ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 3316–3326
Published online 20 June 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13482

ORIGINAL RESEARCH ARTICLE

Prognostic impact of Clinical Frailty Scale in patients with heart failure with preserved ejection fraction

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Abstract

Aims Frailty is associated with prognosis of cardiovascular diseases. However, the significance of frailty in patients with heart failure with preserved ejection fraction (HFpEF) remains to be elucidated. The purpose of this study was to examine the prognostic significance of the Clinical Frailty Scale (CFS) in real-world patients with HFpEF using data from a prospective multicentre observational study of patients with HFpEF (PURSUIT-HFpEF study).

Method and Results We classified 842 patients with HFpEF enrolled in the PURSUIT-HFpEF study into two groups using CFS. The registry enrolled patients hospitalized with a diagnosis of decompensated heart failure. Median age was 82 [interquartile range: 77, 87], and 45% of the patients were male. Of 842 patients, 406 were classified as high CFS (CFS $\geq$ 4, 48%) and 436 as low CFS (CFS $\leq$ 3, 52%). The primary endpoint was the composite of all-cause mortality and heart failure admission. Secondary endpoints were all-cause mortality and heart failure admission. Patients with high CFS were older (85 vs. 79 years, $P < 0.001$), predominantly female (65% vs. 46%, $P < 0.001$) and more likely to have New York Heart Association (NYHA) $\geq$ 2 (75% vs. 53%, $P < 0.001$) and a higher level of NT-proBNP (1360 vs 838 pg/mL, $P < 0.001$) than those with low CFS. Patients with high CFS had a significantly greater risk of composite endpoint (Kaplan–Meier estimated 1-year event rate 39% vs. 23%, log-rank $P < 0.001$), all-cause mortality (Kaplan–Meier estimated 1-year event rate 17% vs. 7%, log-rank $P < 0.001$) and heart failure admission (Kaplan–Meier estimated 1-year event rate 28% vs. 19%, log-rank $P = 0.002$) than those with low CFS. Multivariable Cox regression analysis revealed that high CFS was significantly associated with composite endpoint (adjusted HR 1.92, 95% CI 1.35–2.73, $P < 0.001$), all-cause mortality (adjusted HR 2.54, 95% CI 1.39–4.66, $P = 0.003$) and heart failure admission (adjusted HR 1.55, 95% CI 1.03–2.32, $P = 0.035$) even after adjustment for covariates. Moreover, change in CFS grade was also significantly associated with composite endpoint (adjusted HR 1.23, 95% CI 1.11–1.36, $P < 0.001$), all-cause mortality (adjusted HR 1.32, 95% CI 1.13–1.55, $P = 0.001$) and heart failure admission (adjusted HR 1.15, 95% CI 1.02–1.30, $P = 0.021$).

Conclusions Frailty assessed by the CFS was associated with poor prognosis in patients with HFpEF.

Keywords Frailty; Heart failure with preserved ejection fraction; Clinical Frailty Scale

Received: 5 October 2020; Revised: 24 May 2021; Accepted: 6 June 2021
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Introduction

The number of patients with heart failure with preserved ejection fraction (HFpEF) is rapidly increasing with the development of ageing society.[1–3] However, the pathophysiology and optimal management of HFpEF remain largely unknown. In addition to cardiac abnormalities, various extracardiac comorbidities may also contribute to HFpEF.

Frailty is characterized by decreased physiological reserve and vulnerability to stressors.[4,5] The prevalence of frailty increases with age and is reportedly from 16% to 26% in octogenarians.[6] Frailty is associated with the incidence of heart failure[7] and prognosis in various cardiovascular diseases including HFpEF.[8,9] Few reports have examined the significance of frailty and its severity in HFpEF patients.[9]

A number of tools are available for evaluating frailty, most of which include items that are difficult to obtain in daily clinical practice, such as walking speed, grip strength and questionnaires.[4,5,10] These complexities in evaluating frailty have made it difficult to examine frailty in elderly patients. The Clinical Frailty Scale (CFS) is a semi-quantitative, ease-of-use tool that can be evaluated at a glance[11] and was reportedly easier to use, required less time and had less missing data than Fried index.[12] The CFS evaluates various comprehensive aspects of frailty including comorbidity, disability and cognitive impairment.[13,14] CFS was associated with prognosis at a comparable level with the more complicated rules-based definition[15] and deficit models[16] such as the frailty index.[17] However, the prognostic significance of the CFS in patients with HFpEF remains unknown.

In this study, we examined the prognostic impact of CFS to clarify the clinical significance of frailty in real-world patients with HFpEF hospitalized for acute decompensated heart failure using data from a prospective multicentre observational study of patients with HFpEF (PURSUIT-HFpEF study).

