Relationship between the Kihon Checklist and the clinical parameters in patients who participated in cardiac rehabilitation

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Short running title: KCL and clinical profiles in CR patients

Abstract

Aim: The Kihon Checklist is a useful screening tool for assessing frailty in elderly individuals. However, the clinical significance of the Kihon Checklist in cardiac rehabilitation patients remains unclear. The present study aimed to evaluate the relationship between the Kihon Checklist and the clinical parameters in patients who participated in cardiac rehabilitation.

Methods: We enrolled 845 consecutive patients (584 men, mean age: 71 years) who participated in cardiac rehabilitation at our University Hospital between November 2015 and October 2017. The patients were divided into non-frailty (n=287), pre-frailty (n=270), and frailty (n=288) groups according to their Kihon Checklist scores. Cardiopulmonary exercise testing was performed in 302 patients.

Results: The frailty group was older and had a higher prevalence of history of heart failure than the non-frailty group, although left ventricular ejection fraction did not differ significantly between groups. Nutritional index, trunk and limb muscle mass, lean body weight, and grip strength were significantly lower in the frailty and pre-frailty groups than those in the non-frailty group. In the cardiopulmonary exercise test, a stepwise significant decrease in peak oxygen uptake was observed across the three groups (non-frailty: 17.2 ± 3.6, pre-frailty: 16.0 ± 3.4, frailty: 14.4 ± 3.5 mL/kg/min, *P*

< 0.01). Multivariate regression analyses demonstrated that Kihon Checklist score was significantly and independently associated with peak oxygen uptake ($r = –0.34$, $P <$ 0.0001).

Conclusions: The Kihon Checklist that was associated with frailty and exercise tolerance could be employed as a clinical assessment method for patients who participated in cardiac rehabilitation.

Keywords: cardiac rehabilitation, exercise tolerance, frailty, Kihon checklist

Introduction

Frailty is regarded as a geriatric syndrome associated with high vulnerability to stressors for adverse health outcomes, resulting from the decreased reserves of multiple physiological systems.[1] It has been reported that 25–50% of patients with cardiovascular disease (CVD) are frailty.[2] Frailty increases the risk of CVD and is associated with an approximately three-fold higher risk of death from CVD.[3] Pre frail individuals have an approximately two-fold higher risk of becoming frail than non-frail individuals do; thus, pre-frailty may also increase the risk of developing CVD.[1] Given these risks, it is important to manage and to treat frailty and pre-frailty as well as any comorbid chronic diseases.[4]

Several measurement tools have been developed for assessing frailty. Among them, the Cardiovascular Health Study index, known as Fried's frailty phenotype, is widely used.[1] However, there is no international standard measurement for frailty.[5] The Kihon Checklist (KCL), a self-administered questionnaire, is considered a useful tool for frailty screening in elderly populations.[6] The KCL consists of simple questions and does not involve any special examinations, such as muscle strength or cardiopulmonary exercise testing (CPX).[6] Total KCL scores have been shown to correlate significantly with Fried's frailty phenotype values.[7] However, whether KCL is also a useful tool for

assessing patients with CVD remains unclear, since associations between KCL and physical function in CVD patients have not been specifically addressed. Therefore, the objective of the present study was to evaluate the relationship between KCL assessment and the clinical parameters in patients with CVD who have participated in CR.

Methods

Study Population

This was a retrospective cross-sectional study. We enrolled 1,000 consecutive patients who participated in phase II CR at our University Hospital between November 2015 and October 2017. In Japan, the indication for CR in CVD patients are acute myocardial infarction, angina pectoris, after open heart surgery or transcatheter aortic valve implantation, chronic heart failure, major vessel disease, and peripheral artery disease. CR comprises medical evaluation of patients, exercise therapy, education for secondary prevention, and support of psychosocial factors. The effectiveness of CR for patients with CVD has already been proven.[8] This study enrolled the patients who participated in CR who were evaluated for clinical parameters, including risk profiles and physical function. Of these, 109 patients were excluded for being <50 years old, 22 patients lacked KCL evaluation scores, and 24 patients were duplicate cases. This resulted in

845 patients being included in the study (Supplemental figure). The KCL assessment was performed by the patients at the beginning of CR. Written informed consent was provided by all the patients and the study protocol was approved by the ethical committee of our institution. This study was conducted in accordance with the Helsinki Declaration.

Kihon Checklist

The KCL is a 25-item self-administrated questionnaire developed by the Japanese Ministry of Health, Labor, and Welfare to identify frail elderly individuals who are at risk of requiring new certification for long-term care insurance (LTCI).[7] The KCL comprises seven types of questions assessing instrumental activities of daily living (IADL), physical function, nutritional status, oral function, social ADL, cognitive function, and depressive mood. Thus, the KCL is a comprehensive evaluation method that focuses on the social and psychological aspects in addition to the physical aspects of frailty. Given its ability to assess frailty across multiple domains, the KCL is regarded as an effective screening tool.[7] The questions on the KCL require a simple yes or no answer, and are scored as 1 or 0 points, respectively. A score of 8 points or more is considered to indicate frailty, while a score of 4–7 points indicates pre-frailty.[7]

Data collection

The clinical characteristics of the patients, including age, gender, smoking history, comorbidities, and medical history, were obtained from medical records. We used laboratory test results, medication use, and echocardiographic data from the time closest to the start of the CR when multiple data were available for one patient. Blood samples were collected in the early morning after overnight fasting. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2, calculated by the renal disease equation with a Japanese coefficient using baseline serum creatinine and a modification to the diet.[9] In the present study, the Geriatric Nutritional Risk Index (GNRI) was used as a nutritional index.[10]

Measurements

We assessed body composition, muscle strength, and exercise tolerance at the beginning of the CR, as described previously.[8] In brief, anthropometric parameters, including the percentages of body fat, lean body weight, and muscle mass were measured by bioelectrical impedance analysis (TANITA, MC-780A®). In addition, we measured grip strength and the six-minute walking distance. Grip strength testing was carried out in

both hands in a standing position and we used the higher grip strength value. The six-minute walking test was performed according to the guidelines established by the American Thoracic Society.[11] Exercise tolerance was assessed by CPX on a cycle ergometer (Strength ergo 8®) with an expiratory gas analysis machine (AE-310S®) using a ramp protocol with a workload increase of 10 W/min to measure anaerobic threshold (AT) and peak oxygen uptake (peak VO_2). A standard 12-lead electrocardiogram was continuously recorded and blood pressure was registered every minute during exercise testing. Peak VO_2 was defined as the highest VO_2 value recorded during CPX, and the AT point was determined by the ‘‘V-slope’’ method.

