ESC HEART FAILURE
ESC Heart Failure 2022; **9**: 1574–1583
Published online 19 February 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13844

ORIGINAL ARTICLE

Prevalence and prognostic impact of cognitive frailty in elderly patients with heart failure: sub-analysis of FRAGILE-HF

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Abstract

Aims Although evidence suggests that cognitive decline and physical frailty in elderly patients with heart failure (HF) are associated with prognosis, the impact of concurrent physical frailty and cognitive impairment, that is, cognitive frailty, on prognosis has yet to be fully investigated. The current study sought to investigate the prevalence and prognostic impact of cognitive frailty in elderly patients with HF.

Methods and results This study is a sub-analysis of FRAGILE-HF, a prospective multicentre observational study involving patients aged ≥65 years hospitalized for HF. The Fried criteria and Mini-Cog were used to diagnose physical frailty and cognitive impairment, respectively. The association between cognitive frailty and the combined endpoint of mortality and HF rehospitalization within 1 year was then evaluated. Among the 1332 patients identified, 1215 who could be assessed using Mini-Cog and the Fried criteria were included in this study. Among those included, 279 patients (23.0%) had cognitive frailty. During the follow-up 1 year after discharge, 398 combined events were observed. Moreover, cognitive frailty was determined to be associated with a higher incidence of combined events (log-rank: $P = 0.0146$). This association was retained even after adjusting for other prognostic factors (hazard ratio: 1.55, 95% confidence interval: 1.13–2.13). Furthermore, a sensitivity analysis using grip strength, short physical performance battery, and gait speed to determine physical frailty instead of the Fried criteria showed similar results.

Conclusions This cohort study found that 23% of elderly patients with HF had cognitive frailty, which was associated with a 1.55-fold greater risk for combined events within 1 year compared with patients without cognitive frailty.

Keywords Frailty; Cognitive impairment; Heart failure; Elderly; Prognosis

Received: 2 August 2021; Revised: 12 January 2022; Accepted: 4 February 2022
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Introduction

Given the increase in lifestyle-related diseases and the ageing population, the number of patients with heart failure (HF) in Japan has continued to increase dramatically over the past few decades and is expected to continue increasing over the next 20 years.[1,2] Despite the significant decrease in the mortality rate of chronic HF over the past 20 years, rehospitalization rates after hospital discharge have not decreased significantly and remain high at 20–40% per year.[3,4] While several prognostic factors for patients with HF have been reported to date, most reports come from randomized controlled trials that exclude elderly patients with HF and focus specifically on the heart (e.g., cardiac function and cardiac biomarkers).

The concept of 'frailty' has been gaining attention recently as a characteristic of elderly patients.[5,6] Frailty is defined as a state of increased vulnerability to health problems due to various functional changes and decreased reserve capacity associated with ageing.[7,8] Several large cohort studies have reported an association between physical frailty and increased risk for disability, mortality, hospitalization, sarcopenia, cachexia, and so forth.[9–11] Likewise, cognitive frailty, which is characterized by the coexistence of cognitive impairment without neurodegenerative diseases and physical frailty, has been found to be prevalent among elderly patients with HF.[12–14] Reports have shown that HF predisposes patients to cognitive impairment.[15] The coexistence of reduced cognitive impairment and gait speed, known as 'motoric cognitive risk syndrome', has been reported to be associated with adverse health outcomes similarly to cognitive frailty.[16,17] Previous studies have suggested that physical frailty and cognitive impairment were individually associated with worsening HF. In our previous study (i.e. FRAGILE-HF), we reported that 56% and 37% of elderly patients with HF had physical frailty and cognitive impairment, respectively.[13] However, predictors of cognitive frailty and its association with adverse outcomes in elderly patients with HF have yet to be fully explored. Moreover, although the frailty criteria developed by Fried *et al*. have been extensively utilized for determining physical frailty, many other assessments tools for physical function have been used in clinical settings.[18] Furthermore, it remains unclear whether the aforementioned tools yield similar results with regard to the definition of physical frailty.