Methods

Study patients

Of the 871 patients registered in the prospective multicentre observational study of patients with HFpEF (PURSUIT-HFpEF) registry between June 2016 and December 2019, three patients without CFS, 16 patients with in-hospital death and 10 patients with amyloidosis, pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension or sarcoidosis were excluded. A total of 842 patients were studied. The detailed design of the PURSUIT-HFpEF registry is described elsewhere.[18] The registry enrolled patients hospitalized with a diagnosis of decompensated heart failure based on the Framingham criteria and who met the criteria of left ventricular ejection fraction (LVEF) $\geq$ 50% on a transthoracic cardiac echocardiographic (TTE) test on admission and N-terminal pro-brain natriuretic peptide (NT-proBNP) $\geq$ 400 pg/mL or brain natriuretic peptide $\geq$ 100 pg/mL on admission and started June 2016. We adopted the cut-off value of LVEF 50% for the definition of HFpEF according to the clinical guideline.[18] We used the same cut-off value of natriuretic peptide for both patients with sinus rhythm and atrial fibrillation, because it was uncommon practice to change the cut-off value of natriuretic peptide based on patients' rhythm when the study began. We excluded patients with severe aortic stenosis, aortic regurgitation, mitral stenosis or mitral regurgitation due to structural changed in the valve detected by TTE on admission. We also excluded patients under 20 years old, patients with acute coronary syndrome on admission, patients with poor life prognosis within 6 months due to non-cardiac diseases, patients who had received heart transplantation and patients considered not to be appropriate for the study by the attending physician (Table S1). Thirty-one facilities participated in this study.

We collected data such as detailed past history, comorbidities, quality of life assessed by 5-Level EuroQol 5 Dimension (EQ-5D-5L, Marten Meesweg, Rotterdam, The Netherlands), frailty score (CFS), medication history, laboratory and echocardiographic data. We followed up each patient and collected outcome data on mortality, cause of death, number and cause of hospitalization. All patients provided written informed consent for their participation in this study, which was approved by the ethics committee of each participating hospital. This study followed the ethical guidelines outlined by the Helsinki Declaration. The study protocol was approved by the institutional review board of all participating facilities.

Data collection

Research cardiologists and specialized research nurses recorded the patients' data during their hospital stay. In-hospital data were transmitted to the data collection centre for processing and analysis. Medical history, smoking and CFS were obtained on admission. Vital signs, body mass index (BMI), New York Heart Association (NYHA) classification, echocardiography, laboratory data and medication use were obtained at discharge.

In echocardiography, tricuspid annular plane systolic excursion (TAPSE) and inferior vena cava (IVC) diameter were measured using the standard method. LVEF was measured using the Teichholz method. Left atrial volume (LAV) was measured using the ellipse method, and the LAV index was calculated by dividing LAV by body surface area. E/e′ was the mean of septal E/e′ and lateral E/e′. Tricuspid pressure gradient (TRPG) was measured using the simplified Bernoulli equation.

DOI: 10.1002/ehf2.13482

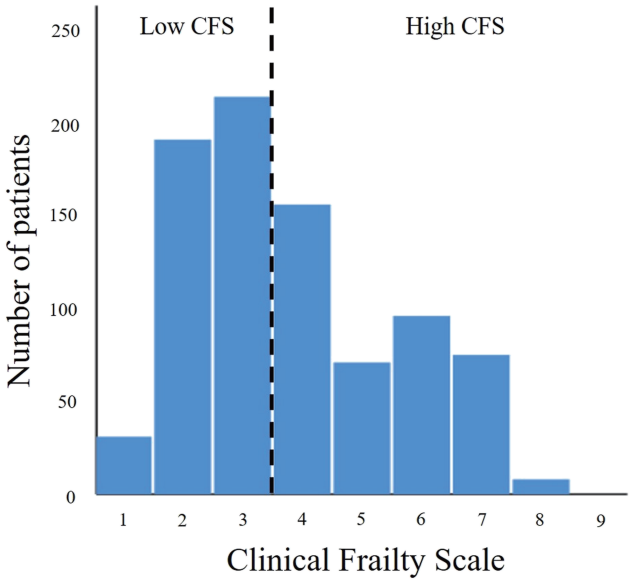
CFS

Patient frailty was assessed using the CFS, a rapid screening tool for frailty that does not require data on walking speed, grip strength or questionnaires. We determined CFS score at the stable phase before admission, but not at the acute phase during hospitalization, at the judgement of the attending physician, based on interviews with the patients and their family. The CFS classified patients' conditions into (1) very fit, (2) well, (3) managing well, (4) vulnerable, (5) mildly frail, (6) moderately frail, (7) severely frail, (8) very severely frail and (9) terminally ill (*Table S2*).[11]