Statistical analysis

Continuous variables are presented as mean ± standard deviation. Differences among the three groups were analyzed by one-way analysis of variance followed by Tukey's honest significant difference test. Chi-square tests were used to compare categorical variables. Spearman's correlation coefficient was used to calculate the correlations between the variables. Differences were considered significant at $P < 0.05$. A stepwise multiple linear regression analysis was performed to determine the association between KCL score and peak VO_2. As explanatory variables, besides age, gender and KCLw

score, we selected factors related to cardiac, respiratory, and skeletal muscle functions, including ejection fraction, presence or absence of chronic obstructive pulmonary disease (COPD), grip strength, and skeletal muscle mass, and factors with significant differences. JMP version 12.0 (SAS Institute, Cary, NC, USA) was used to analyze all the data.

Results

According to their KCL assessment, the patients were divided into a non-frailty group (n=287), pre-frailty group (n=270), and frailty group (n=288) (Supporting Figure 1). Tables 1 and 2 present the clinical characteristics, physical functions and the medications of the subjects. The frailty group was older than the non-frailty group (67.8 ± 9.2 vs 73.0 ± 8.5 years old, $P < 0.05$). The frailty group had high prevalence of CKD, COPD and atrial fibrillation and history of heart failure. There were no significant differences in the prevalence of hypertension, diabetes, dyslipidemia, or current smoking among the three groups. The hemoglobin level, GNRI, and eGFR were significantly different among the three groups (all $P < 0.01$); however, there was no significant difference in the left ventricular ejection fraction (EF). Lean body weight, trunk and limb muscle mass, grip strength, and six-minute walking distance were

significantly lower in the pre-frailty and frailty groups compared to the non-frailty group (all $P < 0.01$). Analysis of the anthropometric parameters by gender showed a similar trend (Supporting Table 1).

Figure 1 shows each parameter by age group. Even for subjects in their 50s, lean body weight, trunk and limb muscle mass, and six-minute walking distance were significantly lower in the frailty group than in the non-frailty group (all $P < 0.05$). Comparison of anthropometric data by age -groups and gender are shown in the Supporting Figures 3 and 4.

In the study population, CPX was able to be performed in 302 patients (35.7%) who provided consent at the early beginning of phase II CR. Of these patients, 153 were in the non-frailty group, 89 were in the pre-frailty group, and 60 were in the frailty group (Table 3). Data regarding to clinical background and other parameters of patients who underwent CPX are shown in the Supporting Tables 2, 3, and 4. AT level was significantly lower in the frailty group than the non-frailty group (11.5 ± 2.3 vs 10.3 ± 2.3 mL/kg/min, $P < 0.01$), while minute ventilation/carbon-dioxide output (VE/ VCO_2) was significantly higher in the frailty group than in the non-frailty group (30.5 ± 6.3 vs 33.5 ± 8.4, $P < 0.05$). Peak VO_2 levels decreased in a stepwise manner across the three groups and were significantly lower in the pre-frailty and frailty groups compared to the

non-frailty group (non-frailty: 17.2 ± 3.6, pre-frailty: 16.0 ± 3.4, frailty: 14.4 ± 3.5 mL/kg/min, $P < 0.01$). Supporting Figure 2 shows the correlation between KCL score and peak VO_2, which was negative and significant ($r = –0.34$, $P < 0.01$). Even after adjusting for age, gender, and other explanatory variables, KCL score remained a significant explanatory variable for peak VO_2 ($\beta = –0.17$, $P < 0.0001$) (Table 4).

Discussion

The present study showed that patients in the pre-frailty and frailty groups had lower nutritional status and physical function, including grip strength, muscle mass, and exercise tolerance, than patients in the non-frailty group. These trends were also observed even in patients below age 60. In addition, the KCL score was a significant and independent factor of exercise tolerance in patients who participated in CR. To the best of our knowledge, this is the first study demonstrating associations between KCL score and clinical data, including CPX measurement, in patients who participated in CR.

The prevalence of frailty and pre-frailty is reported to be 7–12% and 35–50%, respectively, in community-dwelling people aged 65 years or older.[12] In Japan, the prevalence of frailty and pre-frailty in the general elderly population is estimated at 6.9% and 49.6%, respectively.[13] In patients with heart failure, the prevalence of frailty

estimated by multidimensional frailty measures is about 47%.[14] The proportion of each group, based on the frailty status by KCL, was consistent with that of previous studies. The KCL may appropriately evaluate the frailty status of patients who participated in CR without the need for specific equipment.

A previous cross-sectional study using the KCL reported that community-dwelling elderly people at high risk for LTCI had lower ADL and more depressive symptoms.[15] Another population-based longitudinal observational study reported that elderly people identified as pre-frailty or frailty by the KCL had a significantly higher rate of new LTCI compared to the non-frailty group.[16] Elderly people who require LTCI service are likely to have increased malnutrition and frailty, and decreased physical performance. Our results are consistent with these findings from previous studies. In addition to previous studies, data on nutritional status and physical function have demonstrated the validity of KCL stratification in our study patients.

