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ORIGINAL ARTICLE

Frailty interferes with the guideline-directed medical therapy in heart failure patients with reduced ejection fraction

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Abstract

Aims Guideline-directed medical therapy (GDMT) in patients with heart failure with reduced ejection fraction (HFrEF) is recommended in clinical guidelines, but elderly patients have not fully received GDMT in the clinical situation. The aim of this study was to determine the clinical characteristics of patients who have not received GDMT and the association between implementation of GDMT at discharge and physical frailty in patients with HFrEF who were hospitalized for acute decompensated heart failure (ADHF).

Methods and results This study was a cross-sectional study with a retrospective analysis of the Kochi YOSACOI study, a prospective multicentre observational study that enrolled 1061 patients hospitalized for ADHF from May 2017 to December 2019 in Japan. Of 339 patients (32.0%) with HFrEF, 268 patients who were assessed for physical frailty by the Japanese version of the Cardiovascular Health Study criteria were divided into two groups: those with GDMT (135 patients, 50.4%) and those without GDMT (133 patients, 49.6%). GDMT was defined as the prescription of a combination of renin-angiotensin system (RAS) inhibitors (angiotensin-converting inhibitors or angiotensin receptor blockers) and beta-blockers. The median age of patients with HFrEF was 76 years (interquartile range, 67–83 years). Patients without GDMT were older than patients with GDMT (73 years vs. 78 years, $P < 0.001$). Patients without GDMT tended to have more prior HF admission than did patients with GDMT ($P = 0.004$), and patients without GDMT had lower levels of estimated glomerular filtration rate ($P < 0.001$) than those in patients with GDMT. Physical frailty was observed in 54.1% of the patients without GDMT and in 38.5% of the patients with GDMT ($P = 0.014$). Patients without GDMT had a higher rate of cognitive impairment than that in patients with GDMT ($P = 0.009$). RAS inhibitors only, beta-blockers only, and both RAS inhibitors and beta-blockers were less frequently prescribed in patients with physical frailty than in patients with physical non-frailty (52.0% vs. 86.7%, $P < 0.05$; 70.1% vs. 100.0%, $P < 0.05$; 42.5% vs. 86.7%, $P < 0.01$, respectively). In logistic regression analysis, compared with physical non-frailty, physical frailty was significantly associated with no implementation of GDMT (odds ratio: 6.900, 95% confidence interval: 1.420–33.600; $P = 0.017$), independent of older age and severe renal dysfunction.

Conclusions The results of this study suggest that physical frailty is one of the factors that may withhold GDMT in patients with HFrEF.

Keywords Heart failure; Reduced ejection fraction; Medication; Frailty; Older adult

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Introduction

Heart failure (HF) is associated with high rates of mortality and morbidity, and it has become a major public health burden.[1,2] The prevalence of HF has been increasing with aging of populations. In Japan, one of the countries in which the population has been aging, the number of patients with HF, particularly elderly patients with HF, has been increasing.[3,4] Many elderly patients with HF have comorbidities, frailty, and polypharmacy, resulting in higher morbidity and mortality.[5–7] Guideline-directed medical therapy (GDMT), including treatment with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, and mineralocorticoid receptor antagonists (MRAs), has been shown to reduce mortality and morbidity in patients with heart failure with reduced ejection fraction (HFrEF).[8,9] Clinical trials demonstrated that angiotensin receptor-neprilysin inhibitor (ARNI) and sodium-glucose cotransporter (SGLT)2 inhibitors reduced the risk of HF hospitalization and death.[10–12] The newest guidelines recommend the use of ARNI and SGLT2 inhibitors.[8,9] In those guidelines, these drugs are recommended for all patients with HFrEF unless contraindicated or not tolerated.[8,9,13] In many large-scale randomized clinical trials that demonstrated a prognostic effect of GDMT in patients with HFrEF, most of the elderly patients with HF over 80 years old were excluded due to exclusion criteria by upper age limit, comorbidities including renal disease, liver disease and cancer, cognitive impairment, and physical disability.[14] On the other hand, studies in the Swedish Heart Failure Registry demonstrated that a renin-angiotensin system (RAS) inhibitor and a beta-blocker improved clinical outcomes in patients with HF who were over 80 years of age.[15,16] Although GDMT in patients with HFrEF is recommended in clinical guidelines, GDMT is not used in many patients with HFrEF, especially elderly patients. One reason for this is poor tolerability due to various factors including low blood pressure, low heart rate, renal insufficiency, and hyperkalaemia.[17] Frailty is a clinical status in which there is increased vulnerability to stressors resulting from decreased reserves of multiple physiological systems.[18] Although the vulnerabilities may interfere with the implementation of GDMT in patients with HFrEF, there have been few studies in which the association between GDMT implementation and physical frailty was investigated. Therefore, the aim of this study was to determine the clinical characteristics of patients without GDMT and the association between GDMT implementation at discharge and physical frailty in patients with acute decompensated heart failure (ADHF).

