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ORIGINAL RESEARCH PAPER

Sarcopenia and physical activity in older male cardiac patients

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26 Work was performed in the Department of Rehabilitation Medicine, St. Marianna University

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28

29 **Running title:** Physical Activity and Sarcopenia in the Elderly

30

31 **Abbreviations:** ANCOVA = one-way analysis of covariance, AUC = area under the curve, BMI

32 = body mass index, CABG = coronary artery bypass graft surgery, CI = confidence interval, GS =

33 gait speed, HS = handgrip strength, LVEF = left ventricular ejection fraction, MACE = major

34 adverse cardiac events, PA = physical activity, ROC = receiver-operating characteristic, SD =

35 standard deviation, SMI = skeletal muscle index.

36 **ABSTRACT**

37 Background: There are few information of the relation between sarcopenia and physical activity
38 in elderly cardiac patients. The purpose of this study was to determine the differences in physical
39 activity and cutoff values for physical activity according to the presence or absence of sarcopenia
40 in elderly male cardiac patients. Methods and Results: We registered 67 consecutive male
41 patients aged ≥ 65 years with cardiac disease in the present study. The patients were divided into
42 two groups: the sarcopenia group ($n = 25$) and non-sarcopenia group ($n = 42$). In the patients with
43 and without sarcopenia of physical activities were evaluated to determine cutoff values of
44 physical activity. After adjusted for patient characteristics, both the average daily number of steps
45 (3361.43 ± 793.23 vs. 5991.55 ± 583.57 steps, $P = 0.021$) and the average daily energy
46 expenditure of physical activity (71.84 ± 22.19 vs. 154.57 ± 16.18 kcal, $P = 0.009$) were
47 significantly lower sarcopenia group than non-sarcopenia group. With receiver-operating
48 characteristic analysis of these patients with and without sarcopenia, we identified a cutoff value
49 for steps of physical activity of 3551.80 steps/day for 1 week. The receiver-operating
50 characteristic analysis also identified a cutoff value for energy expenditure of physical activity of
51 85.17 kcal/day for 1 week. Conclusions: Compared with male cardiac patients without sarcopenia,
52 physical activity in those with sarcopenia were significantly lower. The cutoff values reported
53 here may be one of the useful values for identifying elderly male cardiac patients with sarcopenia.

1. Introduction

Physical activity (PA) among cardiac patients with myocardial infarction, coronary artery bypass graft surgery (CABG), and heart failure is associated with health-related quality of life, mortality, major adverse cardiac events (MACE), and length of hospital stay [1-5]. The effects of PA on the prognosis of patients with CABG were found to be an important predictor of MACE and length of hospital stay [3,5]. Our earlier studies also determined that daily step count of PA objectively measured by accelerometer may be a prognostic indicator of mortality in heart failure patients [4,5].

Sarcopenia is defined as the loss of skeletal muscle mass and strength that occurs with advancing age and is related to physical function, activities of daily living, and mortality in elderly people [6,7]. It would be of great interest to know the prevalence of sarcopenia and the relation between sarcopenia and PA status in cardiac patients because sarcopenia in cardiac patients has not been well studied. We hypothesized that sarcopenia in cardiac patients is related to reduced PA. Therefore, the purposes of the present study were to evaluate the prevalence of sarcopenia and the relation between PA and sarcopenia in male cardiac patients, and to determine cutoff values of PA useful in the assessment of these patients.

2. Methods

2.1. Study design

In this cross sectional study, 241 consecutive patients with cardiac conditions such as myocardial infarction, CABG, valve replacement, and heart failure who visited the St. Marianna University School of Medicine Hospital as outpatients were selected for evaluation of handgrip strength, gait speed, skeletal muscle index (SMI) [8], and PA as measured by accelerometer.

Inclusion criteria included age > 65 years old, male sex, and the ability to have both SMI and PA, as measured by accelerometer, evaluated. Patients with neurological, peripheral vascular, orthopedic, or pulmonary disease were excluded [9].

Clinical characteristics were evaluated by review of the patients' medical records and included age, body mass index (BMI), left ventricular ejection fraction (LVEF), hemoglobin, etiology, and medications [9]. A cardiologist assessed LVEF as the index of cardiac function by echocardiography in all patients [5].

The St. Marianna University School of Medicine Institutional Committee on Human Research approved this study, and informed consent was obtained from each patient.