There were significant differences in muscle mass, grip strength, six-minute walking distance, and peak VO_2 among the three groups in the present study. These results have not been previously reported especially in patients with CVD. Grip strength and six-minute walking distance are recognized as strong predictors of poor survival.[17, 18] Peak VO_2, which is associated with cardiac function as well as age, gender, and

skeletal muscle mass, is a very important predictor of prognosis in patients with CVD.[19,20] Indeed, the KCL score was significantly correlated with peak VO_2 and was an independent factor for peak VO_2 after adjustment for other factors. Peak VO_2 is determined mainly by respiratory function, cardiovascular function, and skeletal muscle function.[21] The content of KCL, specifically the questions regarding IADL, physical function, and nutritional status, are associated with skeletal muscle function,[22-24] and associations between decline in social ADL and incidence of CVD have been reported.[25] Furthermore, the KCL also includes other evaluations, such as oral function, cognitive function, and depressive symptoms. Relationships of the other content of KCL—including oral function, cognitive function, and depressive symptoms—with skeletal muscle function, vascular function, and respiratory function have also been reported.[26-28] Taken together, these findings suggest that the KCL can assess exercise tolerance comprehensively. However, the mechanism through which the KCL is directly or indirectly related to cardiopulmonary function, skeletal function, and vascular function has not been elucidated yet, and further studies are needed to explore the relationship.

As already mentioned, frailty is regarded as a geriatric syndrome. However, we found a significant decrease in muscle mass and six-minute walking distance in the frailty group even in individuals in their 50s. These results suggest that physical changes

associated with frailty may be observed at a younger age in patients who participated in CR. Thus, it is important to evaluate the state of frailty in both elderly patients and middle-aged patients who participated in CR.

Frailty has been shown to be an independent predictor of death and re-hospitalization in patients with CVD.[3,29] Adequate interventions, such as exercise and nutritional support, are reported to improve frailty.[30] Early identification and intervention may help prevent future frailty-associated events in patients who participated in CR. Therefore, simple evaluation of the frailty status using the KCL may be a helpful self-assessment questionnaire for the early detection of frail or pre-frail patients who participated in CR.

The present study had several limitations. First, it was a single center study with a small sample size. Second, CPX was performed in about one-third of patients only. Third, due to its cross-sectional nature, our data could not demonstrate the association between KCL and prognosis in our study patients. Future investigations are needed to confirm the relationship between KCL and clinical events in patients who participated in CR. Fourth, we did not perform KCL evaluation in CVD patients who could not participate in the CR. Finally, in our study, we enrolled Japanese patients who participated in CR only. Since the KCL has been translated into English and Brazilian

Portuguese already, future studies are needed in order to evaluate the usefulness of the KCL for patients who participated in CR in other countries.[6]

In conclusion, the patients classified as having different levels of frailty using the KCL showed significant differences in the clinical characteristics, including nutritional status, physical parameters, and exercise tolerance. These results suggested that the KCL may be a helpful assessment method for evaluating the frailty status in patients who participated in CR.

Acknowledgements

The authors wish to thank all study participants and members of date collection in Cardiovascular Rehabilitation and Fitness.

Funding

This study was supported in part by JSPS KAKENHI Grant Number 17K01470 and the High Technology Research Center Grant from the ministry of Education, Culture, Science and Technology, Japan.

Disclosures

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Figure legends

Figure 1: Comparison of anthropometric parameters, grip strength, and six-minute walking test by age group.

* P <0.05 vs Non-frailty by Tukey's honest significant difference test.

Supporting Figure 1: Flow chart and patients in this study.

CR, cardiac rehabilitation; KCL, kihon check list

Supporting Figure 2: Correlation with KCL scores and peakVO_2.

peak VO_2, peak oxygen uptake; KCL, kihon check list.

Supporting Figure 3: Comparison of anthropometric parameters, grip strength and six-minute walking distance by age in male patients.

* P <0.05 vs Non-frailty by Tukey's honest significant difference test.

Supporting Figure 4: Comparison of anthropometric parameters, grip strength and six-minute walking distance by age in female patients.

* P <0.05 vs Non-frailty by Tukey's honest significant difference test.

Supporting Table 1: Comparison of anthropometric parameters and physical function by gender.

* P <0.05 vs Non-frailty, ** P <0.01 vs Non-frailty by Tukey's honest significant difference test.

Supporting Table 2: Clinical characteristics of the patients who underwent CPX.

* P <0.05 vs Non-frailty, ** P <0.01 vs Non-frailty by Tukey's honest significant difference test.

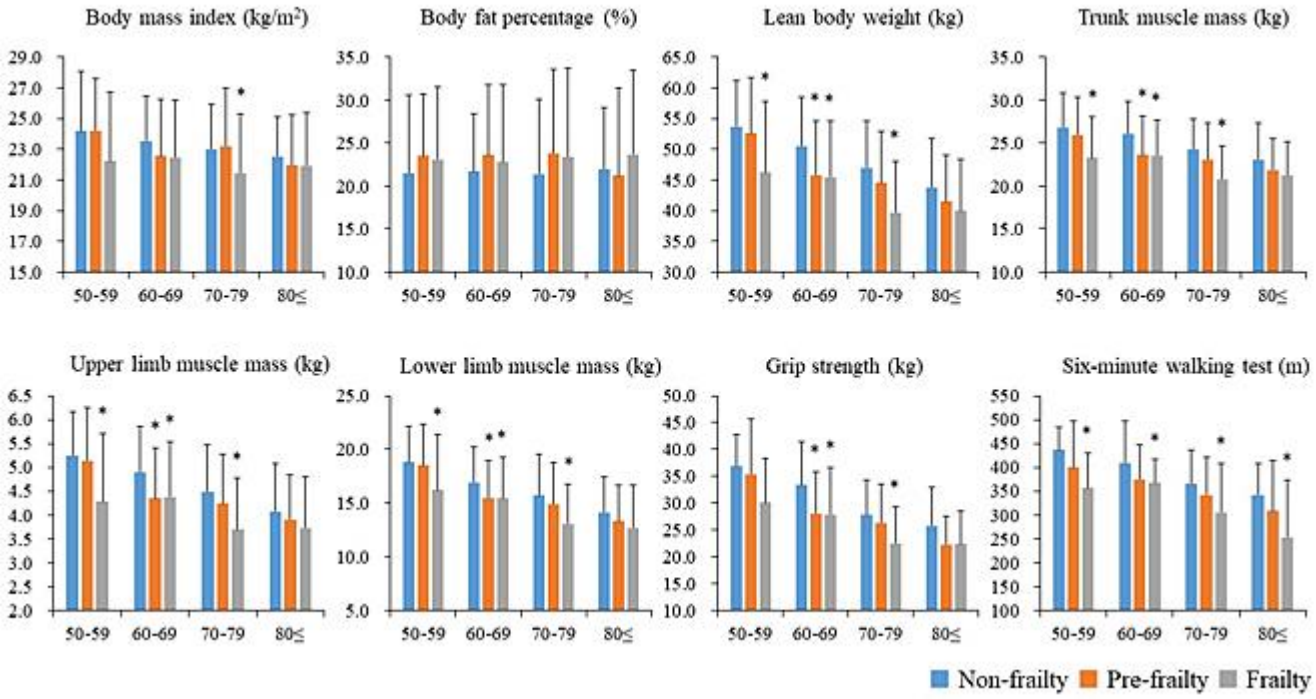
Supporting Table 3: Comparison of clinical parameters and medication in the patients who underwent CPX.