In this sub-analysis of the FRAGILE-HF trial, we investigated the prevalence and prognostic impact of cognitive frailty in elderly patients with HF. Moreover, sensitivity analysis was conducted using other measurements, namely, the short physical performance battery (SPPB), grip strength, and gait speed, as alternatives to the frailty criteria proposed by Fried *et al*., the reliability of which has been verified even in individuals with cognitive impairment.[19,20]

Methods

Study design and patient population

This study is a sub-analysis of FRAGILE-HF, a prospective multicentre observational study conducted in 15 hospitals across Japan. The detailed study design has been published elsewhere. Briefly, all consecutive patients aged ≥65 years, first admitted to hospital for decompensated HF between September 2016 and March 2018, and were ambulatory at discharge were eligible for inclusion. The Framingham criteria were used for the diagnosis of decompensated HF. Exclusion criteria were (i) previous heart transplantation or left ventricular assist device implantation, (ii) either chronic peritoneal dialysis or haemodialysis therapy, (iii) acute myocarditis, and (iv) patients with disability due to cerebrovascular or orthopaedic diseases. Patients with missing data on brain natriuretic peptide (BNP) or N-terminal-proBNP levels and those with a BNP level of <100 pg/mL or N-terminal-proBNP level of <300 pg/mL at admission were also excluded. This study was conducted in compliance with the Declaration of Helsinki and the Japanese Ministry of Health, Labor and Welfare's Ethical Guidelines for Medical and Health Research Involving Human Subjects. All participants were notified of their participation in this study and informed that they were free to withdraw from participation at any time. Given the observational nature of this study without invasive procedures or interventions, written informed consent was not required by the national guidelines. The research protocol was approved by the ethics committee of each participating hospital. All research information is available in the University Hospital Information Network Clinical Trials Registry (unique identifier: UMIN000023929).

Assessment of physical and cognitive functioning

Cognitive frailty assessment—both physical frailty and cognitive impairment—was performed by trained personnel. Patients with at least three of the following factors were considered to have physical frailty: weakness (hand grip), decreased walking speed, weight loss, fatigue, and decreased physical activity using the Fried phenotype.[5] The questionnaire used to identify and diagnose frailty has been published in detail previously.

Hand grip strength was measured using a dynamometer. Briefly, the subjects sat on a bench with their elbow joint flexed at 90° and performed the test alternately with the right and left hands. The maximum value of two trials using both hands was expressed as an absolute value (kg). Patients with a hand grip strength of <28 and <18 kg for men and women were considered physically frail, respectively.[21] The SPPB consisted of three components (standing balance,

normal walking speed, and chair-stand repetition) and was applied according to established methods. SPPB scores ranged from 0 to 12, with a score of 0–4 for each component (0 = *worst*, 12 = *best*).[22] Patients with less than 9 points were considered physically frail.[21] Gait speed was based on a 4 m walk, which is one of the evaluation items in the SPPB, and patients with a gait speed <1 m/s were considered physically frail. Mini-Cog©, a combination of a three-item recall test and clock drawing test, was used to assess cognitive function. The test method was based on the Mini-Cog© website (https://mini-cog.com) wherein patients were scored based on a 5-point scale (0 = *worst*, 5 = *best*), with scores <3 being considered abnormal.[23] All physical and cognitive assessments were performed at hospital discharge.

Assessment of endpoint

This study prospectively collected and analysed data on the prognosis of patients within 1 year of discharge up to March 2019. The endpoints of the study were mortality at 1 year and a combination of mortality and HF readmission within 1 year of discharge. Patients were followed up at an outpatient clinic or another health care facility at least every 3 months. For patients not followed up at the clinic, prognostic data were obtained via telephone interview by the facility's medical records department. Readmission due to HF was only categorized as such if it satisfied the criteria for HF readmission described in the American College of Cardiology/American Heart Association Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials.[24]

Statistical analysis

Normally distributed data were expressed as mean and standard deviation for distribution, whereas non-normally distributed data were expressed as median and interquartile range. Categorical data were expressed as numbers and percentages. The cohort was divided into the following four groups: non-physical frail and non-cognitive impairment group, physical frail and non-cognitive impairment group, non-physical frail and cognitive impairment group, or physical frail and cognitive impairment group. Differences between groups were compared using one-way analysis of variance (ANOVA) or the Kruskal–Wallis test and χ^2 or Fisher exact test for continuous and categorical variables, respectively.