Statistical analysis

We divided patients into two groups: CFS ≤ 3 and ≥ 4 to evaluate the prognostic impact of CFS, based on the fact that CFS ≥ 4 is reportedly associated with lower survival or avoidance of institutional care in the elderly population,[17] the median CFS score in this cohort was CFS = 3 (*Figure 1*) and our preliminary ROC analysis showed that the optimal cut-off of the CFS for predicting the composite endpoint was 3.5 (AUC 0.686). Continuous variables are expressed as median (interquartile range). Categorical data are presented as percentages unless otherwise specified. Tests for significance were conducted using the unpaired *t*-test or Mann–Whitney's *U* test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables. Primary endpoint of this study was the composite of all-cause mortality and heart failure admission. Secondary endpoints were all-cause mortality and heart failure admission. Endpoints were estimated using Kaplan–Meier curves, and statistical significance was determined using the log-rank test. Univariable and multivariable analyses using a Cox proportional hazards regression model were performed. In multivariable analysis, we adjusted the models for age, sex, BMI, diabetes mellitus, hypertension, estimated glomerular filtration rate (eGFR), **the presence of anaemia at discharge**, albumin, cholinesterase, prior heart failure admission, NYHA $\geq$ II, NT-proBNP, left ventricular mass index, E/e′ and use of angiotensin-converting enzyme (ACE-I) or angiotensin II receptor blocker (ARB). We selected these variables based on previous reports that examined prognosis in patients with HFpEF.[3,19–21] Anaemia was classified using the World Health Organization criteria. Adjusted hazard ratios (HR) and 95% confidence intervals (CI) were calculated for each endpoint using Cox proportional hazards regression models. Subgroup analyses were performed for composite endpoint, and *P*-values for interaction < 0.10 were considered statistically significant.[22] To determine the interaction between high CFS and each variable, we set all cut-offs other than that for eGFR to the median value. For eGFR, we used clinical cut-off values used to classify stages of chronic kidney disease (eGFR 60 mL/min/1.73 m^2 for Stages 2 and 3, 30 mL/min/1.73 m^2 for Stages 3 and 4) to examine the interaction between high CFS and chronic kidney disease stages. All statistical analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA). Statistical significance was defined as a $P < 0.05$.

Figure 1 Distribution of the Clinical Frailty Scale. High CFS was defined as Clinical Frailty Scale ≥ 4. CFS, Clinical Frailty Scale.



Results

Baseline characteristics

Out of 842 patients, 406 were CFS ≥ 4 (48%, high CFS group), and 436 were CFS ≤ 3 (52%, low CFS group). Patient baseline characteristics stratified by CFS are shown in *Table 1*. Among the entire study population, the median age was 82 (77, 87) years, and 45% were male. Patients with high CFS were older, mostly female; had lower BMI at discharge; were less likely to be smokers and to have a history of dyslipidaemia, ACE-I or ARB use; were more likely to have NYHA $\geq$ II and echocardiographic diastolic dysfunction; had lower TAPSE; higher TRPG; lower levels of haemoglobin and albumin; and higher levels of NT-proBNP than those with low CFS.

Outcomes

Incidence rate of the all-cause death, cardiac death and non-cardiac death in the two groups stratified by CFS is shown in *Table 2*. All-cause death, cardiac death and non-cardiac death were more frequent in patients with high CFS than those with low CFS. Kaplan–Meier analysis revealed

Table 1 Baseline characteristics

Variable	All $n = 842$	Low CFS $n = 436$	Missing	High CFS $n = 406$	Missing	P
Clinical data						
Age, years	82 [77, 87]	79 [74, 84]	0	85 [81, 89]	0	<0.001
Male, %	45	54	1	35	0	<0.001
Body mass index, kg/m^2						
On admission	23.7 [20.9, 26.8]	24.2 [21.6, 26.9]	14	22.9 [20.4, 26.8]	12	0.130
At discharge	21.4 [18.9, 24.3]	22.0 [19.3, 24.4]	7	20.8 [18.2, 24.0]	2	0.012
Current smoking, %	10	14	8	6	7	<0.001
Systolic blood pressure, mmHg	119 [106, 131]	120 [108, 132]	0	118 [105, 130]	0	0.065
Diastolic blood pressure, mmHg	65 [58, 74]	66 [58, 75]	0	65 [57, 72]	0	0.059
Heart rate, bpm	70 [61, 80]	69 [61, 78]	0	71 [62, 81]	0	0.084
NYHA classification ≥ II, %	64	53	5	75	4	<0.001
Prior heart failure admission, %	25	23	9	27	11	0.197
Hypertension, %	85	85	1	84	1	0.951
Diabetes mellitus, %	34	33	3	34	5	0.728
Dyslipidaemia, %	41	46	3	37	3	0.007
Stroke, %	14	13	3	16	6	0.246
Atrial fibrillation, %	45	47	0	44	0	0.429
Chronic kidney disease, %	40	38	4	42	2	0.227
Malignant disease, %	11	10	8	12	7	0.307
Echocardiography						
LVEF (Teichholz), %	65 [59, 70]	64 [59, 69]	26	65 [59, 70]	20	0.489
LVEF (Simpson), %	61 [55, 66]	61 [56, 66]	64	61 [55, 65]	58	0.423
Left atrial volume index, mL/m^2	42 [31, 55]	42 [31, 54]	68	42 [31, 55]	62	0.905
Left ventricular mass index, g/m^2	102 [84, 124]	104 [86, 125]	32	101 [83, 123]	24	0.076
Left ventricular end diastolic volume index, mL/m^2	53 [41, 66]	54 [41, 69]	72	51 [40, 65]	68	0.034
e′, m/sec	0.06 [0.05, 0.08]	0.06 [0.05, 0.08]	63	0.06 [0.05, 0.08]	53	0.173
E/e′	13 [10, 17]	12 [10, 16]	64	13 [10, 17]	56	0.083
TAPSE, mm	17 [15, 20]	18 [15, 21]	69	17 [14, 20]	55	0.014
Inferior vena cava diameter, mm	13 [11, 17]	13 [11, 16]	33	14 [11, 17]	30	0.523
TRPG, mmHg	27 [22, 33]	25 [21, 31]	67	28 [22, 34]	47	<0.001
Diastolic dysfunction, %	44	38	134	51	121	0.002
Laboratory data						
Sodium, mEq/L	139 [137, 141]	139 [138, 141]	1	139 [137, 141]	1	0.139
Haemoglobin, g/dL	11.3 [10.0, 12.7]	11.7 [10.3, 13.1]	1	11.0 [9.7, 12.3]	0	<0.001
Creatinine, mg/dL	1.1 [0.9, 1.5]	1.1 [0.9, 1.5]	2	1.1 [0.8, 1.6]	0	0.588
eGFR, mL/min/1.73m^2	42 [31, 55]	44 [33, 55]	9	40 [28, 53]	6	0.037
Uric acid, mg/dL	6.6 [5.4, 7.9]	6.6 [5.4, 7.8]	13	6.6 [5.3, 8.0]	18	0.811
Albumin, g/dL	3.4 [3.1, 3.7]	3.5 [3.2, 3.8]	15	3.3 [3.0, 3.6]	7	<0.001
Cholinesterase, IU/L	209 [171, 254]	217 [182, 265]	75	198 [160, 235]	73	<0.001
NT-proBNP, pg/mL	1066 [478, 2430]	838 [418, 2040]	53	1360 [628, 2895]	69	<0.001
Medications						
ACE-I or ARB, %	55	61	0	50	0	0.002
Calcium channel blocker, %	49	51	0	46	1	0.169
Beta blocker, %	55	58	0	52	1	0.098
Diuretics, %	82	79	0	84	0	0.067
Aldosterone antagonist, %	38	37	0	40	0	0.456
Statin, %	34	37	0	31	1	0.054