* P <0.05 vs Non-frailty, ** P <0.01 vs Non-frailty by Tukey's honest significant difference test.

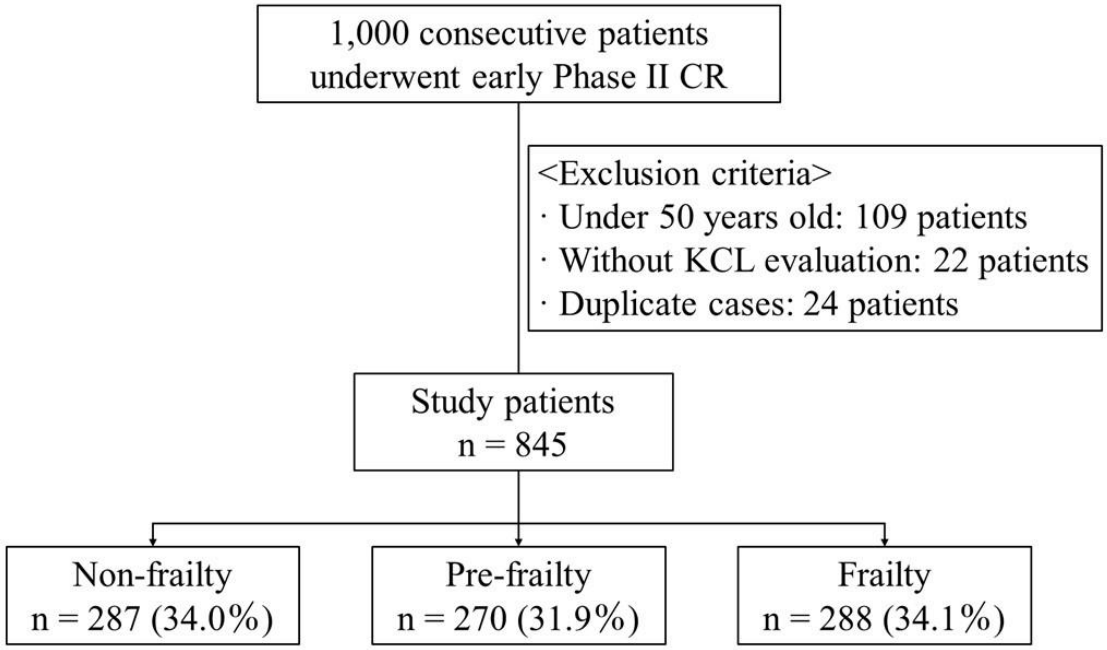
Supporting Table 4: Comparison of anthropometric parameters and physical function in the patients who underwent CPX by gender.

* P <0.05 vs Non-frailty, ** P <0.01 vs Non-frailty by Tukey's honest significant difference test.

Figure1

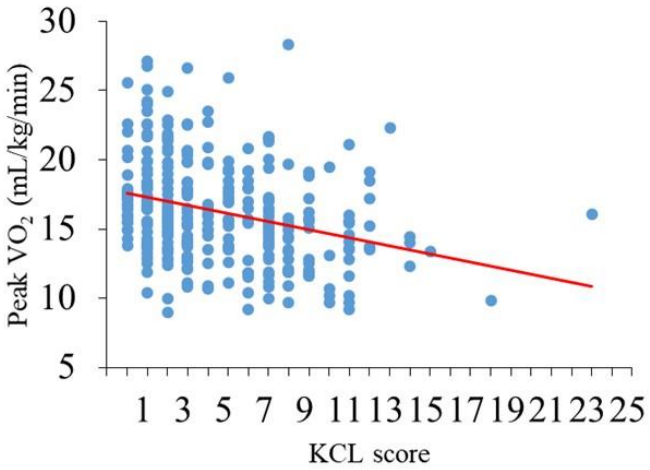

Body mass index (kg/m²)
Body fat percentage (%)
Lean body weight (kg)
Trunk muscle mass (kg)
Upper limb muscle mass (kg)
Lower limb muscle mass (kg)
Grip strength (kg)
Six-minute walking test (m)
50-59
60-69
70-79
80≦
Non-frailty
Pre-frailty
Frailty

Supporting Figure 1: Flow chart and patients in this study.



