Original Articles

Motor functions and interventions to improve frailty in patients with heart failure

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ABSTRACT

Background. There is limited research on the factors influencing frailty improvement and on whether exercise therapy is effective in the general population with heart failure. We aimed to examine the factors and interventions that affect the improvement of frailty in older patients with heart failure during hospitalization.

Methods. This multicentre prospective cohort study included patients with heart failure admitted and treated in the participating hospitals. Cox regression analysis was done to determine factors and interventions that affect improvement of frailty. After the Cox regression analysis, the receiver operating characteristic (ROC) curve was calculated for significant predictors to assess the cut-off point.

Results. The factors that affect improvement of frailty were the high short physical performance battery (SPPB) chair-stand test and hand grip strength values. The results of the ROC analysis revealed that the cut-off values of the SPPB chair-stand test and hand grip strength were 2 points and 13.7 kg, respectively. Interventions that affect frailty improvement were use of dobutamine, low resting heart rate, early days to start until aerobic exercise, and light intensity or higher of aerobic exercise. Moreover, the cut-off values of the resting heart rate, number of days to start until aerobic exercise, and intensity of aerobic exercise were 80 beats per minute, 7 days, and 31.6%, respectively.

Conclusions. Our results suggest that pharmacotherapy and exercise will be effective to improve frailty in patients with heart failure. In particular, early exercise therapy, including aerobic exercise, started within 7 days, may be effective to improve frailty in older patients with heart failure with low resting heart rate, depending on their condition on admission.

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INTRODUCTION

Heart failure increases with age, and its incidence increases rapidly after 80 years of age.[1] The number of patients with heart failure worldwide at the present pace may reach 30 million.[2] Older patients with heart failure often experience frailty, and its prevalence is reported to vary between 19% and 52% in outpatients[3–5] and 50% and 76% in inpatients.[6–8] Patients with heart failure and frailty have a 57% higher risk of hospitalization and 80% higher risk of death than those without frailty.[4] These adverse events may explain persistently high re-hospitalization rates, the majority of which are not due to recurrent heart failure.[9,10] Importantly, 'Frailty is a condition that is reversible with appropriate intervention'.[11] Therefore, early diagnosis of frailty and appropriate interventions are important aspects of rehabilitation in older patients with heart failure so as to improve their frailty.

Generally, aerobic and resistance exercises are encouraged in patients with heart failure without frailty.[12–15] Aerobic and resistance exercises of moderate intensity or higher improved frailty in older patients.[16,17] These studies included relatively young patients, including those in their seventh and eighth decade of life. Further, conventional cardiac rehabilitation programmes are not designed to address the multi-domain functional impairments common in patients with heart failure. Commencing rehabilitation without doing so can increase impairments.[10] Consequently, the role of physical rehabilitation intervention in heart failure patients with or without frailty and widespread functional impairments has been identified as a critical evidence gap.[18] In fact, aerobic exercises of moderate intensity or higher are often challenging to perform in older patients with heart failure, and the safety and efficacy of such exercises are unknown. Reeves *et al.*[19] reported that 12 weeks of aerobic and resistance exercises during hospitalization in patients with heart failure and frailty improved motor functions after 3 months and decreased re-admission after 6 months. However, they did not examine whether exercise therapy could improve frailty. In other words, the type, intensity, and frequency of exercise therapy to improve frailty in older patients with heart failure has not yet been established. Generally, aerobic exercise is recommended at the anaerobic threshold level, which is assessed by the cardiopulmonary exercise test. Older patients may fail to perform cardiopulmonary exercise tests. If patients cannot perform this test, the exercise intensity is determined by heart rate, rate of perceived exertion, talk test, etc.

Studies have identified age,[20] nutrition,[21] walking speed,[21] heart function,[20] hand grip strength,[22] and knee extension strength[22] as factors that affect improvement of frailty in older patients with heart failure.

We aimed to examine factors and interventions that affect the improvement of frailty in older patients with heart failure during hospitalization. The findings could provide information that may help establish an exercise routine that improves frailty in patients with heart failure.