Methods

Study design and patient population

This study was a cross-sectional study with a retrospective analysis of the Kochi Registry of Subjects with Acute Decompensated Heart Failure (Kochi YOSACOI) study, a prospective multicentre community-based cohort study. We used data for 1061 patients with ADHF who were enrolled between May 2017 and December 2019. Details of the Kochi YOSACOI study have been previously described.[19] Briefly, the Kochi YOSACOI study consists of six hospitals that are responsible for acute treatment of cardiovascular diseases in Kochi Prefecture, Japan, where the proportion of people aged 65 years or older has reached 35%. We enrolled patients aged 20 years or older with ADHF who were admitted to six participating hospitals in the registry. Patients under 20 years of age and those who did not consent to registry enrolment were excluded. The diagnosis of ADHF was based on the presence of at least two major criteria or one major criterion in conjunction with two minor criteria in the Framingham criteria. Clinical information for all of the patients who were enrolled in the registry was collected by investigators at each participating hospital. The information we obtained included information on baseline characteristics, underlying diseases, comorbidities, results of laboratory examinations, results of echocardiographic examinations, nutritional status, physical frailty status, cognitive impairment, and medication at discharge.[19]

In the present study, we analysed 268 patients with HFrEF in our registry whose physical frailty was assessed by the Japanese version of the Cardiovascular Health Study (J-CHS) criteria. Patients whose physical frailty could not be assessed by the J-CHS criteria and those with inadequate assessment were excluded.

The Kochi YOSACOI study was conducted in compliance with the Declaration of Helsinki and the Japanese Ministry of Health, Labor and Welfare's Ethnical Guidelines for Medical and Health Research Involving Human Subjects. The study protocol was approved by the Ethics Committees on Medical Research of Kochi Medical School (Approval Number 28-68) and the Ethics Committee of all participating hospitals. Informed consent was obtained from all patients or their proxies according to the guidelines of the Ethics Committee on Medical Research of Kochi Medical School.

Data collection and definitions

Information on baseline characteristics and results of blood tests were obtained on admission, and information on cogni-

tive function, information on physical frailty, echocardiographic data, and information on medication were obtained before discharge. We evaluated left ventricular ejection fraction (LVEF) in all patients by echocardiographic data at the time when HF status was stabilized during hospitalization. We defined LVEF of 40% or less as HFrEF, LVEF of 40–49% as HF with mildly reduced ejection fraction (HFmrEF), and LVEF of 50% or more as HF with preserved ejection fraction (HFpEF) in line with the recent clinical guidelines. We used the geriatric nutritional risk index (GNRI) to assess the nutritional status of patients. GNRI is a simple index to assess the nutritional status of the elderly that is calculated by the following formula: GNRI = 14.89 × serum albumin (g/dL) + 41.7 × body mass index (BMI)/22.[20] Physical frailty was diagnosed according to the J-CHS criteria in patients who were haemodynamically stable before discharge. The J-CHS criteria consist of five physical components (walking speed, handgrip strength, shrinking, exhaustion, and physical inactivity), modified from the original CHS criteria.[18,21] Patients with none of these components were considered to be patients with physical non-frailty, patients with one or two of the components were considered to have physical prefrailty, and patients with three or more components were considered to have physical frailty. Cognitive function was assessed by the Revised Hasegawa's Dementia Scale (HDS-R). Patients with a score of 20 or less were considered to have cognitive impairment. Hasegawa's Dementia Scale, developed in 1974 by Kazuo Hasegawa, is widely used in Japan. In 1991, it was revised and renamed the HDS-R.[22] The English version of the HDS-R was published in 1994.[23] The total score is 30 points, and a score of 20 points or less indicates the presence of dementia. GDMT was defined as the prescription at discharge of a combination of RAS inhibitors (ACE inhibitors or ARBs) and beta-blockers. Because patients with HFrEF in this study were mainly elderly, MRAs were assumed to be used less frequently because of the risk of adverse events due to hyperkalaemia when MRAs are added to RAS inhibitors. Therefore, we did not include MRAs as GDMT in this study. In addition, ARNI and SGLT2 inhibitors were not approved during the registration period of our registry in Japan.