Event-free survival curves were generated using the Kaplan–Meier survival method and compared using log-rank statistics. Moreover, the following variables were used for adjustment during multivariable Cox regression: age; gender; body mass index (BMI); left ventricular ejection fraction; current smoking status; history of HF, hypertension, diabetes, coronary artery disease, chronic obstructive pulmonary disease, and atrial fibrillation; systolic blood pressure; estimated glomerular filtration rate; haemoglobin; serum sodium level; serum albumin; log-transformed BNP; prescription of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, beta-blocker, and mineralocorticoid receptor antagonist; and New York Heart Association classification III/IV at discharge. These variables were selected based on their clinical importance as described in previous studies. To assess whether cognitive frailty, in addition to known risk factors, affects the composite endpoint and combine events, we constructed a baseline model that incorporated existing risk factors and a model that added the presence of cognitive frailty to the baseline model. Hazard ratios were calculated using the non-cognitive frailty group as reference.

Statistical analyses were performed using STATA version 15.0 (StataCorp, College Station, Texas, USA) and R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria; ISBN 3-900051-07-0, URL http://www.R-project.org), with a two-sided P value of <0.05 indicating statistical significance.

Results

Patients' characteristics

Among the 1332 patients enrolled in the FRAGILE-HF cohort study, 1215 (91.2%) were successfully evaluated using both Mini-Cog and Fried criteria. *Table 1* summarizes the patients' baseline profiles. Among the enrolled patients, 279 (23.0%) had cognitive frailty. Our results also found that the proportion of cognitive frailty increased with age (*Figure 1*). The characteristics of those with and without physical frail and/or cognitive impairment are detailed in *Table 1*. There were significant differences between the four groups in age, male gender, BMI, diastolic blood pressure, left ventricular ejection fraction, haemoglobin, albumin levels, BUN, eGFR, and prescription rate of beta-blocker and loop diuretics.

Association between cognitive frailty and prognosis

Given that 26 patients had no follow-up data, the prognostic impact of cognitive frailty was analysed in only 1189 patients (97.8%). During follow-up 1 year after discharge, 398 combined events (33.5%) and HF readmissions, were observed. The Kaplan–Meier curve for combined events showed that patients with HF and cognitive frailty had a significantly higher event rate during the 1 year observation period after discharge (log-rank test, $P = 0.0146$) (*Figure 2*). Unadjusted