METHODS

This multicentre prospective cohort study was done as per the STROBE statement. All patients provided written informed consent to participate. The institutional review boards of Kure Kyosai Hospital (approval no. 2021–3), Saiseikai Kure Hospital (approval no. 150), and Hiroshima International University (approval no. 20–046) approved this study. All procedures complied with the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects of 1975.

Patients

We included patients with heart failure admitted and treated in the participating hospitals between January 2020 and April 2022. Heart failure was defined as heart failure in stage C or D by the American College of Cardiology Foundation/American Heart Association. Heart failure stage classification was based on the European Society of Cardiology, American College of Cardiology Foundation/American Heart Association, and Japanese Circulation Society/Japanese Heart Failure Society guidelines.[23] The inclusion criteria were as follows: (i) age $\geq$65 years, (ii) frailty on admission, (iii) walked independently before admission, and (iv) had no pacemaker implantation.

The Japanese version of the Cardiovascular Health Study Index (J-CHS) was used to determine frailty.[24] The J-CHS has 5 components: (i) weight loss (whether there is a weight loss of at least 2 kg in 6 months), (ii) muscle weakness (whether there was a hand grip strength of <28 kg and 18 kg for men and women, respectively), (iii) fatigue (whether patients with heart failure tired for no reason in the last 2 weeks), (iv) decrease in walking speed (<1.0 metre/second), (v) and decrease in physical activity (responses to the questions 'Do you do light exercise?' and 'Do you do regular exercise?' with a response of neither). Patients with none of the above components were considered patients without frailty (robust), those with only 1 or 2 components were considered patients with pre-frailty, and those with $\geq$3 components were considered patients with frailty. The exclusion criteria were as follows: (i) complications occurred during hospitalization, and (ii) had severe dementia. Severe dementia was defined as a Hasegawa Dementia Rating Scale-Revised (HDS-R) score of $\leq$9. Measurements were performed by the rehabilitation staff of the participating hospitals. Frailty improvement was defined as frailty at the first visit to the rehabilitation room and pre-frailty or non-frailty at discharge. If frailty improved at discharge, patients were assigned to the frailty improvement group, otherwise to the frailty non-improvement group.

Umehara *et al.*[25] reported that patients with heart failure had approximately 40% improvement in frailty at discharge. Based on this finding, we assumed that the ratio of frailty non-improvement at discharge to frailty improvement at discharge was 6:4. The alpha value was set to 0.05, and the power was set to 0.8. The area under the receiver operating characteristic curve (AUROC) could distinguish between non-predictive (AUROC<0.5), less predictive (0.5<AUROC<0.7), moderately predictive (0.7<AUROC<0.9), highly predictive (0.9<AUROC<1), and perfectly predictive (AUROC=1).[26] The AUROC for the hypothesis was set at 0.7 (moderate power), and the AUC for the null hypothesis was set at 0.5 (no discriminatory power). Consequently, 26 patients were required in the frailty improvement group and 44 in the frailty non-improvement group, a total of 70 cases (MedCalc statistical software version 19.2, MedCalc Software bvba, Ostend, Belgium).

Variables

Age, sex, body mass index (BMI), family members living together, HDS-R, life space assessment (LSA), the severity of sarcopenia, walking from before admission and length of stay were included as basic information. HDS-R and the severity of sarcopenia were measured at the first visit to the rehabilitation room. The mean (SD) duration of rehabilitation visits was 5.7 (5.5) days after admission. Other variables were measured at the time of admission. HDS-R scores 21–30, 15–20, 10–14, and $\leq$9 were considered normal cognition, dementia doubt, light-to-moderate dementia, and severe dementia, respectively.[27]

LSA[28] is an index that evaluates the spatial extent of an individual's life by examining the living space for a month before evaluation. The higher the total score, the wider the living space. We defined sarcopenia using the diagnostic algorithm recommended by the Asian Working Group for Sarcopenia in 2019, which assesses the presence of low muscle mass, low muscle function, and low physical function. Each definition was determined by the skeletal muscle mass index (SMI) for low skeletal muscle mass (<7.0 kg/m^2 and 5.7 kg/m^2 for men and women, respectively), hand grip strength for low muscle function (<28 kg and 18 kg for men and women, respectively), and 5 repetitions of the chair-stand test for low physical function ($\geq$12 seconds). Sarcopenia was determined as low skeletal muscle mass with low muscle mass or low physical function.[29] Severe sarcopenia was also defined as positive for all 3 definitions.[29] The walking form before admission was determined to be a form of independent walking: walking without support, walking with cane, or walking with walker.