2.2. Evaluation of sarcopenia

A multifrequency bioelectrical impedance machine (Muscle- α , Art Haven 9 Co., Kyoto, Japan) was used to estimate muscle mass [8]. This method of determining body composition is

safe, portable, highly reliable, and relatively inexpensive [10]. In the present study, muscle volume and bioelectrical impedance values of the forearm, upper arm, lower leg, and thigh were measured based on previously reported methods [10]. The SMI was calculated as follows: $SMI = \text{lean muscle mass} / \text{height}^2$ [6].

To measure maximum gait speed, the 10-m gait test was performed on flat ground along a 10-m line at a gymnasium. Each patient was asked to walk on the 10-m line as quickly as possible [5,11]. Using a stopwatch, a physiotherapist measured the time required for each patient to walk the 10-m distance over three attempts [5]. Afterwards, gait speed was calculated as $10 \text{ m} / \text{time required in sec}$, with the highest value measured considered as the gait speed in m/sec [8].

Handgrip strength was measured in all subjects with a standard adjustable-handle JAMAR dynamometer (Bissell Healthcare Co., Grand Rapids, MI) set at the second grip position [8,11].

Three measurements were made on each hand, with attention paid to a possible Valsalva effect.

The average of the highest value of the right- plus left-side handgrip strength / 2 (kgf) was calculated, with the highest value measured considered as the index of handgrip strength [8,11].

These values were measured during outpatient visits to the hospital. Sarcopenia was then defined using the measured values of gait speed, handgrip strength, and SMI based on the algorithm of the European Working Group on Sarcopenia in Older People (EWGSOP) [7]. The patients were accordingly divided into two groups: the sarcopenia group and non-sarcopenia group [8].

2.3. Physical activity

We used averages of daily number of steps taken and daily energy expenditure for 1 week as the indices of PA [12]. These indices were measured with the Kenz Lifecorder EX 1-axial accelerometer (Kenz Lifecorder, Suzuken Co., Ltd., Nagoya, Japan), which provides reliable and validated output data [13,14] and stores 100 Kb of data, enough for 200 days of continuous use. All subjects wore the accelerometer on a belt at waist level just above either leg [4,15]. The number of steps taken and energy expenditure are recorded by the accelerometer on the basis of pre-entered data of age, sex, height, and weight [12]. The patients wore the accelerometer continuously for 8 days. Thereafter, the device was retrieved, and the recorded data were downloaded into a computer with Microsoft Excel software [12]. Daily energy expenditure on PA is calculated and counted by the accelerometer every 4 sec, using body weight (W) and a factor Ka (exercise index), which depends upon the exercise intensity level: daily energy expenditure (kcal) = $Ka \text{ (kcal/kg/4 sec)} \times W \text{ (kg)}$ [12,16]. However, the value of factor Ka cannot be provided here because it is confidential and proprietary information of the manufacturer [12,16]. We used the final 7 days of continuous data from the 8-day collection period for assessment of the patient's usual daily PA [12]. The average of daily number of steps taken over 1 week was calculated as total step count over 7 days / 7, and the average of daily energy expenditure as kcal

expended over 7 days / 7 [4,12].

2.4 Statistical analysis

Results are expressed as mean $\pm$ standard error (SE). Parametric and chi-square tests were then used to analyze differences between the two groups [17]. The unpaired *t*-test was used to test for differences in clinical characteristics between the two groups. To compare PA values between the two groups, one-way analysis of covariance (ANCOVA) was performed with the variables as covariates if there were any differences in clinical characteristics. Choice of covariates was guided by chi-square analyses and *t*-tests, which indicated significant differences between the two groups in the values of the clinical characteristics [17].

Finally, a receiver-operating characteristic (ROC) curve [18,19] was constructed by plotting the true-positive rates (sensitivity) against false-positive rates (1-specificity) following calculation of the sensitivity of PA values for patients with and without sarcopenia to determine the best cutoff value [17]. The area under the curve (AUC) was also calculated and is shown with 95% confidence interval (CI). A *P* value of < 0.05 was considered significant. Statistical analyses were performed with IBM SPSS 17.0 J statistical software (IBM SPSS Japan, Inc., Tokyo, Japan) [8].