Table 1 Baseline patient characteristics

Variables	Overall $n = 1215$	Non-physical frail/non-cognitive impairment $n = 352$	Physical frail/non-cognitive impairment $n = 413$	Non-physical frail/cognitive impairment $n = 171$	Physical frail/cognitive impairment $n = 279$	*P* value
Age (years)	81 [74.0, 86.0]	77 [71.0, 82.0]	80 [74.0, 85.0]	83 [77.0, 87.0]	85 [80.0, 89.0]	<0.001
Male gender (%)	695(57.2)	220 (62.5)	243 (58.8)	101 (59.1)	131 (47.0)	0.001
BMI (kg/m^2)	20.9 [18.8, 23.4]	21.6 [19.7, 24.0]	20.6 [18.7, 23.1]	21.1 [18.9, 23.8]	20.3 [17.8, 22.9]	<0.001
NYHA Class III/IV (%)	167 (13.7)	33 (9.4)	65(15.7)	18 (10.5)	51(18.2)	NA
Systolic blood pressure (mmHg)	113.6 (17.0)	114.4 (17.2)	112.7 (17.4)	115.7 (17.2)	112.8 (16.3)	0.164
Diastolic blood pressure (mmHg)	62.0 (10.8)	63.4 (10.9)	62.5 (11.1)	61.5 (10.0)	60.1 (10.4)	0.002
Heart rate (bpm)	71.0 (14.0)	68 [60.0, 78.2]	70 [61.0, 80.0]	68 [60.0, 78.0]	70 [60.0, 78.5]	0.119
Left ventricular ejection fraction	45.0 [32.0, 60.0]	43.0 [30.1, 58.9]	45.0 [30.0, 60.0]	44.0 [32.0, 60.0]	48.5 [33.7, 63.0]	0.042
Heart failure phenotypes						0.206
HFrEF (%)	618 (50.9)	192 (54.5)	205 (49.6)	91 (53.2)	130 (46.6)	
HFpEF (%)	597 (49.1)	160 (45.5)	208 (50.4)	80 (46.8)	149 (53.4)	
Comorbidities (%)						
Atrial fibrillation	540 (44.4)	170 (48.3)	182 (44.1)	79 (46.2)	109 (39.1)	0.131
Coronary artery disease	436 (35.9)	125 (35.5)	145 (35.1)	72 (42.1)	94 (33.7)	0.314
COPD	132 (10.9)	36 (10.2)	51 (12.3)	20 (11.7)	25 (9.0)	0.521
Diabetes	434 (35.7)	125 (35.5)	152 (36.8)	66 (38.6)	91 (32.6)	0.569
Hypertension	866 (71.3)	257 (73.0)	285 (69.0)	120 (70.2)	204 (73.1)	0.549
Laboratory data at discharge						
Haemoglobin (g/dL)	11.7 [10.3, 13.0]	12.1 [10.6, 13.6]	11.6 [10.1, 13.0]	11.7 [10.3, 12.8]	11.3 [10.1, 12.9]	<0.001
Albumin (g/dL)	3.5 [3.2, 3.8]	3.6 [3.3, 3.9]	3.4 [3.1, 3.8]	3.5 [3.2, 3.7]	3.3 [3.0, 3.5]	<0.001
Creatinine (mg/dL)	1.1 [0.9, 1.5]	1.1 [0.9, 1.5]	1.1 [0.9, 1.5]	1.2 [1.0, 1.5]	1.1 [0.8, 1.6]	0.268
BUN (mg/dL)	26.0 [19.8, 36.0]	24.2 [19.0, 33.1]	27.5 [19.0, 37.7]	26.2 [21.0, 34.9]	28.0 [21.0, 38.0]	0.016
eGFR (mL/min/1.73 m^2)	51.9 [35.3, 69.5]	57.7 [37.1, 72.7]	52.1 [35.2, 70.4]	48.3 [34.4, 62.9]	49.8 [33.9, 67.7]	0.009
BNP (pg/mL)	281.1 [139.7, 498.2]	259.5 [132.3, 442.3]	308.9 [157.6, 582.4]	232.1 [125.7, 448.7]	277.0 [129.1, 501.8]	0.059
Prescription at discharge (%)						
ACE-I/ARB	818 (67.3)	247 (70.1)	275 (66.5)	113 (66.0)	183 (65.5)	0.115
Beta-blocker	897 (73.8)	278 (79.0)	313 (75.8)	119 (69.6)	187 (67.0)	0.003
Mineralocorticoid receptor antagonist	601 (49.5)	179 (50.9)	208 (50.4)	86 (50.3)	128 (45.9)	0.596
Loop diuretics	1030 (84.8)	281 (79.8)	372 (90.1)	142 (83.0)	235 (84.2)	0.001
Physical and cognitive functions						
Fried score	3.0 [2.0, 4.0]	2.0 [1.0, 2.0]	3.0 [3.0, 4.0]	2.0 [1.0, 2.0]	3.0 [3.0, 4.0]	<0.001
Mini-Cog score	3.0 [2.0, 5.0]	4.0 [3.0, 5.0]	4.0 [3.0, 5.0]	2.0 [1.0, 2.0]	1.0 [0.0, 2.0]	<0.001
Grip strength	19.5 [14.0, 25.0]	23.2 [18.5, 30.1]	18.3 [13.8, 23.6]	20.0 [14.8, 27.05]	15.5 [11.0, 21.2]	<0.001
Gait speed	0.78 [0.57, 0.99]	0.96 [0.79, 1.12]	0.73 [0.54, 0.93]	0.82 [0.69, 0.96]	0.57 [0.44, 0.7]	<0.001
SPPB	9.0 [6.0, 11.0]	11.0 [9.0, 12.0]	8.0 [6.0, 11.0]	9.0 [7.0, 11.0]	6.0 [4.0, 8.0]	<0.001

Values are median [interquartile range], *n* (%), or mean (standard deviation).

ACE-I, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; LDL, low density lipoprotein; NYHA, New York Heart Association; SPPB, short physical performance battery.

Figure 1 Prevalence of cognitive frailty by age.