The New York Heart Association classification, presence or absence of medical history (heart failure, coronary artery disease, valvular disease, hypertension, diabetes mellitus, dyslipidaemia, atrial fibrillation, chronic renal failure, and stroke), blood data (geriatric nutritional risk index [GNRI], brain natriuretic peptide [BNP], estimated glomerular filtration rate [eGFR], and haemoglobin [Hb]), and left ventricular ejection fraction (LVEF) were obtained from the medical records. These variables were measured at the time of admission.

The SMI was included as physical structure information. The skeletal muscle mass was measured in both upper limbs and both lower limbs using bioelectrical impedance analysis (Inbody 270 or S10, InBody, Tokyo, Japan). Then, SMI (appendicular skeletal muscle mass/height^2, kg/m^2) was calculated as the sum of the lean soft tissue of the two upper and two lower limbs.[30] Motor functions were defined using the short physical performance battery (SPPB), one-leg standing time, hand grip strength, and walking speed.

Motor functions were measured at the first visit to the rehabilitation room. SPPB was measured according to the method of Guralnik *et al*.[31] We used the total SPPB scores, SPPB standing balance test, SPPB gait test (4 m), and SPPB chair-stand test (5 repetitions). Each measurement was scored on a scale of 0–4. Higher scores mean better lower limb function. The one-leg standing time was measured according to the method of Michikawa *et al*.[32] The measurement conditions were as follows: stand on one-leg with eyes open while placing hands on the waist without any aid or falling. The completion criteria for the measurements were as follows: (i) both hands or one hand leave the waist, (ii) the raised lower leg touches the axle, (iii) the axle foot moves, and (iv) any part of the axle foot other than the sole touches the floor or wall. The patient arbitrarily chose the measurement side. Measurements were repeated twice, and the highest value was used as the representative value (60 seconds was the upper limit). The hand grip strength was measured in the standing position using a grip strength meter (TKK-5101; Takei Scientific Instruments, Tokyo, Japan or 12B3X00030; Tsutsumi Works, Chiba, Japan).[33] Two measure-ments were taken on each side, and the maximum value (rounded to the nearest 0.1 kg) was used as the representative value. Walking speed[34] was measured as the time taken to walk a distance of 10 metres at a comfortable speed. Two measurements were taken, and the maximum value (metres/minute) was used as the representative value.

Drug and exercise therapies

The presence or absence of drug therapy was recorded to determine whether the patients were receiving dopamine, noradrenaline, dobutamine, phosphodiesterase III inhibitors, diuretics, or beta-blockers.

Exercise therapy information included the number of days starting until aerobic exercise and the intensity of the exercise. The number of days to start until the aerobic exercise was defined as the number of days from hospitalization to the start of aerobic exercise. The intensity of aerobic exercise was based on the heart rate reserve (%HRR). The %HRR was calculated as (highest heart rate during exercise–resting heart rate)/(220–age)–resting heart rate)×100. The heart rate was measured at rest and during exercise with an electrocardiogram monitor (WEP-5218, Nihon Koden Corporation, Tokyo, Japan; DS-7680, Fukuda Denshi Corporation, Tokyo, Japan). The heart rate during exercise was defined as the maximum heart rate during aerobic exercise for 3 days after the intervention, and the average value was adopted. The %HRR was defined as sedentary for <20%, light for 20%–40%, moderate for 40%–60%, vigorous for 60%–85%, and high for >85% HRR.[35] The resting heart rate was included in the exercise discontinuation criteria and determination of %HRR. Higher resting heart rate was found to be associated with a higher incidence of cardiovascular events and mortality.[36] Therefore, the resting heart rate is necessary for conditions of exercise intervention.