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; TAPSE, tricuspid annular plane systolic excursion; TRPG, tricuspid regurgitation pressure gradient.
Continuous variables are expressed as median [interquartile range].

Table 2 Incidence rate of endpoints between high and low CFS

	Low CFS	High CFS	P
Composite endpoint, 100 person-year	21.7	46.0	<0.001
All-cause death, 100 person-year	6.0	18.0	<0.001
Cardiac death, 100 person-year	2.0	9.5	<0.001
Non-cardiac death, 100 person-year	3.7	8.5	0.003
Heart failure admission, 100 person-year	17.4	29.3	0.002

CFS, Clinical Frailty Scale.

that patients with high CFS had a significantly greater risk of composite endpoint, all-cause death and heart failure admission than those with low CFS (*Figure 2*). Univariable and multivariable analyses with Cox proportional hazards for composite endpoint, all-cause mortality and heart failure admission are shown in *Tables 3*, S3 and S4. Multivariable analysis revealed that high CFS was significantly associated with composite endpoint, all-cause mortality and heart failure admission even after adjustment for covariates (*Tables 3*, *S3* and *S4*). We also performed Kaplan–Meier analysis to compare CFS grade ≤3, 4, 5, 6 and 7 or higher and ≤3, 4 to 5 and 6 or higher (*Figures S1* and *S1*). These analyses showed that the lowest CFS classes have the best prognosis, the highest classes have the worst and the intermediate classes have intermediate prognosis. Moreover, using CFS as a continuous variable, multivariable Cox regression analysis confirmed the presence of a significant association between each change in CFS class and poor prognosis (*Tables 3*, *S3* and *S4*).