Statistical analysis

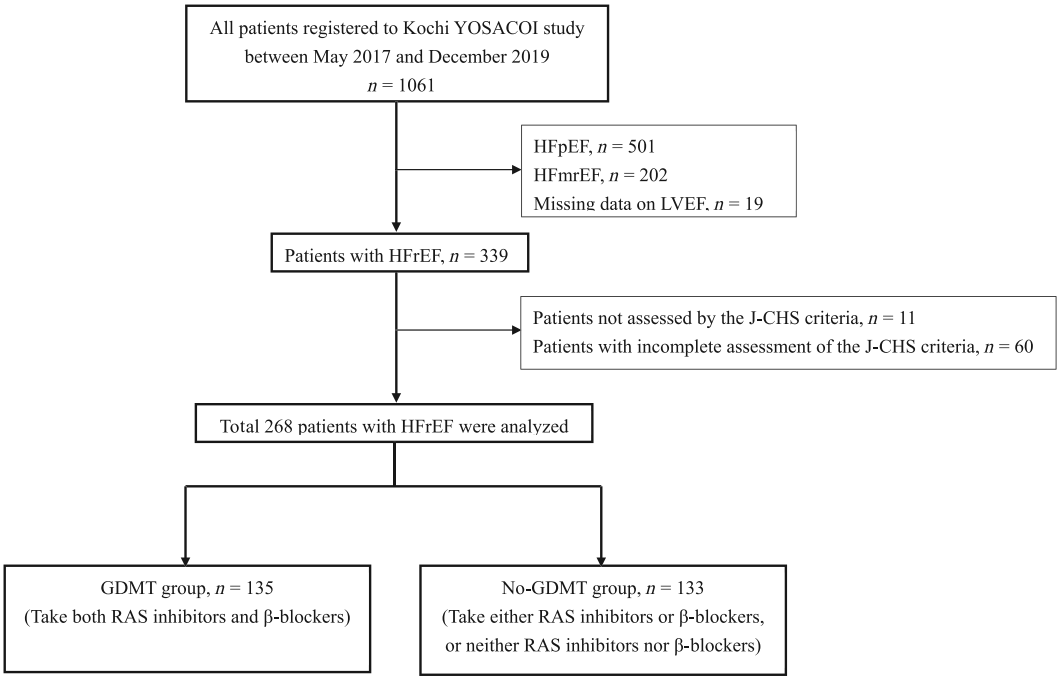
Continuous variables are expressed as means ± standard deviation or medians with interquartile ranges (IQRs) and were compared by using the unpaired *t*-test when normally distributed or by using Mann–Whitney's *U* test when not normally distributed. Categorical variables are expressed as numbers with percentages and were compared by using Pearson's χ^2 test. Fisher's exact test was used when the expected frequency was lower than 5. We compared clinical characteristics and frailty status based on patients without GDMT or patients with GDMT at discharge. Multivariate logistic regression analysis was performed to evaluate the association of physical frailty with non-GDMT prescription with reference to physical non-frailty in patients with HFrEF. Covariates used in the analysis included age sex, BMI, systolic blood pressure (on admission) $<$ 100 mmHg, heart rate (on admission) $<$ 60 b.p.m., old myocardial infarction (OMI), bronchial asthma, cognitive impairment, serum brain natriuretic peptide (BNP) level, serum potassium $\geq$ 5.0 mEq/L, and estimated glomerular filtration rate (eGFR) $<$ 30 mL/min/1.73 m^2 based on clinical practice, and missing data were excluded. Sensitivity analysis was performed to evaluate the association between the implementation of GDMT and physical frailty, defining GDMT as a triple combination of RAS inhibitors, beta-blockers, and MRAs. Statistical significance was defined by two-sided $P \leq 0.05$. All statistical analyses were performed using Microsoft R Open Version 4.0.2 (Microsoft, Redmond, Washington).

Results

Clinical presentation

Among the 1061 patients in our registry, 32.0% of the patients presented with HFrEF (*n* = 339), 19.0% of the patients presented with HFmrEF (*n* = 202), and 47.2% of the patients presented with HFpEF (*n* = 501) (*Figure 1*). The remaining 1.8% of the patients had missing data for LVEF (*n* = 19). We excluded patients with HFmrEF and HFpEF and patients who were not assessed by the J-CHS criteria and those who were assessed incompletely. Finally, 268 patients with HFrEF were included in the present study and were divided into the GDMT group (135 patients, 50.4%) and the no-GDMT group (133 patients, 49.6%). The clinical characteristics of patients with HFrEF in the GDMT group and in the no-GDMT group are summarized in *Table 1*. The median age of patients with HFrEF was 76 years (IQR, 67–83 years), and the proportion of patients aged 80 years or over was 37.3%. The proportion of female patients was 34.3%. Patients in the no-GDMT group were older than those in the GDMT group. Patients in the no-GDMT group tended to have a lower BMI and lower GNRI and had a higher rate of prior HF admission than those for patients in the GDMT group. Systolic blood pressure and heart rate at discharge were also similar in the two groups. Chronic kidney disease (CKD) was the most common comorbidity in patients with HFrEF. More than half of the patients with HFrEF had hypertension and anaemia. There was no difference between the two groups in the frequencies of CKD, chronic obstructive pulmonary disease (COPD), and bronchial asthma, which could limit GDMT implementation. The frequencies of use of non-invasive positive pressure ventilation (NIPPV)/ventilator, mechanical

Figure 1 Flowchart of the present study. Of 1061 patients with ADHF enrolled in the Kochi Registry of Subjects with Acute Decompensated Heart Failure (Kochi YOSACOI) study, 19 patients with unmeasured LVEF, 501 patients with HFmrEF, and 202 patients with HFpEF were excluded. Patients who were not assessed for physical frailty status by the J-CHS criteria and those who were not completely assessed were also excluded. Finally, 268 patients with HFrEF were included in the present study. ADHF, acute decompensated heart failure; GDMT, guideline-directed medical therapy; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; J-CHS, Japanese version of the Cardiovascular Health Study; LVEF, left ventricular ejection fraction; No-GDMT, no guideline-directed medical therapy implementation; RAS, renin-angiotensin system.



circulatory support, and inotropic agents were comparable in the two groups. Patients in the no-GDMT group had lower levels of eGFR and haemoglobin than those in patients in the GDMT group. Serum potassium and serum BNP levels were similar in the two groups.

RAS inhibitors only, beta-blockers only, and both RAS inhibitors and beta-blockers (i.e. GDMT in this study) were less frequently prescribed in patients with physical frailty than in patients with physical non-frailty (51.6% vs. 86.7%, $P < 0.05$; 70.2% vs. 100.0%, $P < 0.05$; 41.9% vs. 86.7%, $P < 0.01$, respectively) (*Figure 2*). MRAs tended to be prescribed more in patients with physical frailty and patients with physical prefrailty than in patients with physical non-frailty, although the differences were not significant. The proportions of patients in those three groups who were receiving triple therapy including RAS inhibitors, beta-blockers, and MRAs were approximately 25%, with no significant difference among the three groups.