3. Results

Of the 241 potential subjects, 81 met the inclusion criteria; however, 14 of these patients were excluded because the data necessary to evaluate their characteristics, i.e., LVEF, hemoglobin, etiology, medications, handgrip strength, gait speed, SMI, and/or PA were incomplete. Thus, 67 patients were included for analysis on the basis of the inclusion criteria and available data. These 67 patients were divided into two groups based on their sarcopenia status: the sarcopenia group ($n = 25$) and non-sarcopenia group ($n = 42$). With the exception of BMI, hemoglobin, and statin medication taken, the patient characteristics were similar between the two groups (Table 1).

Differences in handgrip strength, gait speed, and SMI between the sarcopenia and non-sarcopenia groups are shown in Table 2. Before adjustment for BMI and hemoglobin level, the average daily number of steps in the sarcopenia group was significantly lower than that in the non-sarcopenia group (3638.28 ± 404.12 vs. 5822.46 ± 598.46 steps; $t = 2.58$, $P = 0.013$). The average daily energy expenditure of PA in the sarcopenia group was also significantly lower than that in the non-sarcopenia group (73.84 ± 13.37 vs. 152.13 ± 17.64 kcal; $t = 3.65$, $P = 0.001$). After adjustment for these two factors, the average daily number of steps in the sarcopenia group remained significantly lower than that in the non-sarcopenia group (3361.43 ± 793.23 steps; 95% CI, 1764.72–4958.14 vs. 5991.55 ± 583.57 steps; 95% CI, 4816.89–7166.22; $F = 5.75$, $P =$

0.021). The average daily energy expenditure of PA in the sarcopenia group also was significantly lower than that in the non-sarcopenia group (71.84 ± 22.19 kcal; 95% CI, 27.11–116.56 vs. 154.57 ± 16.18 kcal; 95% CI, 121.94–187.19; $F = 7.42$, $P = 0.009$) (Figure 1).

Sensitivities of each cutoff value for both average daily number of steps and daily energy expenditure of PA and were used to construct ROC curves (Figure 2). With ROC analysis of patients with and without sarcopenia, we identified a cutoff value for steps of PA of 3551.80 steps/day for 1 week, with a sensitivity of 0.73 and 1-specificity of 0.44. The AUC value was 0.70 (95% CI, 0.543-0.857; $P = 0.02$). The ROC analysis also identified a cutoff value for energy expenditure of PA of 85.17 kcal/day for 1 week, with a sensitivity of 0.73 and 1-specificity of 0.27. The AUC value was 0.77 (95% CI, 0.636-0.913; $P = 0.002$) in the elderly male cardiac patients.

4. Discussion

To our knowledge, this is the first time to report a difference in the amount of PA performed, which appeared to be related to sarcopenia in the present study's patients. The results suggested that cardiac patients with sarcopenia might have a reduced level of PA when evaluated by average number of steps taken and energy expended on PA for 1 week.

Yamada et al. [20] previously reported that the prevalences of sarcopenia, as determined by the algorithm suggested by the EWGSOP, in community-dwelling older Japanese men and women aged 65 to 89 years were 21.8% and 22.1%, respectively. The prevalence of sarcopenia in the elderly male cardiac patients in the present study (37.3%) was higher than that reported by Yamada et al. [20]. However, as characteristics in their study of the subjects differed from those in the present study, the comparison of the present study with that of Yamada et al. [20] should be done with caution.

Handgrip strength, gait speed, and SMI in the sarcopenia group were all significantly lower than those in the non-sarcopenia group in the present study (Table 2). Because these values were used for the evaluation of sarcopenia based on the EWGSOP algorithm, they were not surprising findings, and they supported the criteria of sarcopenia used in the present study.

After adjustment for BMI and hemoglobin level, the average daily number of steps and energy expenditure of PA in the sarcopenia group were both significantly lower than those values in the non-sarcopenia group (Figure 1). Therefore, sarcopenia might have some influence on reducing both the step count and energy expended on PA by elderly male cardiac patients.

Hemoglobin levels in the elderly cardiac patients with sarcopenia in the present study were lower than those without sarcopenia. Aging, which is associated with an increased incidence and prevalence of both cancer and anemia [21]. However, a consensus statement was recently

proposed to diagnose cachexia in chronic diseases when there is weight loss exceeding 5% within the previous 3-12 months combined with symptoms characteristic of cachexia (e.g., fatigue), loss of skeletal muscle, and biochemical abnormalities such as anemia or inflammation [22]. Thus, the finding of the present study might favorably support the negative effect of reduced hemoglobin in relation to sarcopenia in elderly male cardiac patients. Hemoglobin levels might be of greater influence in cardiac patients with sarcopenia compare to those without sarcopenia.