The goal of the rehabilitation interventions was to improve deconditioning, improve walking ability, and increase activities of daily living (ADL) during hospitalization. Consideration of safety focused on subjective symptoms and haemodynamics. For risk management, we monitored the blood pressure, SpO_2, and electrocardiogram during rehabilitation. The main index of exercise intensity used the target heart rate, and several other indices such as the Borg scale (11–13) for the chest and lower extremities and the talk test were also used. In order to set the exercise intensity by heart rate, the target heart rate was determined using Karvonen's formula (target heart rate=(220–age)–resting heart rate)×exercise intensity (k)+resting heart rate). The physiotherapist or physician determined exercise intensity (k). Once the condition stabilized, the frequency of intervention was set at 1 hour each in the morning and afternoon. The intervention period started from the time of the prescription by the attending physician until discharge from the hospital.

Bias

In order to reduce selection bias, outcomes were selected based on previous studies.[30–34] The first author was not involved in patient enrollment and data collection. All tests, indices, scales, and software do not require approval for use. Our study was conducted at the participating hospitals for 2 weeks to standardize, as much as possible, the content of cardiac rehabilitation, intervention intensity, and frequency of cardiac rehabilitation.

Statistical analysis

All statistical analyses were done using IBM SPSS Statistics for Windows, version 28.0 (IBM Corp., Armonk, NY, USA). The significance level was set at 5%. First, the two groups were compared using variables for frailty improvement and non-improvement groups. Characteristic data were compared using the Mann–Whitney U-test, t-test, or chi-square test, as appropriate. Then, Cox regression analysis (forward stepwise selection method: likelihood ratio) was done to determine factors that affect improvement of frailty. Dependent variables were defined as a score of 1 for the frailty improvement group and a score of 0 for the non-improvement group. The independent variables included basic medical information, physical structure, and motor functions. Finally, Cox regression analysis (forward stepwise selection method: likelihood ratio) was conducted to determine the interventions that affect frailty improvement. Dependent variables were defined as a score of 1 for the frailty improvement group and a score of 0 for the non-improvement group. The independent variables were the content of drug and exercise therapies. We included the resting heart rate as an independent variable. We estimated the adjusted hazard ratios (HRs) for the incidence of disability with 95% confidence intervals. Variables with correlation coefficients >0.8 were excluded from the Cox regression analysis because of multicollinearity. After the Cox regression analysis, the receiver operating characteristic (ROC) curve was calculated for the significant predictors to assess the cut-off point.

RESULTS

Patients

A total of 99 patients with heart failure met the inclusion criteria. Of these, 11 developed complications during hospitalization, and 4 had severe dementia. Finally, 84 patients were analyzed. There were 30 patients in the frailty improvement group and 54 in the frailty non-improvement group (Table I). The rates of frailty factors in the frailty improvement group at the first visit to the rehabilitation room and discharge were 93.3% and 76.7% for weight loss, 83.3% and 73.3% for muscle weakness, 90.0% and 86.6% for fatigue, 93.3% and 70.0% for reduced walking speed, and 63.3% and 55.5% for reduced physical activity, respectively. The rates of frailty factors in the frailty non-improvement group at the first visit to the rehabilitation room and discharge were 81.5% and 70.4% for weight loss, 87.0% and 87.0% for muscle weakness, 87.0% and 55.6% for fatigue, 98.1% and 98.1% for reduced walking speed, and 66.7% and 66.7% for reduced physical activity, respectively. The degree of sarcopenia, LSA, SMI, total SPPB, SPPB 4-m walk, SPPB 5-repeated chair stands, and hand grip strength significantly