Frailty assessment

Patients in the no-GDMT group had a higher score for the J-CHS criteria than did patients in the GDMT group and had significantly more physical frailty ($P = 0.007$ and $P = 0.014$, respectively) (*Figure 3*, *Table 2*). In the measurements of physical functions, patients without GDMT had significantly slower gait speed and male patients without GDMT had weaker handgrip strength. Moreover, in the cognitive function evaluation, cognitive impairment was significantly more prevalent in patients without GDMT than in those with GDMT ($P = 0.009$). In the social domain, the rates of eating alone in both groups were ~30% and the rates of having supporters in daily life in both groups were ~80%.

Factors related to no guideline-directed medical therapy prescription

The results obtained by using logistic regression models for the association of physical frailty with no GDMT prescription are shown in *Table 3*. In the crude model, physical frailty was independently associated with no GDMT prescription [odds ratio (OR): 9.000, 95% confidence interval (CI): 1.950–41.600; $P = 0.005$] and physical prefrailty was also independently associated with no GDMT prescription (OR: 5.480, 95% CI: 1.190–25.300; $P = 0.029$) compared with physical non-frailty. In addition, after adjustment for age, female

Table 1 Clinical characteristics of patients with and without guideline-directed medical therapy

	All patients (n = 268)	GDMT (n = 135)	No-GDMT (n = 133)	P value
Age, years	76.0 [67.0–83.0]	73.0 [65.0–80.5]	78.0 [70.0–86.0]	<0.001
≥80 years	100 (37.3)	37 (27.4)	63 (47.4)	0.001
Female gender	92 (34.3)	49 (36.3)	43 (32.3)	0.522
BMI, kg/m^2	21.2 [18.8–23.7]	21.6 [19.5–24.3]	20.4 [18.2–22.9]	0.014
GNRI	95.1 [88.5–102.4]	97.0 [90.3–104.2]	94.4 [87.4–100.3]	0.028
Systolic BP on admission, mmHg	134.9 ± 30.3	135.5 ± 27.9	134.4 ± 32.6	0.760
Diastolic BP on admission, mmHg	88.3 ± 21.8	89.2 ± 21.1	87.4 ± 22.5	0.521
Heart rate on admission, b.p.m.	100.0 ± 25.7	100.8 ± 23.8	99.2 ± 27.5	0.620
NYHA class III/IV on admission	209 (88.6)	115 (89.8)	94 (87.0)	0.542
NYHA class III/IV at discharge	6 (2.6)	3 (2.4)	3 (2.8)	1.000
Length of hospital stay, days	18.0 [13.0–28.3]	18.0 [13.0–26.0]	19.0 [14.0–34.0]	0.155
Discharge to home	238 (89.5)	124 (92.5)	114 (86.4)	0.113
Living alone	59 (24.9)	30 (22.9)	29 (27.4)	0.453
Prior HF admission	87 (32.5)	36 (28.3)	51 (47.2)	0.004
Aetiology				
IHD	83 (31.0)	44 (32.6)	39 (29.3)	0.599
Valvular	18 (6.7)	7 (5.2)	11 (8.3)	0.340
Cardiomyopathy	87 (32.5)	52 (38.5)	35 (26.3)	0.037
Hypertensive	17 (6.3)	8 (5.9)	9 (6.8)	0.807
Comorbidities				
Hypertension	145 (54.1)	76 (56.3)	69 (51.9)	0.540
Diabetes mellitus	79 (29.5)	45 (33.3)	34 (25.6)	0.181
Dyslipidaemia	114 (42.5)	60 (44.4)	54 (40.6)	0.539
Atrial fibrillation/flutter	105 (39.2)	53 (39.3)	52 (39.1)	1.000
OMI	55 (20.5)	25 (18.5)	30 (22.6)	0.451
COPD	23 (8.6)	11 (8.1)	12 (9.0)	0.831
Bronchial asthma	11 (4.1)	6 (4.4)	5 (3.8)	1.000
CVA	37 (13.8)	20 (14.8)	17 (12.8)	0.724
Anaemia	139 (52.1)	55 (41.0)	84 (63.2)	<0.001
CKD	193 (72.3)	92 (68.7)	101 (75.9)	0.219
Treatment in the acute phase				
NIPPV/ventilator	39 (14.6)	21 (15.5)	18 (12.5)	1.000
IABP/PCPS	1 (0.4)	1 (0.7)	0 (0.0)	1.000
Inotropic agents	50 (18.7)	28 (20.7)	22 (16.5)	0.434
Laboratory data on admission				
Albumin, g/dL	3.7 [3.4–4.0]	3.7 [3.5–4.0]	3.7 [3.4–4.0]	0.251
BNP, pg/mL	869.5 [608.6–1480.7]	867.0 [611.7–1375.0]	937.0 [606.0–1704.9]	0.374
eGFR, mL/min/1.73 m^2	46.4 [31.9–62.6]	51.0 [37.3–66.3]	41.9 [26.0–56.3]	<0.001
Haemoglobin, g/dL	12.7 [11.4–14.3]	13.0 [11.7–14.8]	12.4 [11.2–14.1]	0.036
Potassium, mEq/L	4.1 [3.8–4.5]	4.1 [3.9–4.5]	4.1 [3.8–4.4]	0.959
LVEF, %	30.0 [24.0–34.0]	29.5 [23.0–34.0]	31.0 [26.0–35.0]	0.099
Medication at discharge				
RAS inhibitors	155 (57.8)	135 (100.0)	20 (15.0)	<0.001
ACE inhibitors	84 (31.3)	73 (54.1)	11 (8.3)	<0.001
ARBs	71 (26.5)	62 (45.9)	9 (6.8)	<0.001
Beta-blockers	202 (75.4)	135 (100.0)	67 (50.4)	<0.001
MRAs	116 (43.3)	70 (51.9)	46 (34.6)	0.005
Diuretics	230 (85.8)	126 (93.3)	104 (78.2)	<0.001
Calcium channel blockers	44 (16.4)	17 (12.6)	27 (20.3)	0.100
Digitalis	2 (0.7)	1 (0.7)	1 (0.8)	1.000
PDE III inhibitors	26 (9.7)	15 (11.1)	11 (8.3)	0.537
Tolvaptan	70 (26.1)	34 (25.2)	36 (27.1)	0.782
Anticoagulant agents	128 (47.8)	68 (50.4)	60 (45.1)	0.395

ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; GNRI, geriatric nutritional risk index; HF, heart failure; IABP, intra-aortic balloon pumping; IHD, ischaemic heart disease; LVEF, left ventricular ejection fraction; MRAs, mineralocorticoid receptor antagonists; NIPPV, non-invasive positive pressure ventilation; No-GDMT, no guideline-directed medical therapy implementation; NYHA, New York Heart Association; OMI, old myocardial infarction; PCPS, percutaneous cardiopulmonary support; PDE, phosphodiesterase; RAS, renin-angiotensin system.
Data were shown as the median [interquartile range] or n (%).

gender, BMI, OMI, bronchial asthma, cognitive impairment, eGFR < 30 mL/min/1.73 m^2, serum potassium level < 5.0 mEq/L, serum BNP level, systolic blood pressure on admission < 100 mmHg, and heart rate < 60 b.p.m., physical frailty (OR: 6.900, 95% CI: 1.420–33.600; P = 0.017) and physical prefrailty (OR: 4.830, 95% CI: 1.010–23.000; P = 0.048) were independently associated with no GDMT prescription. Older age and very low eGFR were associated with

Figure 2 Prescription rates of guideline-directed medical therapy according to frailty status. *$P < 0.05$, †$P < 0.01$. HF, heart failure; MRAs, mineralocorticoid receptor antagonists; RAS, renin-angiotensin system.

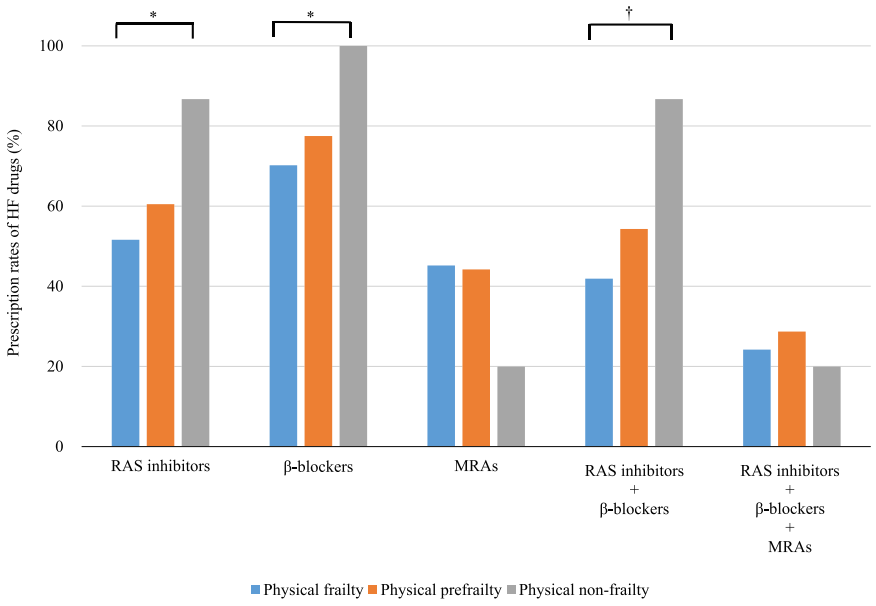


Figure 3 Comparison of physical performance and physical frailty between patients with and those without guideline-directed medical therapy. GDMT, guideline-directed medical therapy; J-CHS, Japanese version of the Cardiovascular Health Study; No-GDMT, no guideline-directed medical therapy implementation.

