF has been increasing worldwide.^{1,2} The prevalence of HF increases with

ageing, and 6–10% of people older than 65 years of age have the disorder.³ Several studies have suggested that outcomes are particularly poor in elderly patients with HF.^{4–6} The population of Japan is ageing more rapidly than that of any other country. The proportion of people in Japan aged 65 years or

older was 27.7% in 2017.⁷ Frailty is a clinical status with increased vulnerability to stressors resulting from decreased reserves of multiple physiological systems.⁸ It was shown that frailty is associated with adverse health outcomes such as disability and mortality in a community-dwelling older population.⁹ However, there have been few studies on clinical features of frailty status of HF patients in a prospective community-based unselected cohort in Japan. Therefore, in 2017, we established a prospective, multicentre, community-based cohort study, named the Kochi Registry of Subjects with Acute Decompensated Heart Failure (Kochi YOSACOI study) in which patients hospitalized for acute decompensated HF (ADHF) in a super-ageing area of Japan were enrolled. This registry consists of six hospitals that are responsible for the acute treatment of cardiovascular diseases in Kochi Prefecture. Although the physical domain of frailty was assessed by Fried *et al.* in previous studies focusing on cardiovascular disease, frailty is recognized as a multidimensional vulnerability consisting of not only physical but also psychological and social domains, and multifaceted assessment of frailty is recommended to improve management of elderly patients with HF and health outcomes.^{10,11} The Kihon Checklist (KCL) was developed by the Japanese Ministry of Health, Labor and Welfare for identifying community-dwelling older adults to have a high risk of requiring care/support in the long-term care insurance (LTCI) system, and has been widely used in Japan. The KCL has been proven to be valid and reliable for assessing multifaceted aspects of frailty, such as functional declines, instrumental activities of daily living (IADL) limitation, physical impairment, depressive mood, and others.^{12,13} The purpose of the present study was to investigate the clinical characteristics and prevalence of frailty based on functional declines of daily living assessed by a comprehensive simple questionnaire, KCL, in patients with ADHF.

Methods

Patient population

In the Kochi YOSACOI study, 1061 consecutive patients with ADHF in Kochi Prefecture, Japan were recruited during the period from May 2017 to December 2019. The six hospitals participating in this registry are in charge of treatment for acute HF in Kochi Prefecture. Standard treatment for acute HF based on guidelines is practiced at all these hospitals. Cardiac surgery can be performed at three hospitals. One of them is a university hospital. Kochi Prefecture is located in the southwest part of Japan and is one of the most ageing areas of Japan. The population of Kochi Prefecture is approximately 706 000, and the proportion of people aged 65 years or older reached 34.7% in 2018. The inclusion criteria for the registry were age of 20 years or older and admission for ADHF

to one of the six hospitals. We diagnosed ADHF by confirming the presence of at least two major criteria or one major criterion based on the Framingham criteria including symptoms, physical examination, chest X-ray, and echocardiographic findings. Exclusion criteria were as follows: (i) unavailable data ($n = 4$) and (ii) patients who have not been assessed by the KCL or have been incompletely assessed ($n = 108$). 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 the ethics committees of all participating hospitals.

Assessment of frailty by the Kihon Checklist

The KCL is a 25-item self-administrated questionnaire, as a screening tool for predicting older adults who are vulnerable to frailty and have a high risk of becoming dependent (Table 1).^{12–14} The KCL is a comprehensive assessment tool that assesses physical, functional, psychological, and social aspects of independent older adults in multiple domains. The questionnaire consists of 25 yes/no questions that are categorized into seven domains: IADL, physical function, nutritional status, oral function, socialization, cognitive function, and depressive mood.¹² In the present study, we defined a total KCL score of ≥ 8 points as frailty, 4–7 points as prefrailty, and 0–3 points as non-frailty according to the previous report.¹² The seven functional categories of the KCL also have cut-off points for assessing frailty that were defined in a previous report.¹³ The criteria for functional declines of the seven categories were defined by the following cut-off points: IADL domain ≥ 3 points, physical function domain ≥ 3 points, malnutrition domain = 2 points, oral function domain ≥ 2 points, socialization domain ≥ 1 point, cognitive function domain ≥ 1 point, and depression domain ≥ 2 points.

Patient data collection

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 LTCI), frailty status (living functions before hospitalization assessed by the KCL), activities of daily living before admission and at discharge, HF symptoms (New York Heart Association class) and vital signs at admission and on discharge, discharge prescription, laboratory data, and echocardiography data. Walking ability just before admission

Table 1 Kihon Checklist

No.	Questions	Answer	
1	Do you go out by bus or train by yourself?	<input type="checkbox"/> 0. YES	<input type="checkbox"/> 1. NO
2	Do you go shopping to buy daily necessities by yourself?	<input type="checkbox"/> 0. YES	<input type="checkbox"/> 1. NO
3	Do you manage your own deposits and savings at the bank?	<input type="checkbox"/> 0. YES	<input type="checkbox"/> 1. NO
4	Do you sometimes visit your friends?	<input type="checkbox"/> 0. YES	<input type="checkbox"/> 1. NO
5	Do you turn to your family or friends for advice?	<input type="checkbox"/> 0. YES	<input type="checkbox"/> 1. NO
6	Do you normally climb stairs without using handrail or wall for support?	<input type="checkbox"/> 0. YES	<input type="checkbox"/> 1. NO
7	Do you normally stand up from a chair without any aids?	<input type="checkbox"/> 0. YES	<input type="checkbox"/> 1. NO
8	Do you normally walk continuously for 15 minutes?	<input type="checkbox"/> 0. YES	<input type="checkbox"/> 1. NO
9	Have you experienced a fall in the past year?	<input type="checkbox"/> 1. YES	<input type="checkbox"/> 0. NO
10	Do you have a fear of falling while walking?	<input type="checkbox"/> 1. YES	<input type="checkbox"/> 0. NO
11	Have you lost 2 kg or more in the past 6 months?	<input type="checkbox"/> 1. YES	<input type="checkbox"/> 0. NO
12	Height: cm, weight: kg, BMI: kg/m ² . If BMI is less than 18.5, this item is scored.	<input type="checkbox"/> 1. YES	<input type="checkbox"/> 0. NO
13	Do you have any difficulties eating tough foods compared to 6 months ago?	<input type="checkbox"/> 1. YES	<input type="checkbox"/> 0. NO
14	Have you choked on your tea or soup recently?	<input type="checkbox"/> 1. YES	<input type="checkbox"/> 0. NO
15	Do you often experience having a dry mouth?	<input type="checkbox"/> 1. YES	<input type="checkbox"/> 0. NO
16	Do you go out at least once a week?	<input type="checkbox"/> 0. YES	<input type="checkbox"/> 1. NO
17	Do you go out less frequently compared to last year?	<input type="checkbox"/> 1. YES	<input type="checkbox"/> 0. NO
18	Do your family or your friends point out your memory loss? e.g. "You ask the same question over and over again."	<input type="checkbox"/> 1. YES	<input type="checkbox"/> 0. NO
19	Do you make a call by looking up phone numbers?	<input type="checkbox"/> 0. YES	<input type="checkbox"/> 1. NO
20	Do you find yourself not knowing today's date?	<input type="checkbox"/> 1. YES	<input type="checkbox"/> 0. NO
21	In the last 2 weeks have you felt a lack of fulfilment in your daily life?	<input type="checkbox"/> 1. YES	<input type="checkbox"/> 0. NO
22	In the last 2 weeks have you felt a lack of joy when doing the things you used to enjoy?	<input type="checkbox"/> 1. YES	<input type="checkbox"/> 0. NO
23	In the last 2 weeks have you felt difficulty in doing what you could do easily before?	<input type="checkbox"/> 1. YES	<input type="checkbox"/> 0. NO
24	In the last 2 weeks have you felt helpless?	<input type="checkbox"/> 1. YES	<input type="checkbox"/> 0. NO
25	In the last 2 weeks have you felt tired without a reason?	<input type="checkbox"/> 1. YES	<input type="checkbox"/> 0. NO

