学位論文

A simple sarcopenia screening test predicts future adverse events in patients with heart failure
（簡易サルコペニアスクリーニングテストは心不全患者の予後を予測する）

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A simple sarcopenia screening test predicts future adverse events in patients with heart failure

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ABSTRACT

Background: Progressive loss of skeletal muscle termed "sarcopenia" is an independent risk factor for mortality in patients with cardiovascular diseases. A simple screening test that can identify sarcopenia using three variables (age, grip strength and calf circumference) was recently developed. We evaluated the clinical utility of this screening test in patients with heart failure (HF).

Methods and results: HF patients were divided into the sarcopenia (n = 82) and non-sarcopenia (n = 37) groups based on the sarcopenia score. Circulating BNP and high-sensitive cardiac troponin T levels were significantly higher, and left ventricular ejection fraction was lower in the sarcopenia group than non-sarcopenia group. Kaplan–Meier curve showed that HF event-free survival rate was significantly lower in the sarcopenia group. Multivariate Cox proportional hazards analysis identified BNP (ln[BNP]) (hazard ratio [HR]: 1.58; 95% CI: 1.09–2.29, p = 0.02), hs-CRP (ln[CRP]) (HR: 1.82; 95% CI: 1.23–2.68; p < 0.01) and sarcopenia score (HR: 1.03; 95% CI: 1.01–1.05, p < 0.01) as independent predictors of HF events. In receiver operating characteristic analysis, adding the sarcopenia score to BNP levels increased an area under the curve for future HF events (sarcopenia score alone, 0.77; BNP alone, 0.82; combination, 0.89).

Conclusions: The sarcopenia screening test can be used to predict future adverse events in patients with HF.

1. Introduction

Reduced skeletal muscle mass and function is one of the main features of end-stage heart diseases. The prognostic importance of muscle wasting has been established in patients with chronic heart failure (HF) [1]. Especially, loss of the leg muscle mass has been shown to be an independent risk of heart disease and premature death [2]. Muscle strength is also reported to be an independent predictor of survival in patients with HF [3], and reduced handgrip strength is associated with increased mortality in these patients [4,5]. In HF patients, exercise designed to increase muscle mass and strength could have favorable effects [6–9], and this type of training is recommended as a complementary exercise modality for patient with cardiovascular disease [10].

The term "sarcopenia" was recently coined to progressive loss of skeletal muscle mass and strength associated with aging [11]. Sarcopenia could worsen in the presence of comorbidities such as HF, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD) and cancer [12]. Previous study showed that sarcopenia is associated with risk of adverse events, such as physical disability, poor quality of life and death [13]. In patients with HF, sarcopenia assessed by the fat-free mass index is associated with an unfavorable prognosis [14]. Accordingly, assessment of sarcopenia may be useful to risk stratification in patients with HF.

The European Working Group on Sarcopenia in Older People (EWGSOP) published a practical guideline for the diagnosis of sarcopenia [15]. The guideline recommends the use of computed tomography (CT scan), magnetic resonance imaging (MRI), and dual energy X-ray absorptiometry (DXA) to evaluate muscle mass. Although these modalities allow precise evaluation of muscle mass, they are not available for routine use in daily clinical practice setting. Recently, Ishii et al. [16] developed a simple screening test that can identify sarcopenia with high accuracy using three easily obtainable variables; age, grip strength and calf circumference. In the present study, we used this simple screening test of sarcopenia and assessed its clinical utility in patients with HF.

2. Methods

2.1. Study population

The study subjects were 119 consecutive patients, aged 65 years or older, hospitalized between March 2012 and April 2013 at Kumamoto

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University Hospital for treatment or diagnosis of HF. HF was defined as the typical symptoms (breathlessness, orthopnea, paroxysmal nocturnal dyspnea, fatigue, tiredness, etc) and signs (elevated jugular venous pressure, hepatojugular reflux, third heart sound, laterally displaced apical impulse, etc) evaluated by physical examination, echocardiography, electrocardiogram and chest X-ray [17]. The exclusion criteria included patients with acute coronary syndrome, malignant tumors, acute infection, chronic hemodialysis and inflammatory diseases.

2.2. Protocol

All participants underwent measurement of hand grip strength and calf circumference just before they discharged from the hospital. Hand grip strength was measured using a digital hand grip strength dynamometer (Takei Scientific Instruments, Niigata, Japan). After two measurements of grip strength of the dominant hand, the higher value of the two measurements was used for estimation of the sarcopenia score. Calf circumference was measured using a measuring tape at the maximum circumference of the non-dominant leg in sitting position with the leg bent 90° at the knee. The sarcopenia score was calculated using a score chart or calculation formula for estimated probability of sarcopenia advocated by Ishii et al. [16]. The calculation formula to the score are as following; in men, $0.62 \times (\text{age} - 64) - 3.09 \times (\text{grip strength} - 50) - 4.64 \times (\text{calf circumference} - 42)$; in women, $0.80 \times (\text{age} - 64) - 5.09 \times (\text{grip strength} - 34) - 3.28 \times (\text{calf circumference} - 42)$. In this study, we defined the presence of sarcopenia as a sarcopenia score ≥ 105 in men and ≥ 120 in women, based on the previous study [16].