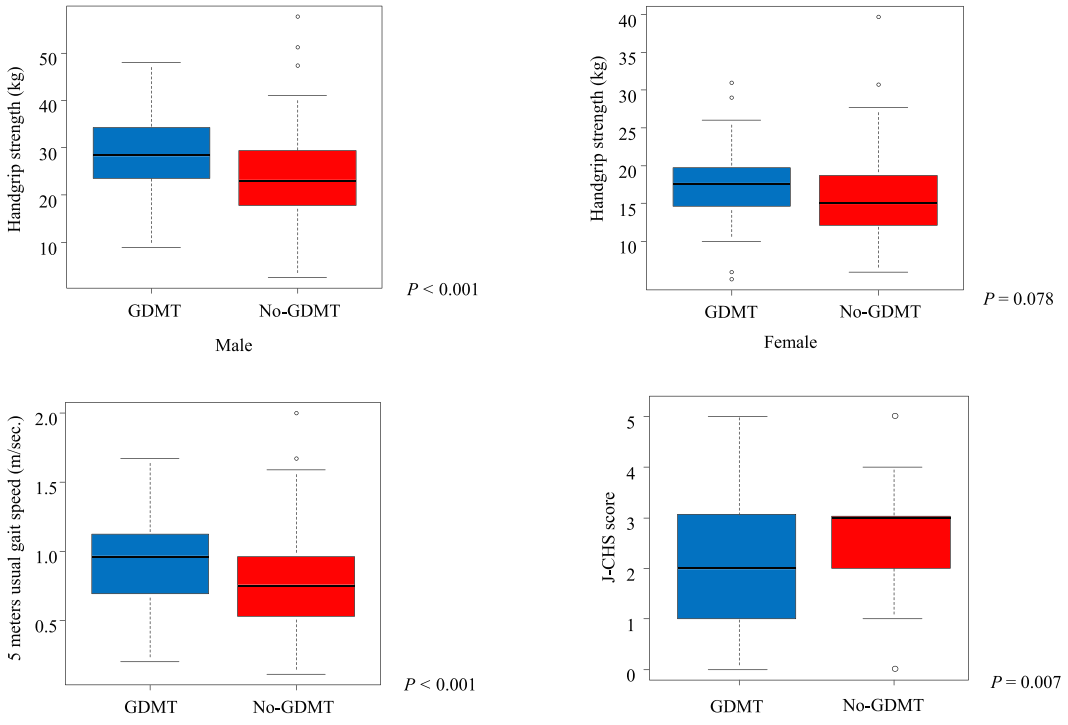


Table 2 Frailty assessment of patients with and without guideline-directed medical therapy

	All patients (n = 268)	GDMT (n = 135)	No-GDMT (n = 133)	P value
Physical frailty assessment				
J-CHS criteria				
Frailty	124 (46.3)	52 (38.5)	72 (54.1)	0.014
Prefrailty	129 (48.1)	70 (51.9)	59 (44.4)	0.225
Non-frailty	15 (5.6)	13 (9.6)	2 (1.5)	0.006
Physical function domain				
Slow gait speed	176 (65.7)	73 (54.1)	103 (77.4)	<0.001
Low handgrip strength	138 (52.1)	58 (43.0)	80 (61.5)	0.003
Cognitive function domain				
HDS-R score	27.0 [22.0–30.0]	28.0 [25.0–30.0]	26.0 [19.3–29.0]	0.008
Cognitive impairment	54 (20.7)	19 (14.1)	35 (27.8)	0.009
Social domain				
Eating alone	76 (28.4)	36 (27.1)	40 (30.8)	0.587
Supporters for daily living	194 (72.4)	105 (78.9)	89 (80.2)	0.874

GDMT, guideline-directed medical therapy; HDS-R, Hasegawa's Dementia Scale-Revised; J-CHS, Japanese version of the Cardiovascular Health Study; No-GDMT, no guideline-directed medical therapy implementation.
Data were shown as the median [interquartile range] or n (%).

Table 3 Logistic regression analysis for the association between no guideline-directed medical therapy implementation and physical frailty

	Crude			Model 1			Model 2		
	Odds ratio	95% CI	P value	Odds ratio	95% CI	P value	Odds ratio	95% CI	P value
Physical non-frailty	Reference			Reference			Reference		
Physical prefrailty	5.480	1.190–25.300	0.029	5.400	1.160–25.300	0.032	5.040	1.050–24.300	0.044
Physical frailty	9.000	1.950–41.600	0.005	7.680	1.620–36.300	0.010	7.100	1.450–34.800	0.016
Age				1.030	1.000–1.050	0.018	1.030	0.998–1.050	0.070
Female gender				0.729	0.425–1.250	0.251	0.764	0.424–1.370	0.368
BMI				0.968	0.904–1.040	0.348	0.967	0.895–1.040	0.398
OMI							1.020	0.516–2.030	0.946
Cognitive impairment							1.170	0.550–2.490	0.682
Bronchial asthma							0.734	0.196–2.740	0.646
Serum potassium level ≥ 5.0 mEq/L							0.621	0.205–1.880	0.400
eGFR < 30 mL/min/1.73 m^2							2.630	1.310–5.290	0.006
BNP							1.000	1.000–1.000	0.788
Systolic BP < 100 mmHg							1.490	0.727–3.040	0.277
Heart rate < 60 b.p.m.							1.770	0.394–7.980	0.455

BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; OMI, old myocardial infarction.

no GDMT prescription (OR: 1.980, 95% CI: 1.070–3.670; P = 0.031, OR: 2.740, 95% CI: 1.360–5.540; P = 0.005, respectively).

As a sensitivity analysis, we defined a triple therapy including RAS inhibitors, beta-blockers, and MRAs as GDMT and investigated the association between physical frailty and GDMT implementation. In a multivariate analysis, physical frailty was not associated with no GDMT implementation compared with physical non-frailty. On the other hand, advanced age, female gender, and severe renal impairment (eGFR < 30 mL/min/1.73 m^2) were significantly associated with no GDMT implementation (supporting information).