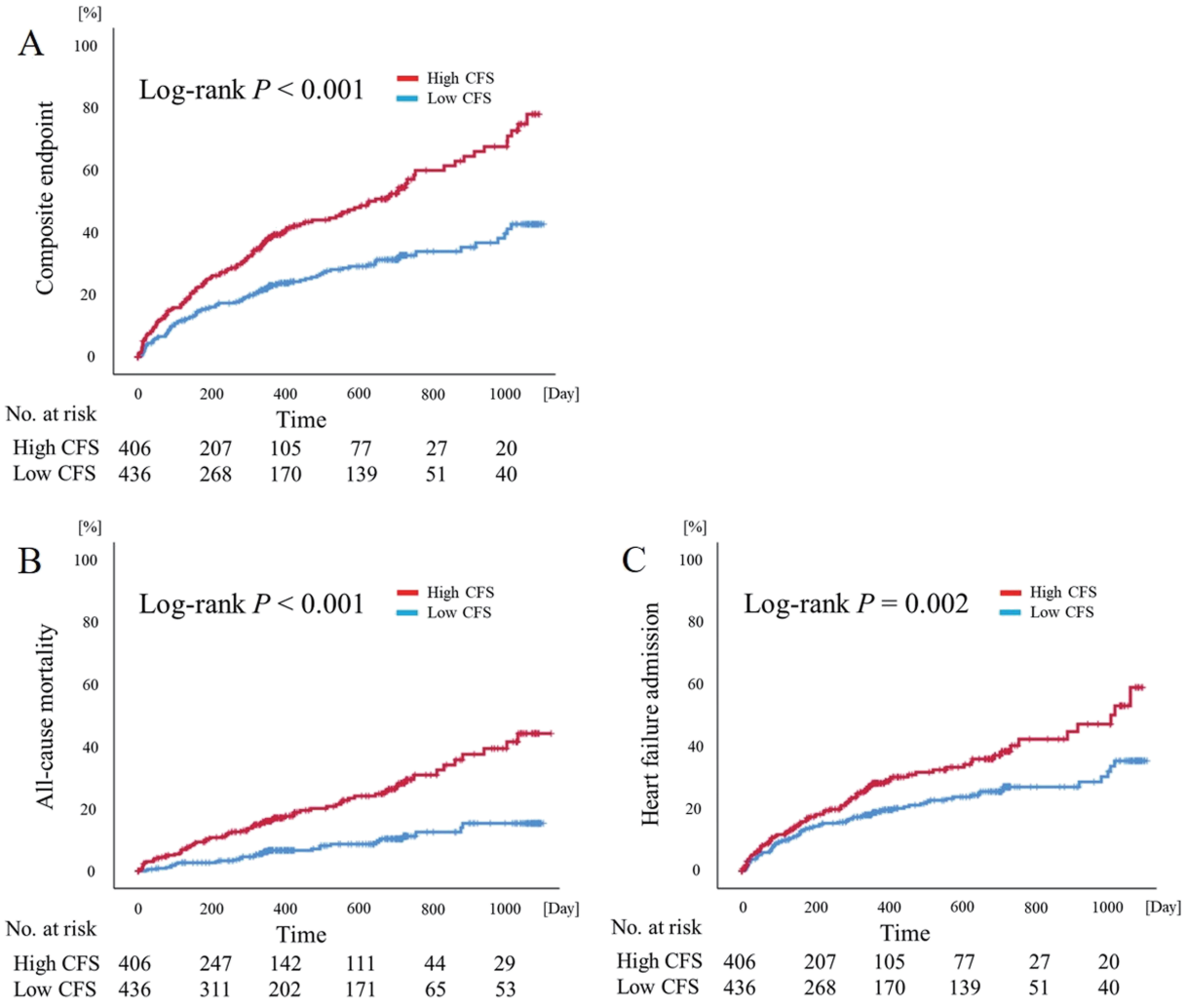
Subgroup analysis revealed a significant interaction with high CFS for composite endpoint between NYHA = I and ≥II, TRPG < 27 and ≥27 mmHg, albumin level < 3.4 and ≥3.4 mg/dL, e′ < 0.062 and ≥0.062, with and without echocardiographic diastolic dysfunction or use of ACEI or ARB (*Figure 3*).

Discussion

Main findings

In this study, we clarified that patients with high CFS (CFS ≥ 4; vulnerable or frail) showed worse composite endpoint,

Figure 2 Kaplan–Meier analysis for patients stratified by high or low CFS regarding composite endpoint of all-cause mortality and heart failure admission (A), all-cause mortality (B), and heart failure admission (C). CFS, Clinical Frailty Scale.



DOI: 10.1002/ehf2.13482

Table 3 Cox proportional hazards regression models for high CFS or each increase in CFS class and composite endpoints

	Unadjusted			Adjusted		
	HR	95% CI	*P*	HR	95%CI	*P*
High CFS (CFS ≥ 4)	2.05	1.58–2.64	<0.001	1.92	1.35–2.73	<0.001
Age	1.03	1.01–1.05	<0.001	1.01	0.99–1.04	0.201
Female	1.17	0.91–1.51	0.212	1.12	0.80–1.56	0.505
Body mass index	0.97	0.94–1.00	0.040	0.98	0.94–1.02	0.394
Diabetes mellitus	1.11	0.85–1.44	0.438	1.12	0.80–1.57	0.499
Hypertension	0.95	0.67–1.33	0.751	0.88	0.55–1.43	0.617
Prior heart failure admission	1.73	1.33–2.26	<0.001	1.46	1.04–2.07	0.031
Anaemia	1.37	1.02–1.83	0.036	0.80	0.53–1.19	0.273
Albumin	0.55	0.42–0.72	<0.001	0.63	0.43–0.92	0.016
Cholinesterase	0.99	0.99–1.00	<0.001	1.00	0.99–1.00	0.119
eGFR	0.99	0.98–0.99	<0.001	0.99	0.98–1.00	0.097
NYHA ≥ II	1.66	1.27–2.18	<0.001	0.94	0.66–1.34	0.732
NT-proBNP for 1000-unit increase	1.05	1.03–1.06	<0.001	1.03	1.01–1.05	0.015
Left ventricular mass index	1.00	1.00–1.01	0.039	1.00	1.00–1.01	0.088
E/e′	1.02	1.00–1.04	0.031	1.01	0.99–1.03	0.458
ACE-I or ARB	0.80	0.63–1.03	0.088	1.10	0.80–1.52	0.556
	Unadjusted			Adjusted		
	HR	95% CI	*P*	HR	95%CI	*P*
Each increase in CFS class	1.24	1.16–1.33	<0.001	1.23	1.11–1.36	<0.001
Age	1.03	1.01–1.05	<0.001	1.01	0.99–1.04	0.260
Female	1.17	0.91–1.51	0.212	1.08	0.77–1.50	0.664
Body mass index	0.97	0.94–1.00	0.040	0.98	0.94–1.03	0.436
Diabetes mellitus	1.11	0.85–1.44	0.438	1.15	0.82–1.61	0.412
Hypertension	0.95	0.67–1.33	0.751	0.89	0.55–1.45	0.639
Prior heart failure admission	1.73	1.33–2.26	<0.001	1.41	0.99–1.99	0.056
Anaemia	1.37	1.02–1.83	0.036	0.75	0.50–1.12	0.163
Albumin	0.55	0.42–0.72	<0.001	0.64	0.44–0.93	0.019
Cholinesterase	0.99	0.99–1.00	<0.001	1.00	0.99–1.00	0.137
eGFR	0.99	0.98–0.99	<0.001	0.99	0.98–1.00	0.049
NYHA ≥ II	1.66	1.27–2.18	<0.001	0.90	0.63–1.29	0.576
NT-proBNP for 1000-unit increase	1.05	1.03–1.06	<0.001	1.03	1.00–1.05	0.025
Left ventricular mass index	1.00	1.00–1.01	0.039	1.00	1.00–1.01	0.058
E/e′	1.02	1.00–1.04	0.031	1.01	0.99–1.03	0.591
ACE-I or ARB	0.80	0.63–1.03	0.088	1.12	0.81–1.55	0.487