Lynch et al. [23] recently suggested an association between statin medication use and improved outcomes during inpatient rehabilitation in 3422 elderly patients (mean age, 81.4 years) with etiologies of stroke, fractured femur neck, or general medical and surgical illnesses. They reported that improvement in the 20-point Barthel scores between admission and discharge was greater in the statin use than non-statin use group after adjustment for age, sex, baseline Barthel score, and comorbid disease. In the present study, the ratio of patients taking a statin medication was significantly lower in the sarcopenia group than in the non-sarcopenia group (Table 1). There are many differences between the findings of the Lynch et al. study and our study (e.g., in the use of inpatients vs. outpatients, and different disease etiologies and levels of disease severity), and we could not determine any mechanism for the effect of protein synthesis by statins. Statin users may experience beneficial effects on handgrip strength, gait speed, SMI, or PA. However, we did not evaluate improvements in inflammation or vascular health, or a reduction in events such as

MACE in the present study. Thus, these factors need to be evaluated in a future study.

We identified cutoff values by ROC curve analysis of 3551.8 steps and 85.1 kcal for energy expenditure of PA in the elderly male cardiac patients (Figure 1). These AUC values fall within the range of values of 0.7-0.9, which indicate the cutoff values were able to distinguish those with and without sarcopenia with moderate accuracy among older men with cardiac diseases.

The indices of PA measured in the present study are easy to evaluate and easy for patients to understand and may be practical for predicting cardiac-related mortality in cardiac patients [1,4]. Step count values reported in previous studies of patients with heart failure ranged from 3571.4 to 4889.4 steps/day [1,4]. The step count value of 3551.8 steps/day in the present patients was similar to but lower than these values. Thus, the cutoff value for step count in elderly cardiac patients with sarcopenia may be less than the value measured in cardiac patients with heart failure.

Ayabe et al. [24] suggested that to achieve the total amount of energy expenditure for PA generally recommended for the secondary prevention of cardiovascular disease, patients should be encouraged to accumulate 6500-8500 steps/day (200-300 kcal/day). PA of the subjects in the present study was considerably lower than that recommended by this previous study. The present study is not designed to address whether cardiac diseases is independently associated with reduced physical activity but future studies are required to clarify this association. This study

revealed that when comparing elderly male cardiac patients with and without sarcopenia, average daily step count and energy expenditure of PA, which so far have not been used as diagnostic criteria for sarcopenia, were clearly decreased in the patients with sarcopenia.

Limitations in this cross-sectional study include its very small sample size and inclusion of only male subjects; therefore, sex-related differences could not be evaluated. We did not evaluate cause and effect relationships between PA threshold and sarcopenia status. In addition, cardiac diseases may limit PA independent of sarcopenia, so future studies are required to evaluate this relationship further. We used a multifrequency bioelectrical impedance machine to evaluate sarcopenia. However, some patients with heart failure were included, and the fluid balance in heart failure may affect measurements made by this machine. The effect of fluid balance on the SMI remains unclear in the present study. Although not cardiac patients, in elderly patients with end-stage renal disease, sarcopenia is closely associated with such factors as inflammatory markers, depression, and cognitive dysfunction [8,25]. We did not evaluate biomarkers of inflammatory reaction such as C-reactive protein; biochemical measurements such as those of insulin-like growth factor, dehydroepiandrosterone sulfate, and 25-hydroxy vitamin D [8,26,27]; nutritional status [11] and depression; severity of cardiac disease; and cognitive dysfunction. These factors might be related in cardiac patients with sarcopenia [8]. Future studies in longitudinal settings performed for longer periods will be needed to evaluate the effect of the

252 improvement of sarcopenia by increasing the PA of these patients, and long-term follow-up
253 evaluation will also be required.

254

255 **5. Conclusion**

256 Compared with male cardiac patients without sarcopenia, the average number of daily steps
257 taken and the energy expenditure of PA over 1 week of physical activity in those with sarcopenia
258 were significantly lower. The cutoff values reported here may be one of the useful values for
259 identifying elderly male cardiac patients with sarcopenia.

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Figure Legends

Fig. 1. After adjustment for body mass index and hemoglobin level, both the average daily number of steps taken and the average daily energy expenditure of physical activity in the sarcopenia group were significantly lower than those in the non-sarcopenia group.