Discussion

The primary finding of the present study is that physical frailty is associated with no prescription of GDMT, which is a combination of RAS inhibitors and beta-blockers, at discharge in elderly patients with HFrEF. In this study, almost half of the patients with HFrEF had physical frailty, and physical frailty was more prevalent in patients without GDMT, particularly those with slow gait speed, than in patients with GDMT. In addition, a larger proportion of patients without GDMT had cognitive decline. Patients without GDMT were significantly older than patients with GDMT, and larger proportions of patients without GDMT had anaemia and severe renal impairment. Physical frailty was associated with no GDMT implementation after adjusting for previously reported barriers to GDMT including hypotension, renal impairment, bradycardia, COPD/bronchial asthma, and hyperkalaemia. Patients without GDMT had a higher rate of prior HF admission than that in patients with GDMT. Such patients may have been intolerant to GDMT at the prior admission, which may have caused the current admission for worsening HF. The Change the Management of Patients (CHAMP) registry reported that admission

for HF is a trigger for initiation or dose escalation of GDMT, but on the other hand, it is also associated with discontinuation of GDMT.[24] In this study, patients without GDMT had a higher rate of prior HF admission. It is possible that some patients without GDMT were previously considered to be intolerant of GDMT, but an attempt was made to reintroduce GDMT during the admission. However, it was also possible that they eventually gave up because they could not tolerate GDMT due to physical vulnerability or other factors. ACE inhibitors/ARBs, beta-blockers, MRAs, SGLT2 inhibitors, and ARNI are recommended as the foundations of pharmacotherapy for patients with HFrEF in the latest clinical guidelines.[8,9] The patients were enrolled in our registry at a time when the use of SGLT2 inhibitors and ARNI for patients with HFrEF was not approved in Japan. In a multivariate analysis, the disuse of the combination of RAS inhibitors, beta-blockers, and MRAs was not associated with physical frailty but was significantly associated with advanced age, female gender, and severe renal impairment. We assumed that elderly patients had a higher frequency of CKD and were at increased risk of hyperkalaemia with the combination of RAS inhibitors and MRAs. Therefore, the addition of MRAs to RAS inhibitors may tend to be avoided in elderly patients with HFrEF. After considering these, we defined GDMT as the combination of RAS inhibitors and beta-blockers in this study. In this study, MRAs tended to be prescribed more often in patients with physical frailty and patients with physical prefrailty than in patients with physical non-frailty. In patients with physical frailty and patients with physical prefrailty, MRAs may have been prescribed because they could not tolerate RAS inhibitors due to hypotension. The percentage of patients in whom the three-drug combination of RAS inhibitors, beta-blockers, and MRAs was used was low, only ~25%, suggesting that the combination of RAS inhibitors and MRAs was not well tolerated in elderly patients with HFrEF. Several studies have shown that patients without GDMT were older than patients with GDMT and that larger proportions of patients without GDMT had renal impairment, lower heart rate, low blood pressure, and hyperkalaemia,[25–28] although there has been no study in which the association between GDMT implementation and physical frailty was assessed. It has been shown that physical frailty is significantly associated with adverse outcomes.[7] The reasons for this are thought to be that patients with physical frailty are older, are more likely to be undernourished, and have comorbidities such as CKD, anaemia, and cognitive impairment that adversely affect the outcomes. In most of the large randomized controlled clinical trials, older patients with HFrEF were indirectly excluded through exclusion criteria such as specific comorbidities (renal disease, liver disease, and malignant disease), medication, and life longevity.[14] Consequently, many patients with HF who had physical frailty may not have participated in the clinical trials and the results of the clinical trials cannot be applied to HFrEF patients with physical frailty in daily clinical practice. Additionally, it is unclear whether the favourable effects on prognosis differ between HFrEF patients with physical frailty and HFrEF patients without physical frailty. In the Change the Management of Patients with Heart Failure (CHAMP-HF) registry, the percentages of patients who did not receive ACE inhibitors/ARBs and beta-blockers were 40.1% and 33.2%, respectively.[25] In the West Tokyo Heart Failure (WET-HF) registry, the prescription rates of ACE inhibitors/ARBs and beta-blockers in elderly patients with HFrEF were significantly lower than those in younger patients with HFrEF (60.2% vs. 72.3% and 66.1% vs. 84.1%, respectively).[29] In the present study, patients without GDMT were older than patients with GDMT and the proportion of patients aged 80 years or older was 47.3%. In addition, patients without GDMT were more likely to have physical frailty and cognitive impairment. Despite evidence that GDMT improves clinical outcomes in patients with HFrEF, GDMT has not been adequately implemented in clinical practice, particularly in elderly patients. In the present study, compared with patients with physical non-frailty, patients with physical frailty had an increased risk of no implementation of GDMT after adjustment for various factors including age, BMI, renal impairment, hyperkalaemia, hypotension, bradycardia, serum BNP level, and comorbidities (OMI and bronchial asthma). Therefore, it is thought that the vulnerability of physical status may influence the decision by clinical physicians to implement GDMT. The WET-HF registry showed that GDMT did not reduce the risk of all-cause death and readmission due to worsening HF in patients with HFrEF aged ≥80 years.[29] On the other hand, in the Korean Acute Heart Failure registry, GDMT reduced the risk of all-cause mortality, even in patients aged 80 years or older.[30] In the Swedish Heart Failure Registry, propensity score-matched analysis showed that RAS inhibitors and beta-blockers reduced adverse outcomes in patients with HFrEF over 80 years of age.[15,16] It has not been sufficiently investigated whether GDMT can reduce adverse outcomes in frail patients and in non-frail patients. In the Kitakawachi Clinical Background and Outcome of Heart Failure (KICKOFF) Registry, the proportion of patients with decreased mobility who received combination therapy (both RAS inhibitors and beta-blockers) was smaller than the proportion of patients without decreased mobility.[31] Combination therapy in patients with HFrEF who had decreased mobility did not reduce the incidence of composite events including all-cause mortality and hospitalization for HF compared with the incidence in patients with HFrEF who did not had decreased mobility.[31] In the present study, the prescription rates of RAS inhibitors only, beta-blockers only, and a combination of RAS inhibitors and beta-blockers were significantly lower in patients with physical frailty than in patients with non-physical frailty, but the reason for the rate of GDMT being lower in patients with physical frailty is not clear. Many patients with physical frailty probably have coexisting vulnerabilities in various domains other than the physical domain as well as multiple comorbidities such as