Working Group on Frailty in Japanese Geriatrics Society. BMI, body mass index.

(categorized as independent outdoor walking, independent indoor walking, indoor walking with assistance, and abasia)¹⁵ was evaluated on admission, and its ability was re-evaluated at discharge. Worsening walking ability during hospitalization was defined as downgrades in the four walking ability categories during the period from admission to discharge. Cognitive function was evaluated by Hasegawa Dementia Scale-Revised. Cognitive decline was defined when the score was 20 or less in Hasegawa Dementia Scale-Revised. Hypertension was defined as peripheral blood pressure >140/90 mmHg or taking medication for hypertension. Diabetes mellitus was diagnosed using haemoglobin A1c (National Glycohemoglobin Standardization Program) $\geq 6.5\%$ and casual blood glucose level ≥ 200 mg/dL as the standard and/or assumed if the patient was taking medicine for diabetes. Dyslipidaemia was diagnosed if total cholesterol was ≥ 220 mg/dL, if low-density lipoprotein cholesterol was >140 mg/dL, if high-density lipoprotein cholesterol was >40 mg/dL, if triglycerides were >150 mg/dL, or if the patient was taking medicine for dyslipidaemia. Chronic kidney disease (CKD) was diagnosed as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m². Anaemia was diagnosed as haemoglobin <13 g/dL in men and <12 g/dL in women. We used echocardiographic data at the time when HF status was stabilized during hospitalization.

Statistical analysis

Normally distributed data are expressed as means \pm standard deviation, non-parametric data are expressed as medians

[interquartile range (IQR)], and categorical data are expressed as numbers and percentages. Differences in continuous variables among the three groups were assessed using one-way analysis of variance. 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 Bonferroni post-hoc test was used to determine differences between the frailty group, prefrailty group, and non-frailty group. Multivariate logistic regression analysis was performed to estimate the odds ratios (ORs) for determinant factors of frailty. Variables with $P < 0.1$ in univariate analysis were incorporated into the multivariate model. The propensity score matching was performed using a logistic regression model that adjusted age and sex to determine differences of baseline characteristics between frail patients and prefrail/non-frail patients. Statistical significance was defined by two-sided $P \leq 0.05$. All statistical analyses were performed using SPSS version 21 (IBM Corporation, Armonk, NY, USA) and Microsoft R Open version 4.0.2 (Microsoft, Redmond, WA, USA).

Results

Clinical characteristics at registration

Of the 1061 patients enrolled in our HF registry, we excluded patients with incomplete evaluation by the KCL ($n = 108$) and

patients for whom information about clinical status was unavailable ($n = 4$). Finally, 949 patients were included in the present study. The median age of the patients at registration was 81 years (IQR, 72–87 years), and 530 patients (51.4%) were men. Patients were classified into the three groups by the KCL: we identified frailty in 510 patients (53.7%), prefrailty in 293 patients (30.9%), and non-frailty in 146 patients (15.4%). The distribution of each frailty status according to age is shown in *Figure 1*. More than half of the patients aged 70 years or older had frailty. Furthermore, the proportion of patients with frailty gradually increased with ageing. On the other hand, even in the patients under the age of 65 years old, frail and prefrail patients accounted for 28.7% and 35.6%, respectively. The clinical characteristics of the patients according to frailty status are presented in *Table 2*. The age of patients in the frailty group was significantly higher among the three groups. The proportion of women in the frailty group was significantly larger than that in the prefrailty group and was larger than that in the non-frailty group. The most common aetiology of HF in all three groups was ischaemic heart disease. The proportion of patients in the frailty group who had a history of HF hospitalization was larger than the proportions of such patients in the prefrailty and non-frailty groups. The median left ventricular ejection fractions determined by echocardiography were

similar in the three groups. Serum albumin, eGFR, and haemoglobin levels in the frailty group were lower than those in the prefrailty and non-frailty groups, and plasma B-type natriuretic peptide (BNP) level in the frailty group was higher than that in the non-frailty group. Compared with prefrail and non-frail patients after adjusting for age and sex, frail patients had a higher prior HF hospitalization (*Table 3*). The proportion of patients with LVEF $\geq 50\%$ was smaller in the frailty group. Frail patients had lower albumin, haemoglobin, and eGFR levels and had higher BNP level at discharge. In multivariate logistic regression analysis, frailty was associated with age (OR 1.031, 95% confidence interval (CI) 1.011–1.052, $P = 0.003$), prior HF hospitalization (OR 1.789, 95% CI 1.165–2.764, $P = 0.008$), BNP level at discharge (OR 1.001, 95% CI 1.000–1.001, $P = 0.020$) and prior cerebral vascular accident (CVA) (OR 2.549, 95% CI 1.484–4.501, $P < 0.001$) (*Table 4*).

Association between comorbidities and frailty

Hypertension, diabetes mellitus, dyslipidaemia, coronary artery disease, chronic obstructive pulmonary disease, bronchial asthma, and malignant disease were equally present among the three groups (*Table 2*). The proportions

Figure 1 Distribution of each frailty status according to age.