Fig. 2. Sensitivities of the cutoff value for both average daily number of steps and daily energy expenditure of physical activity were used to construct ROC curves. With ROC analysis of patients with and without sarcopenia, we identified a cutoff value for steps taken of 3551.80 steps/day for 1 week, with a sensitivity of 0.73 and 1-specificity of 0.44. The cutoff value identified for energy expenditure of physical activity was 85.17 kcal/day for 1 week, with a sensitivity of 0.73 and 1-specificity of 0.27.

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358

359 **Conflicts of interest:** All authors declare no conflicts of interest in relation to the work reported
360 in this manuscript.

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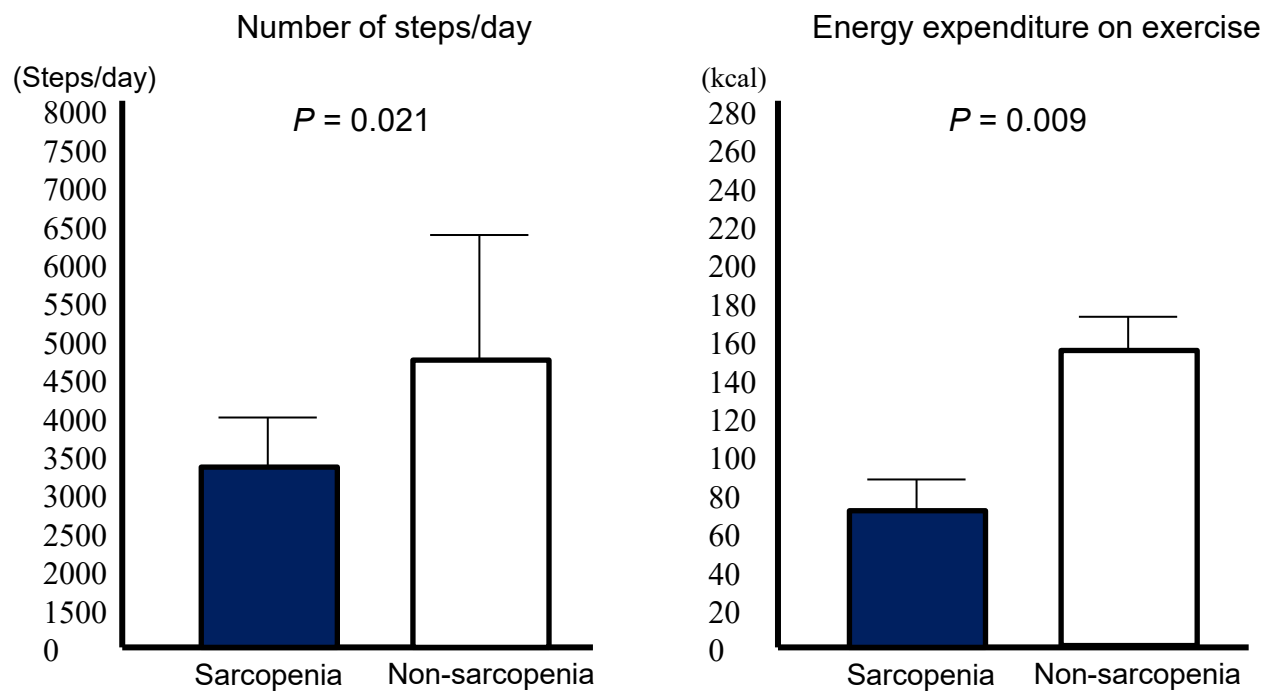