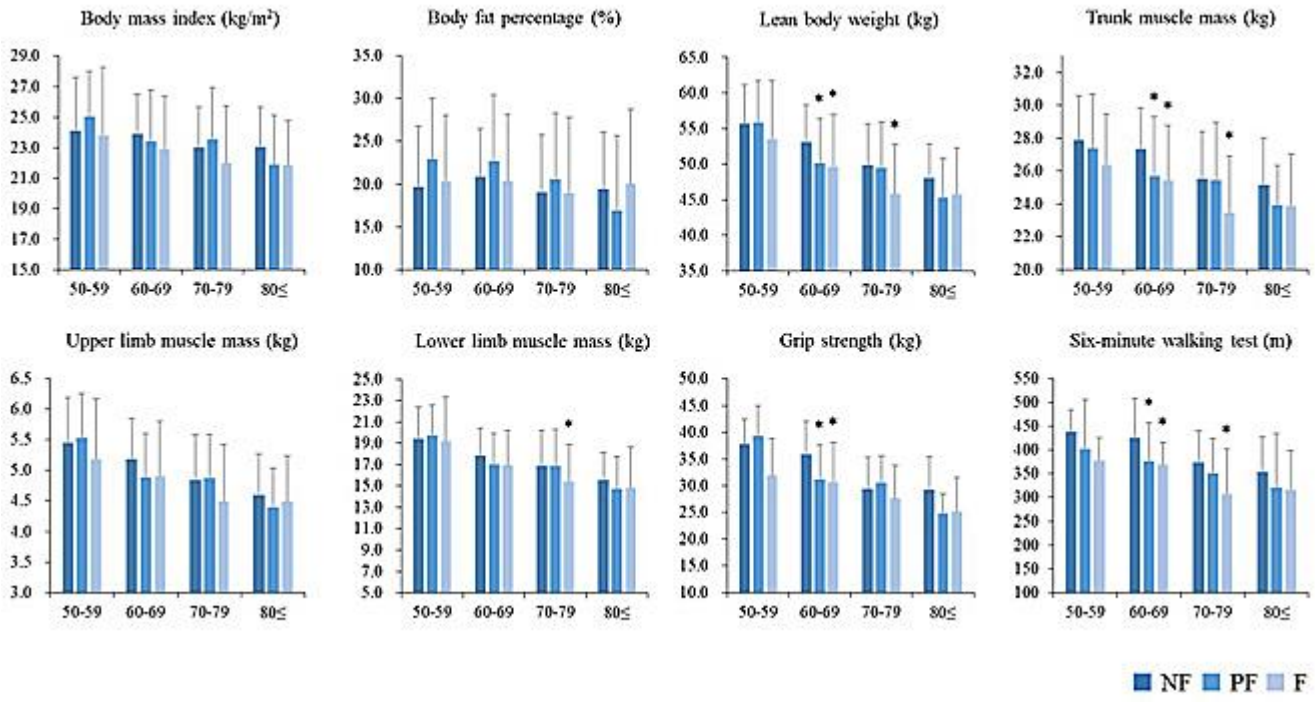
CR, cardiac rehabilitation; KCL, kihon check list

Supporting Figure 2: Correlation of KCL scores and peak VO_2.



KCL, kihon check list

Supporting figure3



Supporting figure4

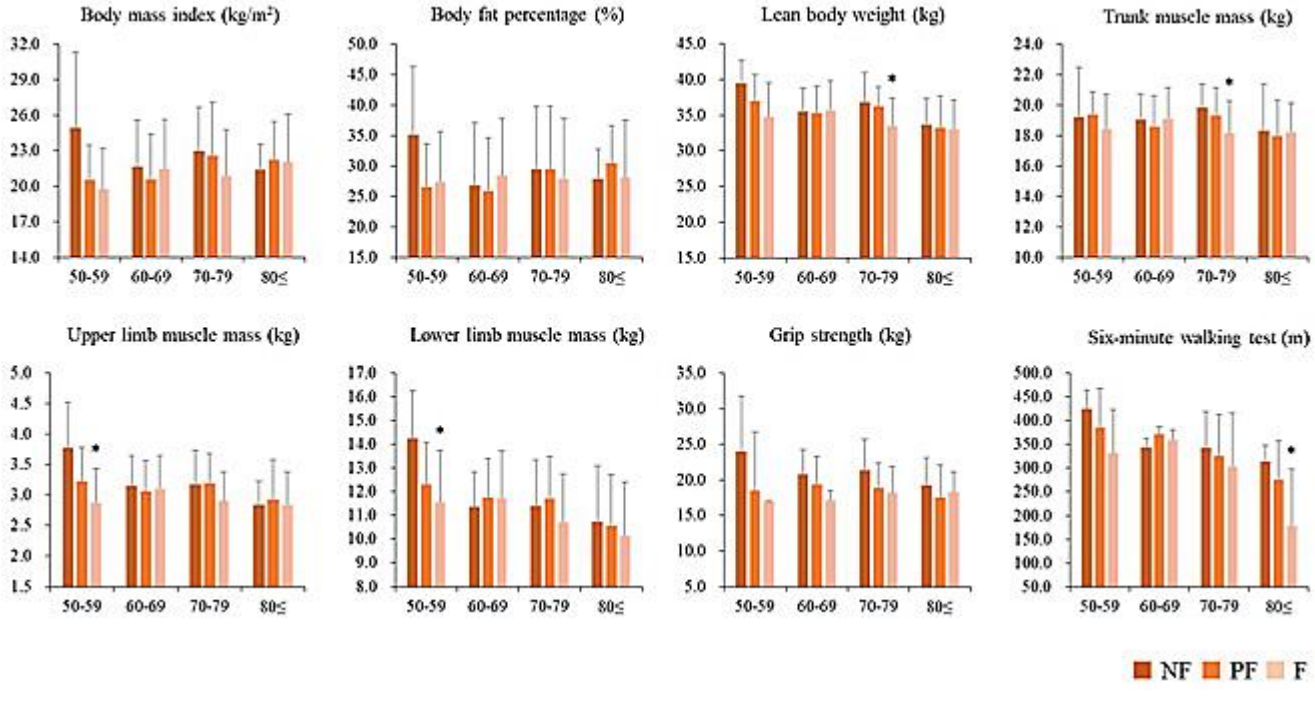


Table 1: Clinical characteristics of the study subjects.