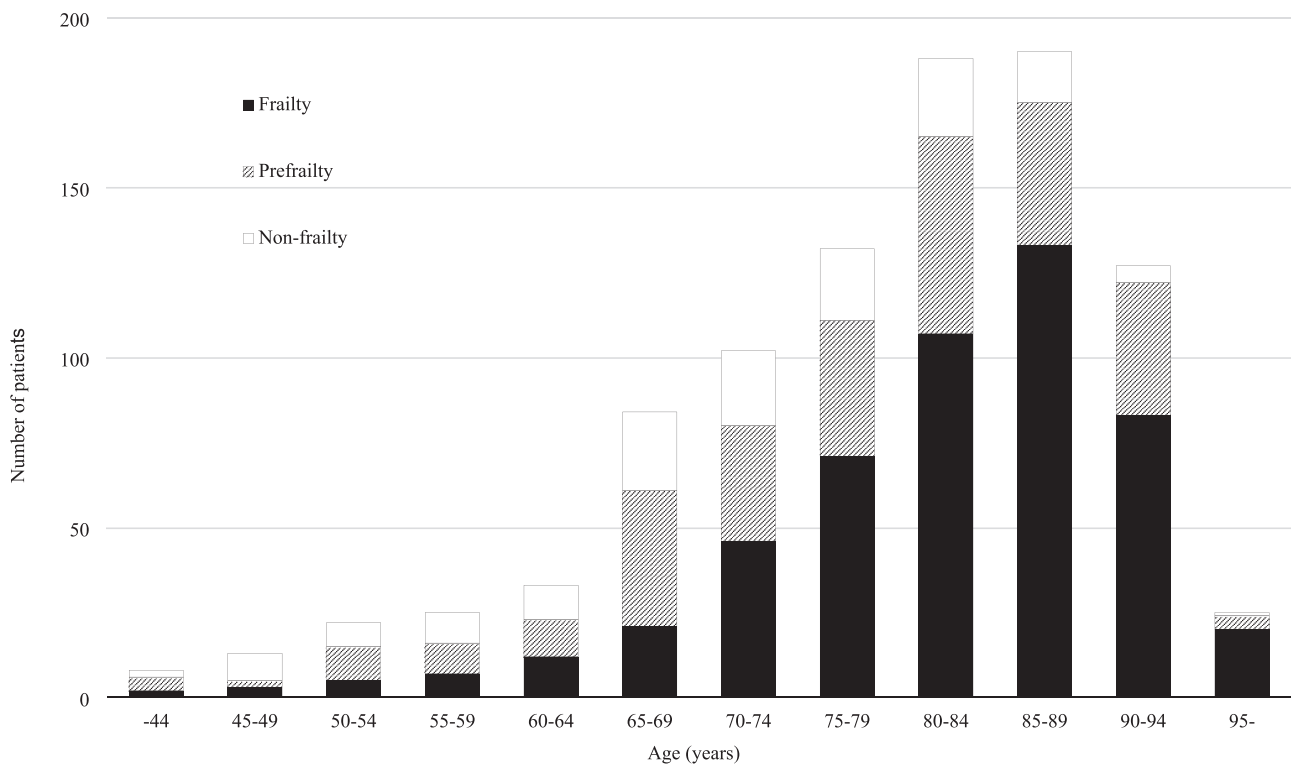


Table 2 Clinical characteristics of patients according to frailty status

	All patients (n = 949)	Frailty (n = 510)	Prefrailty (n = 293)	Non-frailty (n = 146)	P value
Age (years)	81 [72–87]	84 [77–88]***,†††	79 [69–86]†††	72 [65–81]	<0.001
≥80 years	530 (55.8)	343 (67.3)***,†††	143 (48.8)†††	44 (30.1)	<0.001
Women	461 (48.6)	273 (53.5)*	125 (42.7)	63 (43.2)	0.004
BMI (kg/m ²)	21.0 [18.7–23.3]	20.4 [17.9–22.6]***,†††	21.4 [19.5–23.9]†	22.3 [20.0–24.4]	<0.001
NYHA Class III/IV on admission	718 (75.7)	397 (77.8)	219 (74.7)	102 (69.9)	0.094
NYHA Class III/IV at discharge	24 (2.5)	20 (3.9)†	4 (1.4)	0 (0.0)	0.009
Discharge to home	810 (85.4)	399 (78.2)***,†††	271 (92.5)	140 (95.9)	<0.001
Length of hospital stay (days)	18 [13–29]	20 [14–33]***,†††	17 [12–27]	15 [12–21]	<0.001
Aetiology of HF					
IHD	223 (23.5)	118 (23.1)	67 (22.9)	38 (26.0)	0.733
Valvular	163 (17.2)	102 (20.0)	39 (13.3)	22 (15.1)	0.041
Cardiomyopathy	168 (17.7)	91 (17.8)	51 (17.4)	26 (17.8)	0.987
Hypertensive	103 (10.9)	49 (9.6)	35 (11.9)	19 (13.0)	0.390
Laboratory data at discharge					
Albumin (g/dL)	3.5 [3.1–3.7]	3.4 [3.1–3.7]**,†††	3.5 [3.2–3.8]††	3.7 [3.4–3.9]	<0.001
BNP (pg/mL)	278.9 [143.3–499.6]	312.0 [174.4–551.1]††	254.0 [135.0–476.1]	198.0 [119.0–410.8]	<0.001
eGFR (mL/min/1.73m ²)	44.4 [32.2–59.7]	40.7 [29.1–54.9]**,†††	46.0 [33.9–61.9]††	53.3 [40.3–67.8]	<0.001
Haemoglobin (g/dL)	11.4 [10.0–13.0]	10.9 [9.7–12.4]**,†††	11.8 [10.2–13.4]††	12.5 [11.1–13.9]	<0.001
Sodium (mEq/L)	139 [137–141]	139 [137–141]	139 [137–141]	139 [137–141]	0.716
Echocardiographic parameters					
LVEF (%)	49 [35–62]	49 [35–63]	49 [35–62]	46 [32–60]	0.265
≥50%	448 (47.2)	244 (47.8)	142 (48.5)	62 (42.5)	0.485
Frailty assessment					
Total IKCL score	8 [5–12]	11 [9–14]**,†††	5 [4–7]†††	2 [1–3]	<0.001
No. of domains with functional decline	2 [1–4]	4 [3–5]**,†††	1 [1–2]†††	0 [0–0]	<0.001
HDS-R score	26 [21–29]	24 [18–28]**,†††	27 [23–29]†††	29 [27–30]	<0.001
Medical history					
No. of comorbidities	4 [2–5]	4 [3–5]**,†††	3 [2–5]	3 [2–5]	<0.001
≥3	687 (72.4)	398 (78.0)**,†††	197 (67.2)	92 (63.0)	<0.001
Prior hospitalization due to HF	239 (25.2)	151 (29.6)*,††	64 (21.8)	24 (16.4)	0.001
Hypertension	608 (64.1)	325 (63.7)	188 (64.2)	95 (65.1)	0.956
Diabetes mellitus	248 (26.1)	130 (25.5)	75 (25.6)	43 (29.5)	0.611
Dyslipidaemia	361 (38.0)	195 (38.2)	104 (35.5)	62 (42.5)	0.363
Prior myocardial infarction	134 (14.1)	79 (15.5)	34 (11.6)	21 (14.4)	0.312
CAD	279 (29.4)	153 (30.0)	85 (29.0)	41 (28.1)	0.890
COPD	69 (7.3)	39 (7.6)	23 (7.8)	7 (4.8)	0.454
Bronchial asthma	44 (4.6)	27 (5.3)	13 (4.4)	4 (2.7)	0.425
CVA	132 (13.9)	97 (19.0)**,†††	29 (9.9)	6 (4.1)	<0.001
Atrial fibrillation	404 (42.6)	231 (45.3)†	127 (43.3)	46 (31.5)	0.012
Peripheral vascular disease	86 (9.1)	52 (10.2)	25 (8.5)	9 (6.2)	0.304
Malignancy	94 (9.9)	60 (11.8)	23 (7.8)	11 (7.5)	0.117
Dementia	138 (14.5)	107 (21.0)**,†††	26 (8.9)	5 (3.4)	<0.001
Anaemia	637 (67.1)	384 (75.3)**,†††	180 (61.4)	73 (50.0)	<0.001
CKD	715 (75.3)	416 (81.6)**,†††	210 (71.7)	89 (61.0)	<0.001
Treatment in the acute phase					
Respiratory management	577 (60.8)	324 (63.5)	170 (58.0)	83 (56.8)	0.235
Oxygen inhalation	125 (13.2)	64 (12.5)	37 (12.6)	24 (16.4)	0.380
NPPV					