TABLE I. Patient characteristics

Variable	Frailty improvement (n=30)	Frailty non-improvement (n=54)	p value
Age (years)	84.5 (77.0–89.3)	87.0 (81.7–91.0)	0.19
Sex (male/female)	14/16	20/24	0.39
BMI (kg/m²)	21.7 (18.4–23.4)	21.7 (18.4–23.4)	0.45
Family members living together (Yes/No)	14/16	37/17	0.17
HDS-R (score)	23.0 (19.0–26.0)	24.0 (18.8–28.0)	0.31
LSA (score)	46.8 (22.9–74.0)	32.0 (18.0–46.5)	0.02
Severity of sarcopenia			0.001
Nil	15	12	
Sarcopenia	5	2	
Severe	10	38	
Walking form before admission			0.31
Without support	22	31	
With cane	6	15	
With walker	2	8	
Length of stay (days)	23.0 (16.8–31.0)	19.0 (15.0–27.0)	0.14
New York Heart Association Class I/II/III/IV	0/6/11/13	1/11/22/20	0.34
Medical history			
Heart failure	19	39	0.40
Coronary artery disease	8	23	0.15
Valvular disease	7	10	0.81
Hypertension	28	49	0.51
Diabetes mellitus	15	24	0.63
Dyslipidaemia	17	24	0.22
Atrial fibrillation	22	40	1.00
Chronic renal failure	10	25	0.25
Stroke	5	9	1.00
GNRI (score)	110.4 (90.5–137.1)	111.1 (94.3–134.4)	0.32
BNP (pg/ml)	615.0 (285.4–1219.9)	463.9 (243.2–729.6)	0.12
eGFR (ml/min/1.73m2)	40.0 (18.5)	40.5 (17.9)	0.90
Haemoglobin (g/dl)	11.3 (2.9)	11.2 (1.9)	0.95
LVEF (%)	58.1 (40.1–69.9)	55.8 (34.5–65.7)	0.11
SMI	5.8 (5.4–6.7)	5.1 (4.4–6.0)	0.01
SPPB (score)	7.0 (4.0–9.0)	5.0 (4.0–7.0)	0.02
—Static standing balance	2.0 (1.8–4.0)	2.0 (1.0–4.0)	0.66
—4 m walk	2.5 (2.0–3.0)	2.0 (1.0–3.0)	0.01
—5 repeated chair stands	1.5 (1.0–3.0)	1.0 (0.0–2.0)	0.02
One leg standing time (second)	1.9 (0.0–4.0)	0.0 (0.0–4.0)	0.40
Hand-grip strength (kg)	17.5 (13.3–23.7)	14.0 (10.2–18.9)	0.03
Walking speed (m/min)	15.2 (12.4–20.3)	18.4 (13.9–24.5)	0.06
Drug therapy			
Dopamine	0/30	0/54	–
Noradrenaline	0/30	0/54	–
Dobutamine	4/26	1/53	0.05
Phosphodiesterase III inhibitor	1/29	2/52	0.71
Diuretics	26/4	50/4	0.30
Beta-blocker	13/17	22/32	0.82
Exercise therapy			
Resting heart rate	75.8 (18.9)	77.6 (17.4)	0.12
Number of days to start aerobic exercise	4.0 (2.0–8.0)	4.0 (2.0–6.5)	0.76
Intensity of aerobic exercise: %HRR	31.8 (19.5–42.5)	32.0 (24.2–54.4)	0.46

BMI body mass index HDS-R Hasegawa dementia rating scale-revised LSA life space assessment GNRI geriatric nutritional risk index BNP brain natriuretic peptide eGFR estimated glomerular filtration rate LVEF left ventricular ejection fraction SMI skeletal mass index SPPB short physical performance battery HRR heart rate reserve differed between the two groups. Other variables were not significantly different between the two groups.

Factors affecting improvement of frailty

The risk factors that affect improvement of frailty at discharge were determined by Cox regression analysis (Table II). The mean (SD) duration of hospital stay was 23.6 (11.5) days. The final independent variables for factors that affect frailty improvement were age, sex, BMI, presence of family members living together, HDS-R, LSA, degree of sarcopenia, walking form before admission, New York Heart Association classification, medical history, GNRI, BNP, eGFR, haemoglobin, LVEF, SMI, SPPB standing balance test, SPPB gait test (4 m), SPPB chair-stand test, one-leg standing time, and hand grip strength. The results of the Cox regression analysis showed that the model χ^2 test was significant ($p<0.01$), and the SPPB chair-stand test and hand grip strength were extracted as significant factors. The HRs were 1.47 for the SPPB chair-stand test and 1.08 for the hand grip strength. The results of the ROC analysis revealed that the cut-off value of the SPPB chair-stand test was 2, and the sensitivity and specificity were 0.50 and 0.74, respectively. Moreover, the cut-off value of the hand grip strength was 13.7 kg, and the sensitivity and specificity were 0.73 and 0.48, respectively.