	Non-frailty (n=287)	Pre-frailty (n=270)	Frailty (n=288)	*P* value
Age (year)	67.8 ± 9.2	70.9 ± 9.3*	73.0 ± 8.5**	<0.01
Male (%)	233 (81.2)	185 (68.5)	167 (58.0)	<0.01
BMI (kg/m^2)	23.4 ± 3.2	23.0 ± 3.7	21.9 ± 3.8*	<0.01
Hypertension (%)	190 (66.2)	169 (62.6)	183 (63.2)	0.63
Diabetes mellitus (%)	86 (30.0)	99 (36.7)	107 (37.2)	0.13
Dyslipidemia (%)	152 (53.0)	141 (52.2)	128 (44.6)	0.08
Chronic kidney disease (%)	80 (27.9)	99 (36.7)	138 (48.1)	<0.01
Current smoker (%)	33 (11.5)	18 (6.7)	24 (8.3)	0.07
COPD (%)	13 (4.6)	18 (6.7)	29 (10.1)	0.03
Past history of CVD				
History of MI (%)	29 (10.1)	39 (14.4)	31 (10.8)	0.23
History of PCI (%)	41 (14.3)	56 (20.7)	44 (15.3)	0.09
History of CABG (%)	12 (4.2)	17 (6.3)	24 (8.3)	0.12
History of valvular surgery (%)	13 (4.5)	20 (7.4)	25 (8.7)	0.13
History of CHF (%)	42 (14.6)	66 (24.4)	96 (33.3)	<0.01
CVD at the beginning of CR				
Acute myocardial infarction (%)	34 (11.9)	17 (6.3)	12 (4.2)	<0.01

Effort angina pectoris (%)	52 (18.1)	49 (18.2)	41 (14.2)	0.35
PCI (%)	48 (16.7)	28 (10.4)	13 (4.5)	<0.01
CABG (%)	78 (27.2)	74 (27.4)	86 (29.9)	0.73
Valvular disease (%)	104 (36.2)	118 (43.7)	156 (54.2)	<0.01
Valvular surgery (%)	89 (31.0)	89 (33.1)	106 (36.8)	0.33
Aortic disease (%)	34 (11.9)	31 (11.5)	30 (10.5)	0.86
Peripheral artery disease (%)	10 (3.5)	11 (4.1)	16 (5.6)	0.45
Atrial fibrillation (%)	36 (12.5)	54 (20.1)	76 (26.4)	<0.01

Data are presented as the mean value ±SD. BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CHF, congestive heart failure; CR, cardiac rehabilitation.

* P <0.05 vs Non-frailty, ** P <0.01 vs Non-frailty by Tukey's honest significant difference test.

Table 2: Comparison of clinical parameters, anthropometric parameters, grip strength, six-minute walking test and medication.

	Non-frailty (n=287)	Pre-frailty (n=270)	Frailty (n=288)	*P* value
Laboratory data				
Hemoglobin (g/dL)	13.4 ± 1.8	12.8 ± 1.9**	12.3 ± 1.7**	<0.01
Albumin (g/dL)	3.9 ± 0.4	3.8 ± 0.4**	3.7 ± 0.5**	<0.01
HbA1c (%)	6.0 ± 0.8	6.1 ± 0.9	6.0 ± 0.8	0.09
LDL-C (mg/dL)	99 ± 29	100 ± 31	96 ± 30	0.36
HDL-C (mg/dL)	50 ± 16	47 ± 14	50 ± 16	0.09
TG (mg/dL)	121 ± 76	114 ± 67	105 ± 51**	0.01
Creatinine (mg/dL)	0.97 ± 0.96	1.09 ± 1.15	1.39 ± 1.83**	<0.01
eGFR (mL/min/1.73 m^2)	70.6 ± 22.4	65.2 ± 23.7*	61.5 ± 29.6**	<0.01
BNP (pg/nL)	154.6 ± 281.0	231.3 ± 370.8	313.6 ± 614.0**	<0.01
GNRI	102.9 ± 9.8	100.5 ± 9.9*	96.9 ± 11.2**	<0.01
Echocardiography data				
LVEF (%)	59 ± 12	58 ± 14	58 ± 14	0.46
E/A	1.3 ± 0.8	1.4 ± 0.9	1.3 ± 0.9	0.46
E/e'	13.1 ± 7.4	16.1 ± 9.9**	17.8 ± 10.6**	<0.01
Anthropometric parameters and Physical function				

Body fat percentage (%)	21.6 ± 8.0	23.3 ± 9.1	23.3 ± 9.7	0.04
Lean body weight (kg)	49.4 ± 8.4	45.7 ± 9.1**	41.8 ± 9.3**	<0.01
Trunk muscle mass (kg)	25.4 ± 4.0	23.5 ± 4.4**	21.8 ± 4.2**	<0.01
Upper Limb muscle mass (kg)	4.8 ± 1.0	4.4 ± 1.1**	3.9 ± 1.2**	<0.01
Lower Limb muscle mass (kg)	16.7 ± 3.8	15.4 ± 4.0**	13.9 ± 4.1**	<0.01
Grip strength (kg)	31.4 ± 8.0	27.2 ± 8.3**	24.5 ± 7.8**	<0.01
Six-minute walking test (m)	392 ± 78	354 ± 88**	316 ± 101**	<0.01
Medication				
Aspirin (%)	245 (85.7)	215(79.9)	223 (77.7)	0.04
ACE-I/ARB (%)	95 (33.2)	93 (34.6)	90 (31.3)	0.70
Ca antagonist (%)	54 (18.9)	55 (20.5)	67 (23.3)	0.42
β blocker (%)	209 (73.1)	198 (73.6)	220 (76.4)	0.62
Loop diutretics (%)	195 (68.4)	208 (77.3)	226 (78.5)	<0.01
Statin (%)	173 (60.5)	156 (58.0)	137 (47.6)	<0.01
Oral hypoglycemic agent (%)	40 (14.0)	51 (19.0)	55 (19.1)	0.18
Insulin (%)	15 (5.2)	22 (8.2)	25 (8.7)	0.14

Data are presented as the mean value ±SD. HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; eGFR, estimate glomerular filtration rate; BNP, B-type natriuretic peptide; GNRI, geriatric nutritional risk index; LV, left ventricular; EF, ejection fraction; E, early diastolic filling velocity; A, late diastolic filling velocity; e', early diastolic tissue velocity; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

* P <0.05 vs Non-frailty, ** P <0.01 vs Non-frailty by Tukey's honest significant difference test.

Table 3: Comparison of exercise tolerance.