(Continues)

Table 2 (continued)

	All patients (n = 949)	Frailty (n = 510)	Prefrilty (n = 293)	Non-frailty (n = 146)	P value
Intubation	8 (0.8)	3 (0.6)	3 (1.0)	2 (1.4)	0.587
Intravenous					
Inotropes	96 (10.1)	47 (9.2)	33 (11.3)	16 (11.0)	0.609
Diuretics	742 (78.2)	417 (81.8)	218 (74.4)	107 (73.3)	0.015
Carperitide	385 (40.6)	196 (38.4)	122 (41.6)	67 (45.9)	0.244
Nitrates	159 (16.8)	83 (16.3)	52 (17.7)	24 (16.4)	0.860
PDEIII inhibitors	18 (1.9)	7 (1.4)	6 (2.0)	5 (3.4)	0.270
Nicardipine	72 (7.6)	41 (8.0)	20 (6.8)	11 (7.5)	0.822
Oral administration					
Tolvaptan	237 (25.0)	139 (27.3)	73 (24.9)	25 (17.1)	0.045
Medication at hospital discharge					
RAS inhibitors	430 (45.3)	214 (42.0)	139 (47.4)	77 (52.7)	0.041
ACE inhibitor	193 (20.3)	95 (18.6)	66 (22.5)	32 (21.9)	0.366
Angiotensin receptor blockers	239 (25.2)	119 (23.3)	73 (24.9)	47 (32.2)	0.093
β-blockers	538 (56.7)	273 (53.5)	177 (60.4)	88 (60.3)	0.106
MRAs	318 (33.5)	170 (33.3)	96 (32.8)	52 (35.6)	0.831
Diuretics	773 (81.5)	433 (84.9)	229 (78.2)	111 (76.0)	0.011
Tolvaptan	237 (25.0)	142 (27.8) [†]	71 (24.2)	24 (16.4)	0.018

Data were shown as the median [interquartile range] or n (%).

Bonferroni post-hoc test between frailty, prefrilty, and non-frailty.

* $P < 0.05$; frailty vs. prefrilty.

** $P < 0.01$; frailty vs. prefrilty.

*** $P < 0.001$; frailty vs. prefrilty.

[†] $P < 0.05$; frailty vs. non-frailty.

^{††} $P < 0.01$; frailty vs. non-frailty.

^{†††} $P < 0.001$; frailty vs. non-frailty.

[‡] $P < 0.05$; prefrilty vs. non-frailty.

^{‡‡} $P < 0.01$; prefrilty vs. non-frailty.

^{‡‡‡} $P < 0.001$; prefrilty vs. non-frailty.

ACE, angiotensin-converting enzyme; BMI, body mass index; BNP, B-type natriuretic peptide; CAD, chronic kidney disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebral vascular accident; eGFR, estimated glomerular filtration rate; HDS-R, Hasegawa Dementia Rating Scale-Revised; HF, heart failure; IHD, ischaemic heart disease; KCL, Kihon Checklist; LVEF, left ventricular ejection fraction; MRAs, mineralocorticoid receptor blockers; No., number; NPPV, non-invasive positive pressure ventilation; NYHA, New York Heart Association; PDE, phosphodiesterase; RAS, renin-angiotensin system.

ACE, angiotensin-converting enzyme; BMI, body mass index; BNP, B-type natriuretic peptide; CAD, chronic kidney disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebral vascular accident; eGFR, estimated glomerular filtration rate; HDS-R, Hasegawa Dementia Rating Scale-Revised; HF, heart failure; IHD, ischaemic heart disease; KCL, Kihon Checklist; LVEF, left ventricular ejection fraction; MRAs, mineralocorticoid receptor blockers; No., number; NPPV, non-invasive positive pressure ventilation; NYHA, New York Heart Association; PDE, phosphodiesterase; RAS, renin-angiotensin system.