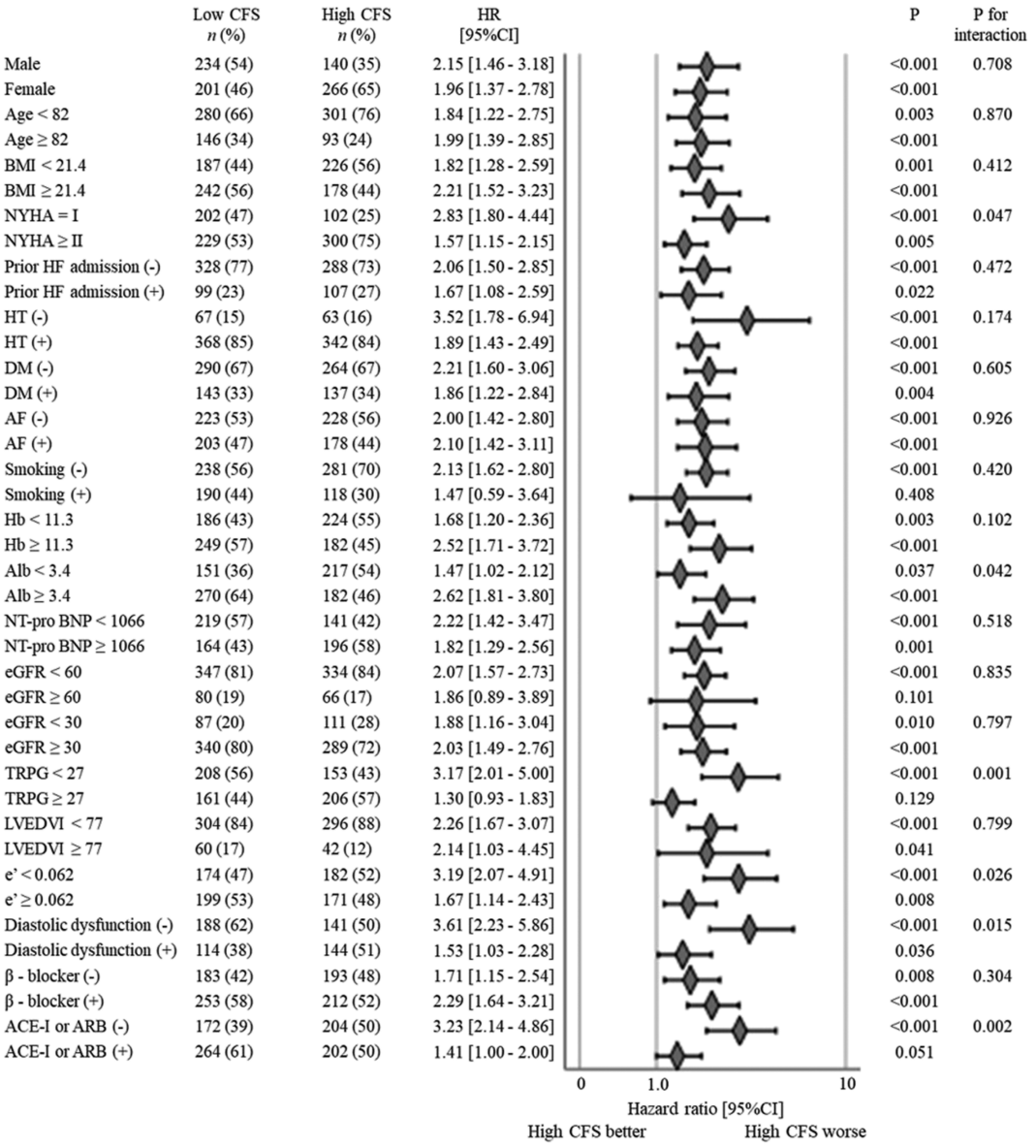
ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CFS, Clinical Frailty Scale; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association.

all-cause mortality and heart failure admission than those with low CFS. CFS ≥ 4 and an increase in CFS class were significantly associated with higher risk of composite endpoint after adjustment for major clinical variables. This study is the first report to clarify the prognostic significance of grading with CFS, hence the association between the frailty and prognosis, in patients with HFpEF. In addition, our findings indicate that CFS is a useful tool for risk stratification in patients with HFpEF.