	Non-frailty (n=153)	Pre-frailty (n=89)	Frailty (n=60)	*P* value
Anaerobic threshold (AT)				
Workload (w)	48 ± 16	41 ± 12**	39 ± 11**	<0.01
AT (mL/kg/min)	11.5 ± 2.3	11.1 ± 2.3	10.3 ± 2.3**	<0.01
%AT	78 ± 15	75 ± 14	71 ± 16*	0.02
Peak exercise				
HR (/min)	115 ± 18	111 ± 20	105 ± 21**	<0.01
SBP (mmHg)	184 ± 28	173 ± 35*	165 ± 28**	<0.01
DBP (mmHg)	88 ± 17	83 ± 14*	82 ± 17*	<0.01
RER	1.11 ± 0.10	1.13 ± 0.12	1.13 ± 0.12	0.29
Workload (watt)	86 ± 21	75 ± 17**	69 ± 17**	<0.01
Peak VO_2 (mL/kg/min)	17.2 ± 3.6	16.0 ± 3.4*	14.4 ± 3.5**	<0.01
% Peak VO_2	71 ± 14	69 ± 15	63 ± 16**	<0.01
VE/VCO_2	30.5 ± 6.3	31.8 ± 7.0	33.5 ± 8.4*	0.02

Data are presented as the mean value ±SD. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; RER, respiratory exchange ratio; peak VO2, peak oxygen uptake.

* P <0.05 vs Non-frailty, ** P <0.01 vs Non-frailty by Tukey's honest significant difference test.

Table 4: Multiple regression analysis for peak VO_2.

Independent variables	β	t	*P* value
Body fat percentage (%)	−0.38	−5.61	<.0001
Grip strength (kg)	0.25	3.17	0.0017
eGFR (mL/min/1.73 m^2)	0.19	3.11	0.0021
KCLscore	−0.17	−2.77	0.0061
Gender (Male)	−0.14	−1.74	0.0837

eGFR; estimate glomerular filtration rate, KCL; kihon check list.

Explanatory variables; age, gender, KCL score, ejection fraction, chronic obstructive pulmonary disease, grip strength, lean body weight, trunk muscle mass, upper/lower limb muscle mass, body mass index, body fat percentage, hemoglobin, albumin, eGFR, B-type natriuretic peptide.

Supporting Table 1: Comparison of anthropometric parameters and physical function by gender.

Male	Non-frailty (n=233)	Pre-frailty (n=185)	Frailty (n=167)	*P* value
Body fat percentage (%)	19.9 ± 6.4	20.9 ± 8.0	19.8 ± 8.3	0.26
Lean body weight (kg)	52.3 ± 6.0	50.2 ± 6.9**	47.8 ± 7.5**	<0.01
Trunk muscle mass (kg)	26.7 ± 2.9	25.7 ± 3.5**	24.5 ± 3.4**	<0.01
Upper Limb muscle mass (kg)	5.1 ± 0.8	4.9 ± 0.8	4.7 ± 0.9**	<0.01
Lower Limb muscle mass (kg)	17.8 ± 3.1	17.2 ± 3.4	16.2 ± 3.7**	<0.01
Grip strength (kg)	33.7 ± 6.7	31.0 ± 6.7*	28.7 ± 7.0**	<0.01
Six-minute walking test (m)	404 ± 75	362 ± 90**	337 ± 80**	<0.01
Female	**Non-frailty (n=54)**	**Pre-frailty (n=85)**	**Frailty (n=121)**	***P* value**
Body fat percentage (%)	29.4 ± 9.7	28.5 ± 9.1	28.0 ± 9.4	0.67
Lean body weight (kg)	36.3 ± 4.0	35.5 ± 3.6	33.9 ± 4.1**	<0.01
Trunk muscle mass (kg)	19.2 ± 2.2	18.9 ± 2.0	18.3 ± 2.1*	0.03
Upper Limb muscle mass (kg)	3.2 ± 0.6	3.1 ± 0.5	2.9 ± 0.5**	<0.01
Lower Limb muscle mass (kg)	11.7 ± 2.2	11.6 ± 1.8	10.8 ± 2.1*	0.01
Grip strength (kg)	20.9 ± 4.1	18.7 ± 4.1	18.0 ± 3.2**	<0.01
Six-minute walking test (m)	345 ± 72	338 ± 83	289 ± 119*	<0.01

Data are presented as the mean value ±SD.

* P <0.05 vs Non-frailty, ** P <0.01 vs Non-frailty by Tukey's honest significant difference test.

Supporting Table 2: Clinical characteristics of the patients who underwent CPX.

	Non-frailty (n=153)	Pre-frailty (n=89)	Frailty (n=60)	*P* value
Age (year)	65.9 ± 8.5	68.5 ± 9.5	69.8 ± 9.4*	< 0.01
Male (%)	128 (83.7)	69 (77.5)	41 (68.3)	< 0.05
BMI (kg/m^2)	23.5 ± 3.0	23.5 ± 3.3	22.9 ± 3.4	0.40
Hypertension (%)	100 (65.4)	52 (58.4)	39 (65.0)	0.53
Diabetes mellitus (%)	50 (32.7)	27 (30.3)	26 (43.3)	0.23
Dyslipidemia (%)	80 (52.3)	50 (56.2)	39 (65.0)	0.24
Chronic kidney disease (%)	32 (20.9)	20 (22.5)	20 (33.9)	0.12
Current smoker (%)	19 (12.4)	10 (11.2)	5 (8.3)	0.72
COPD (%)	5 (3.3)	5 (5.6)	9 (15.0)	< 0.01
Past history of CVD				
History of MI (%)	14 (9.2)	12 (13.5)	6 (10)	0.56
History of PCI (%)	24 (15.7)	21 (23.6)	14 (23.3)	0.23
History of CABG (%)	6 (3.9)	3 (3.4)	4 (6.7)	0.59
History of valvular surgery (%)	6 (3.9)	6 (6.8)	3 (5.0)	0.60
History of CHF (%)	18 (11.8)	15 (16.9)	16 (26.7)	0.03
CVD at the beginning of CR				
Acute myocardial infarction (%)	25 (16.3)	11 (12.4)	3 (5.0)	0.08