Table 3 Comparison of clinical characteristics of patients after adjusting for age and sex

	Frail patients (n = 305)	Non-frail + prefrail patients (n = 305)	P value
Age (years)	82 [75–87]	82 [75–87]	1.000
≥80 years	182 (59.7)	182 (59.7)	1.000
Women	145 (47.5)	145 (47.5)	1.000
BMI (kg/m ²)	20.4 [18–22.4]	21.3 [19.4–23.4]	0.001
NYHA Class III/IV on admission	242 (79.3)	220 (72.1)	0.088
NYHA Class III/IV at discharge	14 (4.6)	2 (0.7)	0.004
Discharge to home	242 (79.3)	280 (91.8)	<0.001
Length of hospital stay (days)	20 [14–32]	16 [12–25]	<0.001
Aetiology of HF			
IHD	77 (25.2)	77 (25.2)	1.000
Valvular	59 (19.3)	46 (15.1)	0.198
Cardiomyopathy	57 (18.7)	39 (12.8)	0.058
Hypertensive	31 (10.2)	38 (12.5)	0.443
Laboratory data at discharge			
Albumin (g/dL)	3.4 [3.1–3.7]	3.5 [3.2–3.8]	0.003
BNP (pg/mL)	312.0 [174.1–543.8]	248.0 [137.0–485.9]	0.006
eGFR (mL/min/1.73 m ²)	40.8 [27.3–54.9]	46.1 [34.9–60.8]	0.002
Haemoglobin (g/dL)	11.0 [9.8–12.5]	11.7 [10.2–13.0]	0.003
Sodium (mEq/L)	139 [137–141]	139 [137–141]	0.623
Echocardiographic findings			
LVEF (%)	48.0 [33.8–62.0]	54.0 [39.0–63.0]	0.017
≥50%	140 (45.9)	173 (56.7)	0.006
Frailty assessment			
KCL score	11 [9–14]	5 [3–6]	<0.001
No. of declined functional domains	4 [3–5]	1 [0–2]	<0.001
HDS-R score	24 [19–28]	27 [24–29]	<0.001
Medical history			
No. of comorbidities	4 [3–5]	4 [2–5]	0.002
≥3	238 (78.0)	216 (70.8)	0.051
Prior HF hospitalization	98 (32.1)	66 (21.6)	0.003
Hypertension	192 (63.0)	207 (67.9)	0.233
Diabetes mellitus	85 (27.9)	76 (24.9)	0.462
Dyslipidaemia	115 (37.7)	124 (40.7)	0.507
Prior myocardial infarction	57 (18.7)	43 (14.1)	0.155
CAD	94 (30.8)	97 (31.8)	0.861
COPD	28 (9.2)	26 (8.5)	0.887
Bronchial asthma	15 (4.9)	12 (3.9)	0.695
CVA	59 (19.3)	26 (8.5)	<0.001
Atrial fibrillation	141 (46.2)	128 (42.0)	0.328
Peripheral vascular disease	34 (11.1)	28 (9.2)	0.503
Malignancy	40 (13.1)	28 (9.2)	0.157
Dementia	63 (20.7)	28 (9.2)	<0.001
Anaemia	227 (74.4)	200 (65.6)	0.017
CKD	246 (80.7)	225 (73.8)	0.052

Data were shown as the median [interquartile range] or n (%).

BMI, body mass index; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebral vascular accident; eGFR, estimated glomerular filtration rate; HDS-R, Hasegawa Dementia Rating Scale-Revised; HF, heart failure; IHD, ischaemic heart disease; KCL, Kihon Checklist; LVEF, left ventricular ejection fraction; No., number; NYHA, New York Heart Association.

of patients who had a prior CVA, anaemia, and CKD were larger in the frailty group than in the other two groups. The number of comorbidities that the patients had was larger in the frailty group than in the other two groups. Moreover, the proportion of patients with three or more comorbidities was larger in the frailty group than in the other two groups. After adjusting for age and sex, prior CVA, dementia, and anaemia were significantly larger in frail patients (Table 3). The prevalence of atrial fibrillation and CKD were not significantly different in the frail and in the prefrail/non-frail patients.

Functional decline in daily functional domains

The total KCL score (median) in the frailty group was significantly higher than those in the prefrailty and non-frailty groups (11 [9–14], 5 [4–7], and 2 [1–3], respectively, $P < 0.001$). The number of domains with functional decline was significantly larger in the frailty group than in the prefrailty and non-frailty groups (Table 2). Of the 510 patients with frailty, 29.8% were diagnosed with frailty based on functional decline in several domains other than the physical function domain. The frequency of functional

decline in all domains increased with frailty status (Figure 2). Seventy per cent of the frail patients were identified as having functional decline in the physical function domain and socialization domain, and 50–60% of the frail patients had functional decline in IADL, cognitive function, and

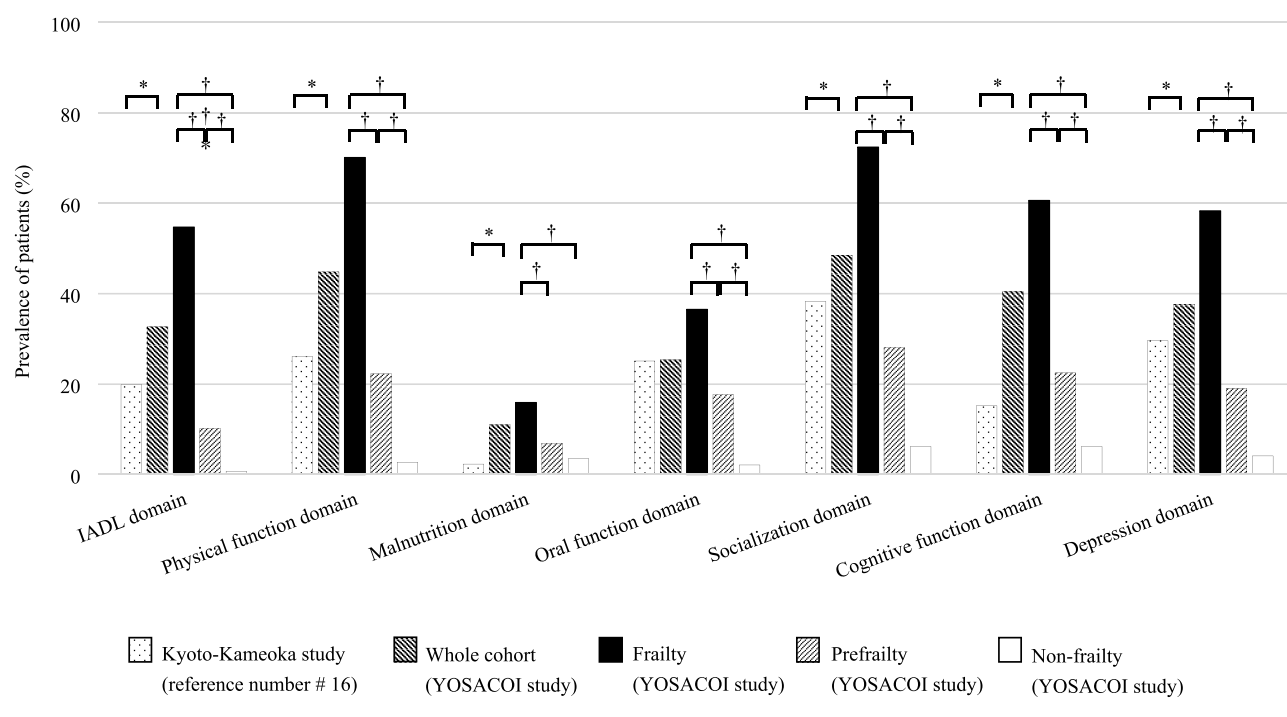
depression domains. In comparison with the Kyoto–Kameoka study, which assessed frailty status with the KCL for community-dwelling older people,¹⁶ the rates of functional decline in all domains were higher in the present study.