Frailty and HFpEF

In this study, we showed that HFpEF patients with high frailty scale (as classified by CFS) were significantly associated with poor prognosis. In addition, we also demonstrated that an increase in CFS grade, which indicated greater severity of frailty, was also associated with poor prognosis. Although previous studies have also reported that frailty is associated with mortality in patients with cardiovascular diseases,[8,23–25] complexities in evaluating frailty have made it difficult to examine frailty in clinical settings. In addition, Yang et al.[26] reported that the presence of frailty was associated with increased risk of death and hospitalization in patients with heart failure in a meta-analysis. Regarding HFpEF, a subanalysis of data from TOPCAT reported that a higher frailty index was associated with poorer prognosis.[9] Consistent with this, our study showed that the severity of frailty assessed using the CFS was significantly associated with poor prognosis. We also demonstrated that the presence of a vulnerable state (CFS ≥ 4) was associated with poor prognosis. Interestingly, patients with high CFS showed high prevalence of women (65%) (*Table 1*). Left ventricular chamber in women do not dilate under increased load compared with men, which causes higher filling pressure in women characteristics to HFpEF.[27] We also reported that female sex was associated

Figure 3 Subgroup analyses of the composite endpoint stratified by high or low CFS. CFS, Clinical Frailty Scale, HR, hazard ratio; NYHA, New York Heart Association; HT, hypertension; DM, diabetes mellitus; AF, atrial fibrillation; BMI, body mass index; Hb, haemoglobin; TRPG, tricuspid pressure gradient; Alb, albumin; NT-proBNP, N-terminal pro-brain natriuretic peptide; eGFR, estimated glomerular filtration rate; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HF, heart failure.



with echocardiographic diastolic dysfunction and poor prognosis.[28] These findings suggest that female sex may be a confounding factor to the relationship between frailty and poor prognosis. On the other hand, our data demonstrated that these associations were significant even after adjustment for age, sex, BMI, comorbidities (diabetes mellitus, hypertension or anaemia), severity of heart failure (NYHA class, NT-proBNP level, E/e′ and left ventricular mass index), nutritional status (choline esterase[21] and albumin) and other clinical conditions. Therefore, the presence of a vulnerable state and frailty may be important risk factors in patients with HFpEF.

CFS

Among more than 20 assessment tools developed for frailty to date,[8] we used the CFS to assess frailty in this study. The CFS appropriately identified frail patients even in our cohort despite its simplicity, because patients with CFS ≥ 4 showed

DOI: 10.1002/ehf2.13482

typical characteristics of frail patients, such as older age, lower BMI and lower albumin level in this study (*Table 1*). Moreover, the number of missing CFS data (n = 3) in our study was very small probably due to high feasibility of the CFS.[17] The CFS is useful for prediction of prognosis in elderly patients as demonstrated in a previous study, which examined the association between frailty and prognosis in elderly patients with aortic valve stenosis, among whom the mean age was more than 80 years old.[29] Therefore, the CFS was also suitable for our study population with median age of 82 years old.

The CFS has a scoring system for frailty in patients with dementia in which the degree of frailty is classified according to the degree of dementia (*Table S2*).[11] Although we did not specifically assess dementia in this study, the frailty of patients with dementia would be classified according to their degree of dementia.

We only assessed CFS at the stable phase before admission due to acute decompensated heart failure. It is possible that patients' severity of frailty may have changed during hospitalization. In a previous report, 74.1% of patients showed an increase in CFS by $\geq$1 grade from baseline to admission and 61.9% of patients showed a decrease in CFS by $\geq$1 grade from admission to 1 month after discharge.[30] This report suggests that 12.2% of patients have deteriorating CFS during hospitalization and do not recover 1 month after discharge.

In this study, CFS was assessed by a single physician, and a second assessment by other research staff was not performed; thus, the data may contain some bias or inter-observer variability. However, recent studies have demonstrated that CFS has good reliability among medical staff[31] and critical care doctors and medical students.[32] Flaatten et al.[31] showed a very high inter-rate agreement (weighted kappa 0.86) of CFS scores among an intensive care unit (ICU) nurse, ICU physician and research staff in 1923 patients from 129 ICUs in 20 countries. Pugh et al.[32] showed that CFS had high reliability (weighted kappa 0.64) even between doctors and medical students. Although some bias is unavoidable, these findings suggest that the assessment of CFS by a single physician may be adequately reliable.

Although frailty is generally defined as CFS $\geq$ 5, our analysis revealed that even CFS $\geq$ 4 was significantly associated with poor prognosis in patients with HFpEF. In this study, we aimed to clarify the usefulness of the CFS for risk stratification and the clinical significance of frailty in patients with HFpEF. Our findings suggest that even patients in pre-frail condition had higher risk than less frail patients in patients with HFpEF. Moreover, considering that the number of patients with CFS = 4 is the third most in our population (*Figure 1*), it should be emphasized that assessment with CFS may be important to identify higher risk patients and should be performed in routine clinical setting. Taken together, these findings indicate the significance and usefulness of CFS in the care of patients with HFpEF.