Effort angina pectoris (%)	24 (15.7)	19 (21.4)	11 (18.3)	0.53
PCI (%)	35 (22.9)	16 (19.1)	5 (8.3)	0.05
CABG (%)	32 (20.9)	21 (23.6)	19 (31.7)	0.25
Valvular disease (%)	53 (34.6)	32 (36.0)	26 (43.3)	0.48
Valvular surgery (%)	51 (33.3)	28 (31.8)	17 (28.3)	0.78
Aortic disease (%)	9 (5.9)	5 (5.6)	6 (10.0)	0.49
Peripheral artery disease (%)	7 (4.6)	3 (3.4)	1 (1.7)	0.58
Atrial fibrillation (%)	16 (10.5)	16 (18.2)	17 (28.3)	< 0.01

Data are presented as the mean value ±SD. BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CHF, congestive heart failure; CR, cardiac rehabilitation.

* P <0.05 vs Non-frailty, ** P <0.01 vs Non-frailty by Tukey's honest significant difference test.

Supporting Table 3: Comparison of clinical parameters and medication in the patients who underwent CPX.

	Non-frailty (n=153)	Pre-frailty (n=89)	Frailty (n=60)	*P* value
Laboratory data				
Hemoglobin (g/dL)	13.8 ± 1.6	13.3 ± 1.8*	12.9 ± 1.6**	< 0.01
Albumin (g/dL)	4.0 ± 0.4	3.9 ± 0.4*	3.9 ± 0.5	0.02
HbA1c (%)	6.0 ± 0.8	6.0 ± 0.7	6.2 ± 0.9	0.20
LDL-C (mg/dL)	99 ± 29	97 ± 28	101 ± 30	0.68
HDL-C (mg/dL)	51 ± 16	49 ± 16	47 ± 12	0.25
TG (mg/dL)	123 ± 69	126 ± 93	118 ± 60	0.80
Creatinine (mg/dL)	0.87±0.58	1.01+1.22	1.04±1.12	0.35
eGFR (mL/min/1.73 m^2)	74.2 ± 21.4	72.0 ± 23.2	68.0 ± 24.6	0.20
BNP (pg/nL)	118 ± 182	172 ± 249	225 ± 365*	0.02
GNRI	104 ± 9	101 ± 9	102 ± 10	0.12
Echocardiography data				
LVEF (%)	59 ± 12	58 ± 12	56 ± 16	0.27
E/A	1.3 ± 0.9	1.4 ± 0.9	1.4 ± 0.9	0.76
E/e'	12.2 ± 7.1	14.1 ± 7.1	16.2 ± 8.9**	< 0.01

Medication				
Aspirin (%)	136 (88.9)	72 (81.8)	44 (73.3)	0.02
ACE-I/ARB (%)	55 (36.0)	32 (36.4)	26 (43.3)	0.58
Ca antagonist (%)	22 (14.4)	14 (15.9)	15 (25.0)	0.16
β blocker (%)	114 (74.5)	62 (70.5)	45 (75.0)	0.75
Loop diutretics (%)	93 (60.8)	62 (70.5)	48 (80.0)	0.02
Statin (%)	97 (63.4)	57 (64.8)	42 (70.0)	0.65
Oral hypoglycemic agent (%)	22 (14.4)	13 (14.8)	14 (23.3)	0.29
Insulin (%)	7 (4.6)	3 (3.4)	6 (10.0)	0.28

Data are presented as the mean value ±SD. HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; eGFR, estimate glomerular filtration rate; BNP, B-type natriuretic peptide; GNRI, geriatric nutritional risk index; LV, left ventricular; EF, ejection fraction; E, early diastolic filling velocity; A, late diastolic filling velocity; e', early diastolic tissue velocity; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

* P <0.05 vs Non-frailty, ** P <0.01 vs Non-frailty by Tukey's honest significant difference test.

Supporting Table 4: Comparison of anthropometric parameters and physical function in the patients who underwent CPX by gender.

Male	Non-frailty (n=128)	Pre-frailty (n=69)	Frailty (n=41)	*P* value
Body fat percentage (%)	19.6 ± 6.0	22.3 ± 9.1*	21.3 ± 7.0	0.04
Lean body weight (kg)	52.7 ± 6.0	50.0 ± 6.4**	49.8 ± 6.3*	<0.01
Trunk muscle mass (kg)	27.2 ± 2.7	25.3 ± 3.3**	25.3 ± 2.7**	<0.01
Upper Limb muscle mass (kg)	5.1± 0.8	4.8 ± 0.7*	4.9 ± 0.8	0.04
Lower Limb muscle mass (kg)	17.8 ± 3.1	17.2 ± 3.0	17.0 ± 3.4	0.25
Grip strength (kg)	34.3 ± 6.6	31.7 ± 5.9	30.4 ± 6.3**	<0.01
Six-minute walking test (m)	412 ± 67	377 ± 67*	362 ± 64**	<0.01
Female	**Non-frailty (n=25)**	**Pre-frailty (n=20)**	**Frailty (n=19)**	***P* value**
Body fat percentage (%)	29.0 ± 9.1	29.3 ± 6.8	29.1 ± 7.2	0.99
Lean body weight (kg)	37.7 ± 3.5	36.9 ± 2.8	36.8 ± 4.0	0.60
Trunk muscle mass (kg)	19.8 ± 1.7	19.4 ± 1.3	19.6 ± 1.7	0.74
Upper Limb muscle mass (kg)	3.3 ± 0.5	3.2 ± 0.4	3.2 ± 0.5	0.62
Lower Limb muscle mass (kg)	12.5 ± 1.7	12.2 ± 1.8	11.9 ± 2.3	0.62
Grip strength (kg)	21.9 ± 3.1	20.4 ± 4.1	20.0 ± 3.5	0.29
Six-minute walking test (m)	376 ± 72	381 ± 60	357 ± 74	0.59

Data are presented as the mean value ±SD.

* P <0.05 vs Non-frailty, ** P <0.01 vs Non-frailty by Tukey's honest significant difference test.