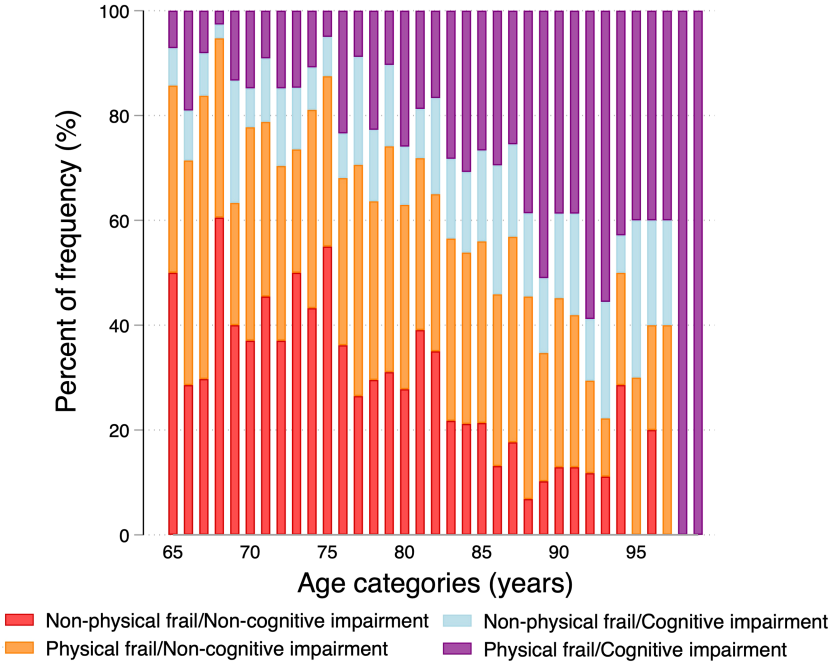
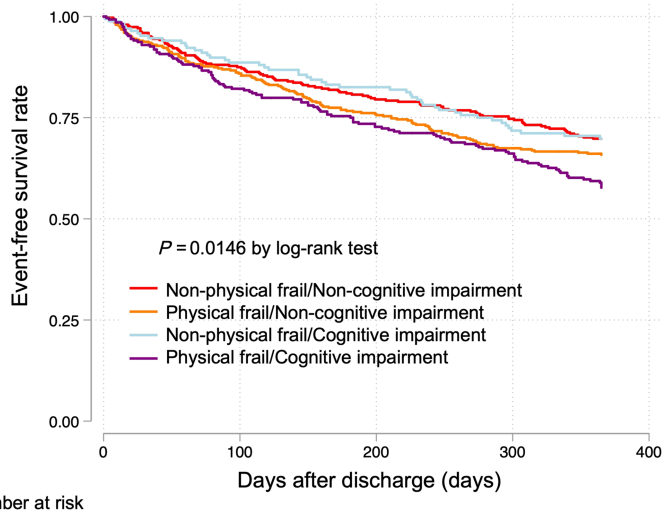


Figure 2 Kaplan–Meier curves for the combined events of all-cause death and heart failure rehospitalization.



Number at risk					
Non-physical frail / Non-cognitive impairment	336	292	264	245	0
Physical frail / Non-cognitive impairment	376	320	279	248	0
Non-physical frail / Cognitive impairment	164	145	134	112	0
Physical frail / Cognitive impairment	252	205	185	163	0

Cox regression analysis showed that cognitive frailty was significantly associated with higher incidence of combined events of all-cause mortality and HF rehospitalization [hazard ratio (HR): 1.49, 95% confidence interval (CI): 1.14–1.95, $P = 0.004$] (*Table 2*). This association was retained in multivariate analysis after adjusting for diverse covariates (HR: 1.55 95% CI: 1.13–2.13, $P = 0.007$). Furthermore, we performed Cox regression analysis by excluding non-cardiovascular-related deaths from all-cause mortality. Accordingly, multivariate Cox regression analysis showed that cognitive frailty was

Table 2 Cox proportional hazard analysis for combined events by using fried criteria