renal impairment, anaemia, cerebrovascular accident, and cognitive impairment. It has been shown that the incidence of frailty was associated with reduced eGFR.[32] Although such a vulnerability of the patient's general condition may be the reason for the poor tolerability of GDMT, the presence of physical frailty itself may influence the decisions by clinical physicians for prescribing GDMT. In the 2021 update to the 2017 American College of Cardiology Expert Consensus Decision Pathway, although there is insufficient evidence for patients aged 75 years or older and those with frailty, implementation of GDMT is recommended with consideration of the risks and benefits.[33] As a result, older and frail patients have been excluded from large randomized controlled clinical trials that showed the efficacy of GDMT for patients with HF. However, in real-world clinical settings, patients with HF are aging. In the present study, approximately 40% of the patients were over 80 years of age and patients with physical frailty accounted for more than half of the study population. Therefore, older patients, frail patients, and patients with multiple comorbidities are the main targets in clinical practice in an aging society. For examining the efficacy of GDMT in patients with HF, it may not be appropriate to exclude older and frail patients from clinical trials. In the future, it will be necessary to examine the effectiveness of GDMT for frail patients. In the current situation in which the effectiveness of GDMT for frail patients has not been proven, it is necessary to carry out GDMT with consideration of tolerability and perform titration as much as possible.

Study limitations

There are several limitations to be acknowledged. First, the number of patients with HFrEF was relatively small as an HF cohort study. However, patients with HF were enrolled in our registry at major facilities in Kochi Prefecture. Therefore, the findings of this study may roughly reflect the status of patients with HF in our aging region. Second, we excluded 71 patients whose physical frailty was not assessed by the J-CHS criteria. Gait speed was not evaluated in any of those 71 patients. Twenty-six patients (37%) of those patients were 'bedridden'. Those patients were in a status of functional disability and should no longer be evaluated for frailty. Of the remaining 45 patients, four patients died during hospitalization, and it is considered that their general condition was not sufficient for evaluating their gait speed during hospitalization. In 41 patients (58%), the reason for non-assessment of frailty was unknown. Probably, such patients were discharged without completing the evaluation for some reason, such as being discharged in a hurry with no time to be evaluated, or their gait speed could not be evaluated due to their poor general condition. However, we showed a relationship between physical frailty and no GDMT in multivariate analysis after adjusting for various factors including age, renal function, systolic blood pressure, and heart rate. Third, the latest guidelines recommend the use of ACE inhibitors/ARNI, MRAs, and SGLT2 inhibitors for all patients with HFrEF unless contraindicated or not tolerated. Patients were enrolled in our registry at a time when ARNI and SGLT2 inhibitors were not available in Japan. In addition, clinical physicians may have tended to avoid the combination of RAS inhibitors and MRAs because the patients were predominantly elderly and more than 70% of them had CKD. Thus, the combination of RAS inhibitors and beta-blockers was defined as GDMT in this study. Finally, we were not able to examine the difference in prognostic effects of GDMT in HFrEF patients with physical frailty and HFrEF patients with non-physical frailty. We are now planning to investigate this clinical issue in future studies.

Future research

We need to investigate whether GDMT improves the prognosis of HFrEF patients with physical frailty. Furthermore, in older and frail patients, it is necessary to establish appropriate comprehensive management including medical therapy and self-management for prevention of readmission due to worsening HF.

Conclusions

In this study, patients without GDMT were older than patients with GDMT and larger proportions of patients without GDMT had severe renal impairment and physical frailty. Physical frailty may interfere with the implementation of GDMT at discharge in a population of predominantly elderly patients with HF.

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Conflict of interest

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

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Supporting information

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

Table S1. Clinical characteristics of patients with and without guideline-directed medical therapy including RAS inhibitors, β-blockers, and MRAs.

Table S2. Frailty assessment of patients with and without guideline-directed medical therapy including RAS inhibitors, β-blockers, and MRAs.

Table S3. Logistic regression analysis for the association between no-GDMT implementation and physical frailty.

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