Table 4 Clinical factors associated with frailty in all patients

	Univariate			Multivariate		
	Odds ratio	95% CI	P value	Odds ratio	95% CI	P value
Age	1.057	1.044–1.071	<0.001	1.031	1.011–1.052	0.003
Female	1.537	1.190–1.990	0.001	1.152	0.776–1.711	0.482
BMI	0.919	0.887–0.952	<0.001	0.979	0.932–1.024	0.356
Prior HF hospitalization	1.746	1.283–2.389	<0.001	1.789	1.165–2.764	0.008
NYHA Class III/IV at discharge	4.439	1.661–15.369	0.007	3.018	0.966–11.403	0.072
IHD	0.958	0.709–1.294	0.777			
LVEF	1.004	0.996–1.012	0.325			
Albumin	0.402	0.287–0.556	<0.001	0.720	0.444–1.160	0.179
BNP at discharge	1.001	1.000–1.001	<0.001	1.001	1.000–1.001	0.020
Haemoglobin	0.804	0.753–0.857	<0.001	0.914	0.816–1.023	0.120
eGFR	0.986	0.981–0.992	<0.001	0.990	0.980–1.001	0.053
Living alone	1.585	1.148–2.198	0.005	1.415	0.912–2.206	0.122
HT	0.968	0.742–1.263	0.813			
DM	0.931	0.696–1.245	0.627			
CVA	2.711	1.816–4.133	<0.001	2.549	1.484–4.501	<0.001
Af	1.273	0.983–1.650	0.068	0.704	0.471–1.046	0.084
COPD	1.129	0.691–1.863	0.631			

95% CI, 95% confidence interval; Af, atrial fibrillation; BMI, body mass index; BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HF, heart failure; HT, hypertension; IHD, ischaemic heart disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Figure 2 Percentage of patients with functional decline in each functional domains of the Kihon Checklist. Comparison of the frequency of functional decline between all patients in YOSACOI study and those in Kyoto–Kameoka study: * $P < 0.001$. Comparison of the frequency of functional decline according to frailty status in YOSACOI study: † $P < 0.001$. IADL, instrumental activities of daily living.



Treatment in the acute phase and medication at discharge

In the acute phase, the frequency of use of respiratory management and the frequency of use of intravenous drugs such as inotropes and vasodilators were not significantly different among the three groups (Table 2). The frequency of use of intravenous diuretics and tolvaptan was significantly higher in the frailty group. Regarding medication at discharge, renin–angiotensin system inhibitors (RAS inhibitors; angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers) were less frequently prescribed in frail patients. β -blockers and mineralocorticoid receptor antagonists were prescribed without significant differences among the three groups. Tolvaptan was more frequently prescribed in frail patients than in non-frail patients.

Social background

The proportion of patients in the frailty group who lived at home was smaller than the proportions of patients living at

home in the prefrailty and non-frailty groups (Table 5). Ten per cent of the frail patients lived in a facility for the elderly. The proportion of patients living alone was larger in the frailty group than in the non-frailty group (23.9% vs. 14.4%, $P < 0.05$). Ninety-three per cent of the prefrail patients and 84% of the non-frail patients did not have certification for the need of LTCl. On the other hand, approximately half of the frail patients were certified as requiring support or care under the LTCl system.

Clinical presentation at discharge

At discharge, the prevalence of New York Heart Association Class III or IV in the frailty group was higher than that in the other two groups. The median length of hospital stay for all patients was 18 days (IQR, 13–29 days). The duration for frail patients was longer than that for prefrail patients and non-frail patients. The proportion of frail patients who were discharged to home was smaller than the proportions of prefrail patients and non-frail patients (Table 2). Compared with prefrail and non-frail patients after adjusting for age and

Table 5 Social background of patients according to frailty status

	All patients (<i>n</i> = 949)	Frailty (<i>n</i> = 510)	Prefrailty (<i>n</i> = 293)	Non-frailty (<i>n</i> = 146)	<i>P</i> value
Living place					
Home	783 (82.5)	402 (78.8) ^{***,††}	255 (87.0)	126 (86.3)	<0.001
Facilities for the elderly people	54 (5.7)	48 (9.4) ^{***,†††}	6 (2.0)	0 (0.0)	<0.001
Hospitals	25 (2.6)	19 (3.7)	3 (1.0)	3 (2.1)	0.075
Living situation					
Alone	203 (21.4)	122 (23.9) [†]	60 (20.5)	21 (14.4)	0.006
With a partner only	252 (26.6)	117 (22.9)	84 (28.7)	51 (34.9)	0.059
With children or other family members	333 (35.1)	167 (32.7)	110 (37.5)	56 (38.4)	0.802
Medical management					
Self-administration of medicine	667 (70.3)	309 (60.6) ^{***,†††}	238 (81.2)	120 (82.2)	<0.001
Supporter for daily living	669 (70.5)	370 (72.5)	201 (68.6)	98 (67.1)	0.618
Long-term care insurance					
Not certified	622 (65.5)	242 (47.5) ^{***,†††}	245 (83.6) [‡]	135 (92.5)	<0.001
Certification of needed support	114 (12.0)	88 (17.3) ^{***,†††}	22 (7.5)	4 (2.7)	<0.001
Support required 1 (e.g. standing on 1foot)	53 (5.6)	40 (7.8) ^{††}	11 (3.8)	2 (1.4)	0.003
Support required 2 (e.g. walking; possibly improved)	61 (6.4)	48 (9.5) ^{**,††}	11 (3.8)	2 (1.4)	<0.001
Certification of needed long-term care	196 (20.7)	167 (32.7) ^{***,†††}	22 (7.5)	7 (4.8)	<0.001
Care Level 1 (e.g. walking maintained)	87 (9.2)	71 (13.9) ^{***,†††}	11 (3.8)	5 (3.4)	<0.001
Care Level 2 (e.g. moving, wear/pull off trousers)	56 (5.9)	47 (9.2) ^{**,†††}	8 (2.7)	1 (0.7)	<0.001
Care Level 3 (e.g. washing face and oral care)	28 (3.0)	26 (5.1) ^{***}	1 (0.3)	1 (0.7)	<0.001
Care Level 4 (e.g. dietary intake and communication)	20 (2.1)	18 (3.5) [*]	2 (0.7)	0 (0.0)	0.004
Care Level 5 (e.g. swallowing and memorization)	5 (0.5)	5 (1.0)	0 (0.0)	0 (0.0)	0.114
Unknown	17 (1.8)	13 (2.5)	4 (1.4)	0 (0.0)	0.099

Data were shown as *n* (%).