	Unadjusted model				Adjusted model[a]				Adjusted model[b]				Adjusted model[c]			
	HR	95% CI		*P* value	HR	95% CI		*P* value	HR	95% CI		*P* value	HR	95% CI		*P* value
Non-physical frail/non-cognitive impairment	Ref				Ref				Ref				Ref			
Physical frail/non-cognitive impairment	1.19	0.92	—	0.195	1.14	0.89	—	0.299	1.14	0.88	—	0.318	1.11	0.83	—	0.500
Non-physical frail/cognitive impairment	0.99	0.70	—	0.952	0.92	0.65	—	0.642	0.93	0.65	—	0.664	0.97	0.67	—	0.871
Physical frail/cognitive impairment	1.49	1.14	—	0.004	1.34	1.02	—	0.042	1.33	1.01	—	0.047	1.55	1.13	—	0.007
	1.54				1.49				1.48				1.49			
	1.39				1.30				1.31				1.42			
	1.95				1.78				1.77				2.13			

CI, confidence interval; HR, hazard ratio; Ref, reference.
[a]Adjusted for age.
[b]Adjusted for age, male gender, and body mass index.
[c]Adjusted for age; male gender; body mass index; estimated glomerular filtration rate; New York Heart Association III/IV; systolic blood pressure; left ventricular ejection fraction; history of atrial fibrillation, coronary artery disease, diabetes mellitus, chronic obstructive pulmonary disease, heart failure, and hypertension; smoking status; albumin, haemoglobin, sodium level, and log-transformed BNP at discharge; and prescription of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, beta-blocker, and mineralocorticoid receptor antagonist at discharge.

significantly associated with a higher incidence of combined events of cardiovascular-related deaths and HF rehospitalization (HR: 1.89, 95% CI: 1.10–3.26, *P* = 0.021) (*Table S1*).

To explore whether the definition of physical frailty significantly influenced this association, sensitivity analyses were performed using grip strength, SPPB, and gait speed to defined physical frailty. The prevalence of cognitive frailty, defined using grip strength, SPPB, and walking speed, was 25.4%, 28.1%, and 32.5%, respectively. The results of the adjusted Cox model using grip strength, SPPB, and walking speed to defined physical frailty showed consistent results (grip strength, HR: 1.55, 95% CI: 1.06–2.25; SPPB, HR: 1.37, 95% CI: 1.05–1.80; and gait speed, HR: 1.41, 95% CI: 1.04–1.92) (*Table 3*, *4*, and *5*).

Discussion

The current study investigated the impact of cognitive frailty on the composite event of HF rehospitalization and all-cause death in elderly patients with HF. To our knowledge, this has been the largest study to investigate the prevalence and prognostic implications of cognitive frailty in patients with HF. Notably, our results showed that 23% of elderly HF patients in Japan had cognitive frailty, which increased with age. Furthermore, among elderly patients with HF, those with cognitive frailty had a 1.55-fold increased risk for combined events within 1 year compared with those without cognitive frailty.

Previous studies reporting on the prevalence of cognitive frailty have mainly focused on patients without HF. Indeed, a cohort study in Singapore that evaluated 5414 community-dwelling older Singaporeans showed a 1.6% prevalence of cognitive frailty.[25] Another cohort study of 542 patients with lifestyle-related diseases showed that 8% had cognitive frailty, with the prevalence increasing with age.[26] Moreover, a French three-city study that evaluated more than 6000 community-dwelling older adults found that 7% of the total population were diagnosed as frail using the Fried criteria and that 22% of the frail population (i.e. 1.5% of the total cohort) were also complicated with cognitive impairment assessed using the Mini-Mental State Examination.[27] In contrast, only a few studies have evaluated the prevalence of cognitive frailty in patients with HF. A sub-analysis of HF only among patients with coronary artery disease (*n* = 66) showed that 15.2% of patients had cognitive frailty.[26] A previous study investigating the impact of concurrent grip weakness and cognitive impairment on prognosis in elderly patients with HF (*n* = 56) found that 9% of patients had combined grip weakness and cognitive impairment.[28]

Regarding the prognostic impact of cognitive frailty, the results of the aforementioned three-city study in France showed that cognitive frailty was associated with a 1.9-fold

Table 3 Sensitivity analysis of Cox proportional hazards model using grip strength