Interventions affecting improvement of frailty

The Cox regression analysis was used to determine the interventions needed to improve frailty at discharge (Table III). The final independent variable of the intervention that affects frailty improvement was the presence or absence of drug therapy (dopamine, dobutamine, noradrenaline, phosphodiesterase III inhibitor, diuretics, or beta-blockers), resting heart rate, number of days to start until aerobic exercise, and intensity of aerobic exercise (%HRR). The results of the Cox regression analysis showed that the model χ^2 test was significant ($p<0.01$), and dobutamine, resting heart rate, the number of days to start until aerobic exercise, and intensity of aerobic exercise (%HRR) were extracted as significant factors. The HRs were 19.46 for dobutamine, 0.95 for the resting heart rate, 0.89 for the number of days to start until aerobic exercise, and 1.01 for the intensity of aerobic exercise (%HRR). The results of the ROC analysis revealed that the cut-off value of the resting heart rate was 80 beats per minute, and the sensitivity and specificity were 0.4 and 0.68, respectively. The results of the ROC analysis revealed that the cut-off value of the number of days to start until the aerobic exercise was 7 days, and the sensitivity and specificity were 0.36 and 0.76, respectively. The results of the ROC analysis revealed the cut-off value of the intensity of aerobic exercise (%HRR) was 31.6%, and the sensitivity and specificity were 0.53 and 0.50, respectively.

DISCUSSION

Factors that affected improvement of frailty were high SPPB chair-stand test and hand grip strength. The SPPB chair-stand test and hand grip strength reflect lower limb muscle strength[37] and is a characteristic of skeletal muscle disorders in heart failure.[38] We assessed physical frailty by the J-CHS which includes muscle weakness. We included patients with heart failure who had frailty on admission: frailty assessment items apply to $\geq$3 of the 5 items. Although the SPPB chair-stand test and hand grip strength were significantly better in the frailty improvement group than in the frailty non-improvement group, percentages for muscle weakness or frailty at the first visit to the rehabilitation room were comparable. The percentages for muscle weakness or frailty at the first visit to the rehabilitation room were 83.3% and 87.0% in the frailty improvement and frailty non-improvement groups, respectively. Muscle weakness at discharge was 73.3% in the frailty improvement group, and 87.0% in the frailty non-improvement group. The rate of improvement in muscle weakness was higher in the frailty improvement group than in the frailty non-improvement group. The results of the ROC analysis revealed that the cut-off values of the SPPB chair-stand test and hand grip strength were 2 points and 13.7 kg, respectively. The 2 points in SPPB chair-stand test (5 repetitions) were achieved in 13.7–16.69 seconds. These cut-off values may help in characterizing those that improve frailty.

There is a concept of a frailty cycle. The frailty cycle refers to decreases in muscle strength and mass due to aging or chronic disease, leading to decreased activity and energy expenditure.[39] This condition is a vicious cycle of reduced food intake, low nutrition, and further muscle strength and mass loss.[39] Thus, frail heart failure patients exhibit muscle atrophy (sarcopenia). The criteria for sarcopenia are SMI for low skeletal muscle mass of <7.0 and 5.7 kg/m^2 for men and women, respectively; hand grip strength for low muscle function of <28 kg and 18 kg for men and women, respectively; and five repetitions of the chair-stand test for low physical function ($\geq$12 seconds).[29] In our study, the frailty improvement group was significantly better than the frailty non-improvement group in

TABLE II. Factors affecting frailty improvement

Independent variable	Partial regression coefficient	HR	95% confidence interval	p value
SPPB chair-stand test	0.39	1.47	1.14–1.90	0.001
Hand grip strength	0.08	1.08	1.02–1.16	0.01

SPPB short physical performance battery HR hazard ratio

TABLE III. Interventions affecting frailty improvement

Independent variable	Partial regression coefficient	HR	95% confidence interval	p value
Dobutamine	2.97	19.46	5.34–70.95	0.001
Resting heart rate	–0.05	0.95	0.92–0.98	0.001
Number of days to start until aerobic exercise	–0.12	0.88	0.81–0.97	0.01
Intensity of aerobic exercise (%HRR)	0.01	1.01	1.00–1.02	0.03

HRR heart rate reserve HR hazard ratio

terms of LSA, degree of sarcopenia, and SMI. These results indicate that the frailty non-improvement group had low muscle strength, muscle mass, and activity than the frailty improvement group. Therefore, the frailty non-improvement group is more likely to be in a frail cycle than the frailty improvement group. In other words, aerobic exercise in patients with heart failure with a frail cycle on admission may not improve frailty at discharge. Conversely, aerobic exercise in patients with heart failure and a non-frail cycle on admission would improve frailty at discharge.