Fig. 1

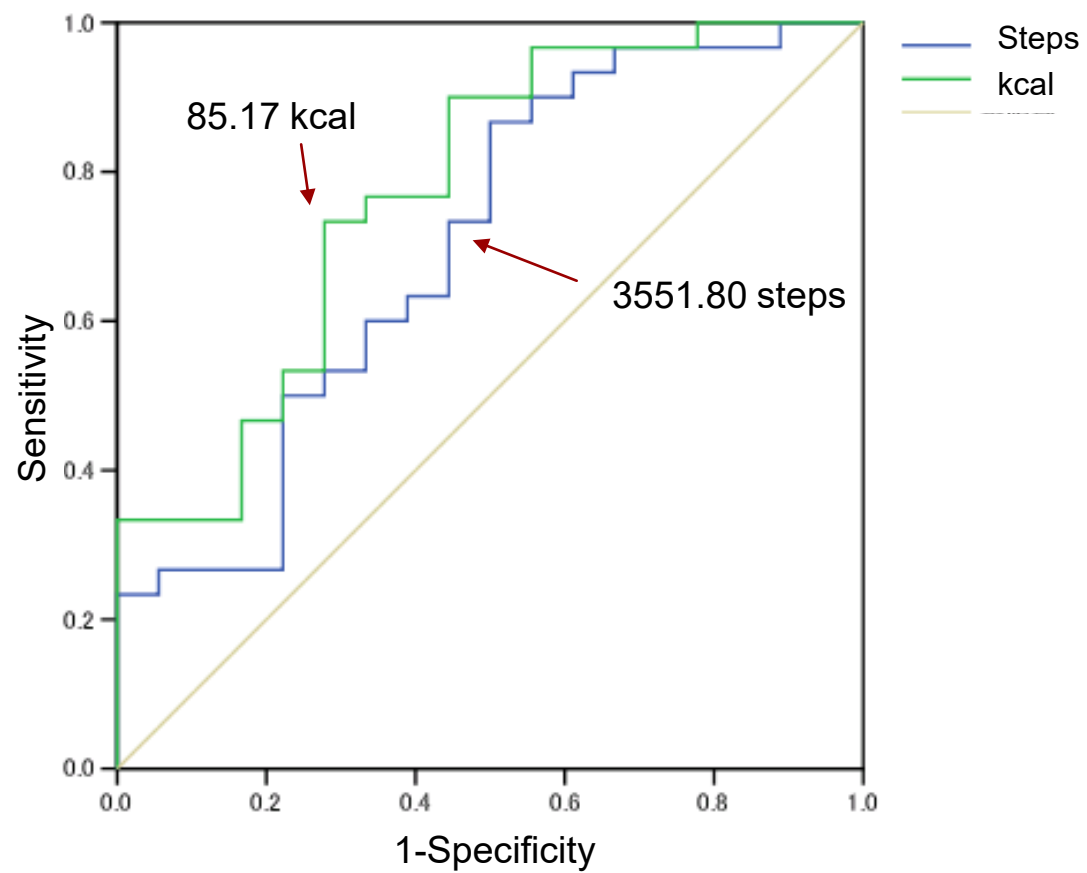


Fig. 2

Table 1 Patient characteristics, LVEF, hemoglobin, etiology, and medications

	Sarcopenia group <i>n</i> = 25	Non-sarcopenia group <i>n</i> = 42	<i>t</i> , χ^2 values	<i>P</i> value
Age (yrs)	70.44 ± 0.92	71.08 ± 0.70	-0.54	0.58
BMI (kg/m ²)	20.45 ± 0.40	24.02 ± 0.33	-6.77	<0.001
LVEF (%)	49.41 ± 3.27	51.37 ± 1.18	-0.52	0.60
Hemoglobin (mg/dl)	11.73 ± 0.29	12.70 ± 0.23	-2.56	0.01
Etiology				
Heart failure (%)	36.00	25.64	0.83*	0.66
Myocardial infarction (%)	56.00	66.67	-	-
CABG/VR (%)	8.00	7.69	-	-
Medications				
Beta-blockers (%)	80.00	74.35	0.27*	0.60
ARB (%)	12.00	25.64	1.75*	0.18
ACEI (%)	60.00	58.97	0.007*	0.93
Statin (%)	44.00	79.48	8.50*	0.004
Diuretic (%)	44.00	38.46	0.19*	0.66

Values are mean ± standard error. * χ^2 value

BMI, body mass index; LVEF, left ventricular ejection fraction; CABG/VR, coronary artery bypass grafting/valve replacement; ARB, angiotensin receptor blocker; ACEI, angiotensin converting enzyme inhibitor.

Table 2 Handgrip strength, gait speed, and skeletal muscle index in the two groups

	Sarcopenia group (<i>n</i> = 25)	Non-sarcopenia group (<i>n</i> = 42)	<i>t</i> value	<i>P</i> value
Handgrip strength (kgf)	25.94 ± 1.49	33.90 ± 1.35	-4.02	<0.001
Gait speed (m/sec)	1.31 ± 0.04	1.57 ± 0.02	-3.32	0.001
Skeletal muscle index (kg/m ²)	6.33 ± 0.13	8.45 ± 0.13	-11.12	<0.001

Values are mean ± standard error.