Bonferroni post-hoc test between frailty, prefrailty, and non-frailty.

* $P < 0.05$; frailty vs. prefrailty.

** $P < 0.01$; frailty vs. prefrailty.

*** $P < 0.001$; frailty vs. prefrailty.

† $P < 0.05$; frailty vs. non-frailty.

†† $P < 0.01$; frailty vs. non-frailty.

††† $P < 0.001$; frailty vs. non-frailty.

‡ $P < 0.05$; prefrailty vs. non-frailty.

‡† $P < 0.01$; prefrailty vs. non-frailty.

‡†† $P < 0.001$; prefrailty vs. non-frailty.

sex, frail patients had a longer length of hospital stay, a lower rate of discharge to home, and a more severe symptom of HF (Table 3). Walking ability before admission was assessed on admission in 920 patients, and the ability at discharge was re-evaluated in 899 patients. Table 6 shows walking abilities before admission, at discharge, and changes in walking ability from before admission to discharge. Before admission, the percentage of patients who could independently walk outdoors was significantly lower in the frailty group than in the prefrailty and non-frailty groups (66.1%, 91.5%, and 95.2%, respectively, $P < 0.001$). At discharge, the percentage of patients who could independently walk outdoors decreased to 42.2% in the frailty group. The percentage of frail patients who could independently walk outdoors or indoors at discharge was lower than that before admission (76.0% at discharge vs. 84.9% before admission). Almost 30% of the frail patients had deterioration of walking ability during hospitalization. The percentage of patients with deterioration of walking ability during hospitalization increased with the frailty status (frailty, 27.5%; prefrailty, 21.9%; non-frailty, 8.9%, $P < 0.001$). Although some patients in the frailty group had improvement in walking ability during hospitalization, the percentage of patients who had preserved walking ability during hospitalization was significantly lower in the frailty group than in the other two groups (frailty, 62.5%; prefrailty, 71.7%; non-frailty, 87.7%, $P < 0.001$).

Discussion

This study is the first study in which comprehensive assessment of frailty was carried out for HF patients using the KCL, which is widely used in Japan for the purpose of screening-like evaluation of daily functions. Management of HF requires a seamless system of care, including the community and hospital, and a multidisciplinary approach.¹⁷ Information obtained by the KCL can be shared seamlessly between medical staff and nursing care staff and is useful for management of elderly HF patients. In addition, this study was conducted in a rural area in which the ageing rate was approximately 35%⁷ and the median age of the patients in this study was 81 years. Patients aged 80 years or older accounted for 55.8% of the patients. The patients enrolled in this study were older than those in HF registries previously reported.^{6,18–20} The majority of HF patients in this cohort in a Japanese rural area was vulnerable to frailty. More than half of the frail patients had functional declines in IADL, physical function, socialization, cognitive function, and depression domains. Frail patients were admitted to the hospital for a longer period than were prefrail and non-frail patients. Additionally, deterioration of walking ability occurred more frequently in frail patients during hospitalization. In multivariate analysis, the determinants for frailty were age, prior HF hospitalization, prior CVA, and BNP level at discharge.

Table 6 Walking ability according to frailty status

	All patients (n = 949)	Frailty (n = 510)	Prefrailty (n = 293)	Non-frailty (n = 146)	P value
Before admission					
Independent outdoor walking	744 (78.4)	337 (66.1) ^{***,†††}	268 (91.5)	139 (95.2)	<0.001
Independent indoor walking	110 (11.6)	96 (18.8) ^{***,†††}	11 (3.8)	3 (2.1)	<0.001
Indoor walking with assistance	27 (2.9)	24 (4.7) ^{*,†}	3 (1.0)	0 (0.0)	0.006
Abasia	39 (4.1)	37 (7.3) ^{***,†††}	2 (0.7)	0 (0.0)	<0.001
Unknown	29 (3.1)	16 (3.1)	9 (3.1)	4 (2.7)	
At discharge					
Independent outdoor walking	547 (57.6)	217 (42.5) ^{***,†††}	205 (69.9) ^{††}	125 (85.6)	<0.001
Independent indoor walking	252 (26.6)	171 (33.5) ^{***,†††}	65 (22.2) [†]	16 (11.0)	<0.001
Indoor walking with assistance	65 (6.9)	60 (11.8) ^{***,†††}	5 (1.7)	0 (0.0)	<0.001
Abasia	35 (3.7)	31 (6.1) ^{***,††}	4 (1.4)	0 (0.0)	<0.001
Unknown	50 (5.3)	31 (6.1)	14 (4.8)	5 (3.4)	
Changes in walking ability during hospitalization					
Improved	24 (2.5)	20 (3.9) [*]	4 (1.4)	0 (0.0)	0.008
Stable	657 (69.2)	319 (62.5) ^{*,†††}	210 (71.7) ^{†††}	128 (87.7)	<0.001
Worsening	217 (22.9)	140 (27.5) ^{†††}	64 (21.8) ^{††}	13 (8.9)	<0.001
Unknown	51 (5.4)	31 (6.1)	15 (5.1)	5 (3.4)	
Not independent walking at discharge	103 (10.9)	94 (18.4) ^{***,†††}	9 (3.1)	0 (0.0)	<0.001

Data were shown as n (%).

Bonferroni post-hoc test between frailty, prefrailty, and non-frailty.

* $P < 0.05$; frailty vs. prefrailty.

** $P < 0.01$; frailty vs. prefrailty.

*** $P < 0.001$; frailty vs. prefrailty.

† $P < 0.05$; frailty vs. non-frailty.

†† $P < 0.01$; frailty vs. non-frailty.

††† $P < 0.001$; frailty vs. non-frailty.

‡ $P < 0.05$; prefrailty vs. non-frailty.

‡‡ $P < 0.01$; prefrailty vs. non-frailty.

‡‡‡ $P < 0.001$; prefrailty vs. non-frailty.

Therefore, it was suggested that the severity of HF was involved in the development of frailty status.