Interventions that affect frailty improvement were the use of dobutamine, low resting heart rate, early number of days to start until aerobic exercise, and light intensity or higher of aerobic exercise. Dobutamine was extracted as drug therapy. Dobutamine is often used in patients with acute heart failure or acute exacerbations of chronic heart failure. Dobutamine increases cardiac contractility. Patients with heart failure using dobutamine often have a low cardiac output condition. Low cardiac output may lead to fatigue and muscle atrophy. In the frailty improvement group, dobutamine may increase cardiac contractility, improve low cardiac output conditions, and increase muscle output. However, since not all patients with heart failure are in a low cardiac output state, this generalization should be considered cautiously. Interventions that affect frailty improvement were resting heart rate <80/minute, days to aerobic exercise <7 days, and aerobic exercise intensity >31%. High resting heart rate predicts cardiovascular mortality in patients with heart failure.[36] Specifically, heart failure patients with resting heart rate >100/minute[40] or resting heart rate >81/minute[41] are at significantly higher risk of mortality. Thus, although there is no consensus, heart failure patients with higher resting heart rates may be more prone to adverse events. Frailty is also associated with an increase in adverse events.[42] In other words, control of resting heart rate is necessary to improve frailty in patients with heart failure.

High-quality studies have suggested that aerobic and resistance exercises at moderate intensity or higher improved motor functions in patients with heart failure.[12–15] In addition, aerobic and resistance exercises at moderate intensity or higher improved frailty in older people.[16,17] Thus, aerobic and resistance exercises at moderate intensity or higher were found to be effective in improving motor functions and frailty. The results of these studies differ slightly from the results in our study regarding exercise intensity. The exercise intensity in our study improved frailty at a light intensity or higher (including the moderate intensity), which is lower than the intensity in previous studies. This difference may be explained by the characteristics of the patients and the frequency of interventions. In previous randomized controlled trials, patients with heart failure reported the effects on motor functions in their late 60s to early 70s, and many patients had New York Heart Association Class II.[12–15] In our study, patients with heart failure were older (in the late 80s) and New York Heart Association classification III–IV on admission. Therefore, performing exercise at a lower intensity was necessary. As regards the amount of daily intervention, previous studies have reported that a daily intervention for patients with heart failure was 60 minutes.[12–15] In our study, if the condition of patients with heart failure was stable and exercise therapy was possible, exercise therapy was done twice a day for 60 minutes (morning and afternoon). A previous study reported that low-intensity exercise had similar effects on muscle to high-intensity exercise when the number of repetitions increased.[43] Although the intensity was lower than in previous studies, we had a long daily intervention time. Aerobic exercise at a light intensity or higher improves frailty in patients with heart failure who are not in a frail cycle, if exercise was performed as an intervention.

Our study has two limitations. The first relates to the method of assessing frailty. Our patients with heart failure were older patients with acute heart failure or acute exacerbation of chronic heart failure. Frailty is characterized by muscle weakness, fatigue, and slow walking speed. These may also be observed in heart failure, making it difficult to distinguish whether the symptoms are due to frailty or heart failure. However, the same frailty assessment was used in similar patients with acute heart failure.[44] The second limitation is that we considered only the intensity of exercise at the start of the intervention. Generally, exercise intensity should vary depending on the patient's condition. The duration of hospitalization of patients was approximately 20 days, and the intensity of exercise might be modified during hospitalization. However, it was practically difficult to analyze these intensity changes in detail.

In conclusion, we examined factors and interventions that affect frailty improvement at discharge. Our results suggest that pharmacotherapy and exercise therapy is effective in improving frailty in patients with heart failure. In particular, early exercise therapy, including aerobic exercise, started within 7 days may be effective in improving frailty in older patients with heart failure.

Conflicts of interest. None declared

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