Renin–angiotensin–aldosterone system and frailty

The results of subgroup analysis shown in *Figure 3* demonstrate a significant interaction of prognosis with the relationship between high CFS and use of ACE-I or ARB. This suggests that the impact of high CFS may be attenuated by the use of ACE-I or ARB or vice versa, indicating the positive effects of ACE-I or ARB on prognosis in HFpEF patients with high CFS. In support of this, a previous report showed that elderly women taking ACE-I had less muscle weakness and reduced walking speed than those who were not,[33] suggesting that use of ACE-I or ARB may be associated with improved frailty. Several mechanisms have been hypothesized to explain the potential association between the renin–angiotensin–aldosterone system (RAAS) and frailty. First, inhibiting RAAS may lead to an improvement in cardiac and vascular function[34] that, consequently, is associated with an improvement in physical function and lower risk of frailty. Second, inhibiting RAAS can attenuate inflammation,[35] which plays an important role in the development of frailty and poor muscle function.[36–38] Finally, inhibiting RAAS can prevent age-related mitochondrial dysfunction, further contributing to improved muscle function.[39]

Clinical implications

Assessment of frailty is not performed in typical clinical settings for patients with HFpEF. This is partially due to the complexity of frailty assessment. Our study showed that the CFS, a simple and feasible diagnostic method for frailty, is a powerful prognostic factor. Therefore, assessment using the CFS in diverse clinical settings may improve risk stratification in patients with HFpEF. A previous research suggests that frailty may be improved by exercise, caloric and protein supplements, vitamin D and reduction of polypharmacy.[11] Our results imply that such interventions to frailty in addition to standard treatment for heart failure may be useful in patients with HFpEF and frailty.

Limitations

This study has several limitations. First, although there are a large number of tools for assessing frailty, we did not compare CFS with all of them. Therefore, the frequency and impact of frailty may be different when using other tools. Second, CFS is a subjective rather than objective measure and may therefore be associated with some bias. In addition, it remains controversial whether objective or subjective measure is better. Third, assessment of CFS was performed on admission but not at discharge or during hospitalization. It is possible that the severity of frailty may have changed

during hospitalization. Fourth, because we studied patients recovering from acute decompensated heart failure, generalization of the results should be performed with caution. Fifth, the CFS was recently updated.[40] Because our study started in 2016, we used a previous version of the CFS in this study. Therefore, the CFS scoring performed in this study may differ from that of the updated CFS. Finally, it is unclear whether an improvement in frailty will lead to a better outcome. Prospective trials using appropriate interventions are needed to investigate this point.

Conclusions

CFS $\geq$ 4 and an increase in CFS score at the stable phase before admission for worsening of heart failure were associated with poor prognosis after discharge in patients with HFpEF hospitalized for acute decompensated heart failure. These findings may indicate the significance and importance of the CFS in the risk stratification in patients with HFpEF. The assessment with CFS in clinical settings might be important for the management of patients with HFpEF.

Acknowledgements

The authors thank Nagisa Yoshioka, Kyoko Tatsumi, Satomi Kishimoto, Noriko Murakami and Sugako Mitsuoka for their excellent assistance with data collection.

Conflict of interest

Shungo Hikoso has received remuneration from Daiichi Sankyo Company and received research funding from Roche Diagnostics, FUJIFILM Toyama Chemical and Actelion Pharmaceuticals. Yoshiharu Higuchi has received remuneration from Daiichi Sankyo Company. Hiroya Mizuno has received endowed department from Terumo. Yohei Sotomi has received remuneration from Abbott Vascular Japan, Boston Scientific Japan and received research funding from Abbott Vascular Japan and endowed department from Terumo. Yasushi Sakata received remuneration from Otsuka Pharmaceutical, Ono Pharmaceutical, Daiichi Sankyo Company and AstraZeneca K.K. and received research funding form Otsuka Pharmaceutical, Daiichi Sankyo Company, Mitsubishi Tanabe Pharma Corporation, Astellas Pharma, Kowa Company, Boehringer Ingelheim Japan and Biotronik. Other authors (Akihiro Sunaga, Takahisa Yamada, Yoshio Yasumura, Shunsuke Tamaki, Haruhiko Abe, Yusuke Nakagawa, Hisakazu Fuji, Toshiaki Mano, Hiroyuki Kurakami, Tomomi Yamada, Tetsuhisa Kitamura, Taiki Sato, Bolrathanak Oeun, Hirota Kida, Takayuki Kojima, Tomoharu Dohi, Katsuki Okada, Shinichiro Suna and Daisaku Nakatani) have no conflicts of interest to report.

Funding

This work was funded by Roche Diagnostics K.K. and FUJIFILM Toyama Chemical Co., Ltd.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Inclusion and exclusion criteria of the PURSUIT-HFpEF study (taken from reference 18).
Table S2. Clinical Frailty Scale.
Table S3. Cox proportional hazards regression models for high CFS or each increase in CFS class and all cause death.
Table S4. Cox proportional hazards regression models for high CFS or each increase in CFS class and heart failure admission.
Figure S1. *Kaplan-Meier analysis for patients stratified by CFS grade ≤3, 4, 5, 6 and 7 or higher regarding composite endpoint of all-cause mortality and heart failure admission (A), all-cause mortality (B), and heart failure admission (C). CFS, Clinical Frailty Scale.*
Figure S2. *Kaplan-Meier analysis for patients stratified by CFS grade ≤3, 4 to 5, and 6 or higher regarding composite endpoint of all-cause mortality and heart failure admission (A), all-cause mortality (B), and heart failure admission (C). CFS, Clinical Frailty Scale.*

Appendix

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