	Unadjusted model				Adjusted model[a]				Adjusted model[b]				Adjusted model[c]			
	HR	95% CI		*P* value	HR	95% CI		*P* value	HR	95% CI		*P* value	HR	95% CI		*P* value
Normal grip strength/non-cognitive impairment	Ref				Ref				Ref				Ref			
Low grip strength/non-cognitive impairment	1.43	1.08	—	1.92	0.015	1.35	1.00	—	1.82	0.047	1.32	098	—	1.77	0.071	1.25	0.88	—	1.77	0.209
Normal grip strength/cognitive impairment	1.03	0.63	—	1.69	0.914	0.99	0.60	—	1.63	0.974	1.01	0.61	—	1.65	0.981	1.12	0.65	—	1.92	0.691
Low grip strength/cognitive impairment	1.63	1.21	—	2.20	0.001	1.46	1.05	—	2.02	0.023	1.42	1.02	—	1.96	0.037	1.55	1.06	—	2.25	0.021

CI, confidence interval; HR, hazard ratio; Ref, reference.
[a]Adjusted for age.
[b]Adjusted for age, male gender, and body mass index.
[c]Adjusted for age; male gender; body mass index; estimated glomerular filtration rate; New York Heart Association III/IV; systolic blood pressure; left ventricular ejection fraction; history of atrial fibrillation, coronary artery disease, diabetes mellitus, chronic obstructive pulmonary disease, heart failure, and hypertension; smoking status; albumin, haemoglobin, sodium level, and log-transformed BNP at discharge; and prescription of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, beta-blocker, and mineralocorticoid receptor antagonist at discharge.

Table 4 Sensitivity analysis of Cox proportional hazards model using SPPB

	Unadjusted model				Adjusted model[a]				Adjusted model[b]				Adjusted model[c]			
	HR	95% CI		*P* value	HR	95% CI		*P* value	HR	95% CI		*P* value	HR	95% CI		*P* value
High SPPB score/non-cognitive impairment	Ref				Ref				Ref				Ref			
Low SPPB score/non-cognitive impairment	1.22	0.94	—	1.58	0.138	1.22	0.94	—	1.58	0.128	1.22	0.94	—	1.58	0.134	1.15	0.88	—	1.51	0.274
High SPPB score/cognitive impairment	1.00	0.67	—	1.51	0.988	0.99	0.66	—	1.48	0.971	0.97	0.64	—	1.46	0.893	0.95	0.63	—	1.43	0.813
Low SPPB score/cognitive impairment	1.40	1.08	—	1.81	0.011	1.39	1.07	—	1.79	0.012	1.39	1.06	—	1.81	0.014	1.37	1.05	—	1.80	0.019

CI, confidence interval; HR, hazard ratio; ref, reference.
[a]Adjusted for age.
[b]Adjusted for age, male gender, and body mass index.
[c]Adjusted for age; male gender; body mass index; estimated glomerular filtration rate; New York Heart Association III/IV; systolic blood pressure; left ventricular ejection fraction; history of atrial fibrillation, coronary artery disease, diabetes mellitus, chronic obstructive pulmonary disease, heart failure, and hypertension; smoking status; albumin, haemoglobin, sodium level, and log-transformed BNP at discharge; and prescription of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, beta-blocker, and mineralocorticoid receptor antagonist at discharge.

Table 5 Sensitivity analysis of Cox proportional hazards model using gait speed

	Unadjusted model				Adjusted model[a]				Adjusted model[b]				Adjusted model[c]			
	HR	95% CI		*P* value	HR	95% CI		*P* value	HR	95% CI		*P* value	HR	95% CI		*P* value
Normal gait speed/non-cognitive impairment	Ref				Ref				Ref				Ref			
Lower gait speed/non-cognitive impairment	1.24	0.93	—	0.149	1.24	0.92	—	0.151	1.24	0.93	—	0.132	1.16	0.87	—	0.304
Normal gait speed/cognitive impairment	0.79	0.46	—	0.463	0.78	0.43	—	0.441	0.77	0.43	—	0.435	0.73	0.41	—	0.326
Lower gait speed/cognitive impairment	1.47	1.09	—	0.012	1.45	1.08	—	0.014	1.46	1.07	—	0.015	1.41	1.04	—	0.027
	1.66				1.67				1.68				1.57			
	1.45				1.43				1.43				1.35			
	1.98				1.97				1.98				1.92			