Frailty is considered to be a vulnerable condition that includes not only the physical domain but also multidimensional domains such as psychological and social domains.²¹ The Cardiovascular Health Study criteria focusing on physical domain, reported by Fried *et al.*,⁸ were widely used in HF patients. The Comprehensive Geriatric Assessment has been used for assessment of multifaceted aspects in addition to assessment of physical aspects. A previous study showed that the prevalence of frailty in HF patients was 44.5%.²² Additionally, the prevalence of frailty was higher in studies in which multifaceted aspects were assessed than in those in which only the physical domain was assessed (47.4% vs. 42.9%).²² In the present study, we used the KCL, which is a multidimensional assessment tool focusing on functional domains of daily living. As a result, 53.7% of the HF patients were identified as having frailty in the present study. This high frequency of frailty might be due to the older population than those in previous studies. The frequency of functional decline in each of the seven functional domains of the KCL significantly increased with increase in the degree of frailty. More than half of the frail patients with HF had functional decline in five domains including IADL, physical function, socialization, cognitive function, and depression domains. In addition, the number of domains with functional decline increased with the increase in frailty status. Approximately 30% of frail patients were diagnosed as having frailty based on functional decline in multiple domains other than the physical function domain. It has been suggested that multifaceted assessments as well as assessment of physical function are important for assessing frailty status in elderly HF patients. Compared with community-dwelling older people in the Kyoto–Kameoka study,¹⁶ the frequency of functional declines in IADL, physical function, malnutrition, and cognitive function domain was significantly higher in HF patients in the present study. The reason for these findings might be due to the difference of age between the two studies (81 years in the present study and 74 years in the Kyoto–Kameoka study). In addition, HF itself might lead to declines in multiple daily functional domains such as IADL, physical function, malnutrition, socialization, cognitive function, and depression. Several studies showed that frailty assessed by Fried criteria was associated with increased risks of mortality, hospitalization, and functional disability independent of the severity of HF.^{23–25} Additionally, elderly patients with HF often had deterioration of self-management such as medication adherence and self-monitoring due to physical and cognitive decline. Deterioration of self-management was the main cause of rehospitalization due to exacerbated HF,²⁶ and decreased activities of daily living functioning were risk factors for mortality and hospitalization.^{27,28} Early intervention with social support for decreased activities of daily living function and poor self-management is expected to improve clinical

outcomes.²⁸ Therefore, it is possible to identify the domain with functional decline based on KCL assessment, and it is expected that early intervention will improve the disease management of HF at home and quality of life, which finally might lead to reduced mortality and reduction in rehospitalization for worsening HF. In elderly patients with HF, the use of KCL for assessing multiple aspects such as physical, social, and psychological/cognitive aspects provided important information for multiple-disciplinary intervention for appropriate home service and care.

Investigation of the association between frailty status and changes in walking ability during hospitalization showed that most patients in the non-frailty group maintained independence of walking ability, whereas patients in the frailty group had decreased walking ability during hospitalization compared with those in the non-frailty group. It was reported that frail patients with HF had reduction in exercise tolerance as evaluated by cardiopulmonary exercise testing.²⁹ These findings suggest that frail patients with HF have poor exercise tolerance and an increased risk of physical impairment during hospitalization. In previous studies, it was shown that HF patients with lower limb function assessed by a short physical performance battery before discharge had high risks of post-discharge ADL decline, readmission, and mortality.^{30,31} Cardiac rehabilitation improved exercise tolerance and quality of life and reduced rehospitalization and cardiovascular death,³² which might be particularly beneficial for frail and prefrail patients with HF. Deterioration of walking ability during hospitalization was shown to be an independent risk factor for rehospitalization for worsening HF and mortality.³³ In elderly HF patients, especially frail patients, it is necessary to maintain and improve walking ability during hospitalization by cardiac rehabilitation.

Study limitations

There are several limitations to be acknowledged. First, the number of patients was not large as an HF cohort study. However, the population in the present study was considered to reflect the actual situation in an ageing region. Second, the KCL is self-administered and may not be accurate in patients with severe status of HF and cognitive impairment. Evaluation by the KCL in the present study reflected living functional status before hospitalization and may not reflect changes in physical and cognitive functions during hospitalization. The KCL is a simple questionnaire that can be repeated, and it is necessary to perform re-evaluation after discharge and use the information for intervention in clinical practice. Third, our registry has non-consecutive enrolment of patients. It might not be able to fully reflect the actual situation of HF patients in our area. However, because the hospitals participating in this registry are in charge of treatment for acute HF in Kochi Prefecture, it can be presumed that this registry

reflects the actual situation. Finally, this study is an observational study, and we are not able to investigate the effect of intervention on frailty. What kind of intervention contributes to improve frailty status and clinical outcomes for frail patients is an important issue in the future.

Future research

It is expected that home management of HF will be improved by evaluating living functions, introducing social support for functional decline in daily functional domains, and improving the living environment by coordinating with a caregiver. We need to investigate whether frailty status assessed by the KCL is associated with clinical outcomes in HF patients. Furthermore, it is necessary to examine whether interventions in the domain of impaired daily function will lead to improved quality of disease management and prognosis for HF patients.

Conclusions

More than half of patients with ADHF in a super-aged region in Japan were frail and had functional declines across multiple domains. The KCL provided useful and valuable information for easily identifying frail patients and for comprehensive management of HF. Moreover, information obtained by the KCL enables individualized interventions for each patient's problems.

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Acknowledgements

Participating investigators from the study hospitals were Saho Tsumura, RN; Shinya Katata, PT; Takayuki Maeda, PT (Kochi Medical School, Kochi University); Takako Fujita, MD; Hideyuki Matsuda, MD (Chikamori Hospital); Katsutoshi Tanioka, MD; Naoto Osawa, MD (Kochi Prefectural Hata Kenmin Hospital); Masanori Kuwabara, MD (Kochi Prefectural Aki General Hospital); Mana Kusunose, MD (Susaki Kuroshio Hospital); and Yasumasa Kawada, MD (Japanese Red Cross Kochi Hospital). We thank all of the physicians who made this study possible.

Conflict of interest

H. K. reports the receipt of personal fees from Takeda Pharmaceutical Company, Ltd, Daiichi-Sankyo Company, Mitsubishi Tanabe Pharma Corporation, Ltd., and grants from Takeda Pharmaceutical Company, Ltd; Daiichi Sankyo Company; Bayer Yakuhin, Ltd; Otsuka Pharmaceutical, Ltd; and Actelion Pharmaceuticals Japan, Ltd.

Funding

This work was supported by a Kochi Prefecture sponsorship project.

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