CI, confidence interval; HR, hazard ratio; ref, reference.
[a]Adjusted for age.
[b]Adjusted for age, male gender, and body mass index.
[c]Adjusted for age; male gender; body mass index; estimated glomerular filtration rate; New York Heart Association III/IV; systolic blood pressure; left ventricular ejection fraction; history of atrial fibrillation, coronary artery disease, diabetes mellitus, chronic obstructive pulmonary disease, heart failure, and hypertension; smoking status; albumin, haemoglobin, sodium level, and log-transformed BNP at discharge; and prescription of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, beta-blocker, and mineralocorticoid receptor antagonist at discharge.

greater risk for all-cause mortality compared with those normal cognitive function and no physical frailty. Likewise, a study on 5113 Chinese older adults (≥60 years old) demonstrated that cognitive frailty was associated with both a decline in activities of daily living and all-cause death independent of other comorbidities.[29] Unfortunately, only a few studies with very limited number of patients have investigated the prognostic impact of cognitive frailty in patients with HF.[12,26,30] One of the strengths of our study is that we were able to demonstrate the prevalence and prognostic impact of cognitive frailty in a sufficient number of patients and events, which allows for a reliable analysis regarding the association between cognitive frailty and poor prognosis independent of other potential prognostic factors. Moreover, we demonstrated that the negative prognostic impact of cognitive frailty remained constant regardless of the tool used to define physical frailty. This additional result supports our conclusion that cognitive frailty was strongly associated with poor prognosis in elderly patients with HF.

Although the mechanism behind this association has yet to be clearly demonstrated, the decrease in cardiac output may play an important role therein. Unfortunately, the current study has not been designed to determine the disease mechanism. Indeed, decreased cardiac output in patients with HF has been shown to be a potential cause of not only sarcopenia[31] but also cognitive impairment by directly decreasing cerebral blood flow. Reports have shown that during HF, the decrease in blood flow to the hippocampus, the brain area responsible for memory, was associated with the severity of cognitive impairment.[32] Regarding causality, only randomized control studies that investigate the prognostic impact of certain interventions that are able to improve cognitive frailty can determine whether cognitive frailty can be a therapeutic target.

The current study has several limitations worth noting. First, although no universally accepted tool has been available to diagnose cognitive impairment, the current study used only Mini-Cog© to define cognitive impairment. Hence, our conclusion may be affected by the diagnostic tool used. Second, physical assessment is expected to be biased based on the symptoms of acute cardiac disease, such as dyspnoea. We attempted to avoid bias as much as possible by conducting physical assessment at hospital discharge. Third, this study may have included HF patients with asymptomatic cerebrovascular disease, which can directly affect cognitive impairment. Lastly, this study was conducted in Japan, which has been known to have better cardiovascular outcomes compared with Western populations, the results of this study may not be directly applicable to Western countries.

In conclusion, the present study found that 23% of elderly patients with HF had cognitive frailty, which was associated with a 1.55-fold increased risk for combine events of HF rehospitalization and all-cause death within 1 year.

Acknowledgements

We would like to thank Dr Masaaki Sato, Mr Daichi Tsukakoshi, Ms Natsuko Oguchi, and Mr Keisuke Furuhashi for their help in measurements and data collection.

Conflict of interest

Dr Yuya Matsue and Takatoshi Kasai are affiliated with a department endowed by Philips Respironics, ResMed, Teijin Home Healthcare, and Fukuda Denshi; and Dr Yuya Matsue received an honorarium from Otsuka Pharmaceutical Co and Novartis Japan. Dr Kagiyama reports grants from Philips, grants from Asahi KASEI Corporation, grants from Toho Holdings Co. Ltd, and grants from Inter Reha Co. Ltd outside the submitted work. Dr Kamiya has received research and scholarship funding from Eiken Chemical Co., Ltd. Other authors have nothing to declare.

Funding

FRAGILE-HF was supported by Novartis Pharma Research Grants and Japan Heart Foundation Research Grant. This work was also partially supported by JSPS KAKENHI (grant numbers 18K15862 and JP18K17715).

Supporting information

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

Table S1. Cox proportional hazard analysis for cardiovascular related mortality and HF readmission by using fried criteria.

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