Serum and plasma samples were withdrawn from resting participants at supine position and kept frozen at −80 °C until analysis. Plasma B-type natriuretic peptide (BNP) levels were measured using the MI02 Shionogi BNP kit (Shionogi, Osaka, Japan). Serum high-sensitive cardiac troponin T (hs-TnT) levels were measured using the Elecsys 2010 Troponin T hs kit (Roche Diagnostics, Indianapolis, IN). Estimated glomerular filtration rate (eGFR) was calculated using following equation according to recommendations of the Japanese Society of Nephrology; eGFR in male $= 194 \times (\text{Serum Creatinine})^{-1.094} \times (\text{Age})^{-0.287}$, eGFR in female $= 194 \times (\text{Serum Creatinine})^{-1.094} \times (\text{Age})^{-0.287} \times 0.739$.

Echocardiography was conducted in all participants using Aplio XG (Toshiba, Tokyo, Japan) or Vivid 7 (GEVingmed Ultrasound, Horton, Norway) ultrasound systems and the results were evaluated by two independent investigators who were blinded to all clinical data. LVEF was calculated by the modified Simpson method. Early (E) diastolic transmitral flow velocity was measured from mitral inflow velocities. Early diastolic mitral annular (e′) velocity was determined after pulsed wave tissue doppler imaging and E/e′ was calculated.

2.3. Follow up for mortality and cardiovascular events

After calculation of sarcopenia score, patients were followed in the outpatient clinic for a median of 495 days (interquartile range [IQR] 211 to 715 days). The endpoint of this study was HF events, included HF-related hospitalization and death due to HF. HF-events were identified by searching the medical records.

2.4. Statistical analysis

Continuous variables were expressed as mean ± SD, but BNP, hs-TnT and high sensitive C reactive protein (hs-CRP) showed skewed distribution and were therefore expressed as median (IQR) and log transformed before other analyses. Categorical variables were expressed as number (percentage). Continuous and categorical variables were compared using Mann–Whitney U-test and Fisher's exact test, respectively. We assessed the prognostic association using the Kaplan–Meier method, log-rank test, and simple and multiple Cox proportional hazards

Table 1
Clinical characteristics of the study participants.

	All patients (n = 119)	Sarcopenia group (n = 82)	Non-sarcopenia group (n = 37)	P-value
Age (years)	76.1 ± 6.2	77.6 ± 5.4	72.0 ± 5.9	<0.01
Male sex	73 (61%)	53(65%)	20 (54%)	0.28
Body mass index (kg/m^2)	23.2 ± 3.6	22.2 ± 3.2	25.5 ± 3.3	<0.01
Abdominal circumference (cm)	85.8 ± 9.8	83.3 ± 9.1	91.3 ± 9.0	<0.01
Hand grip strength (kg)	23.0 ± 8.3	19.9 ± 6.9	29.8 ± 7.0	<0.01
Calf circumference (cm)	30.8 ± 3.3	29.4 ± 2.6	34.0 ± 2.6	<0.01
Sarcopenia score	130.5 ± 36.9	133.5 ± 23.7	86.2 ± 16.1	<0.01
Hypertension	77 (65%)	55 (67%)	22 (59%)	0.27
Diabetes mellitus	46 (39%)	32 (39%)	14 (38%)	0.58
Dyslipidemia	49 (41%)	35 (43%)	14 (38%)	0.58
Current smoker	7 (6%)	3 (4%)	4 (11%)	<0.01
Albumin (g/dl)	3.8 ± 0.5	3.8 ± 0.5	3.9 ± 0.4	0.21
Hemoglobin (g/dl)	12.5 ± 2.0	12.2 ± 2.0	13.1 ± 1.8	0.03
eGFR (ml/min/1.73 m^2)	50.0 ± 20.2	49.0 ± 20.8	52.3 ± 19.0	0.41
BNP (pg/ml)	123.6 (57.7–362.6)	182.6 (77.1–419.2)	72.7 (42.3–139.6)	<0.01
hs-TnT (ng/ml)	0.020 (0.011–0.048)	0.026 (0.014–0.058)	0.011 (0.008–0.022)	0.01
hs-CRP (mg/dl)	0.10 (0.04–0.21)	0.11 (0.04–0.22)	0.06 (0.04–0.21)	0.83
LVEF (%)	55.4 ± 12.3	53.8 ± 12.3	58.8 ± 11.8	0.04
LVDd (mm)	48.3 ± 8.5	48.3 ± 8.5	48.1 ± 8.5	0.87
E/e′	16.5 ± 9.0	16.7 ± 8.2	16.2 ± 10.6	0.78
Medication				
Ca channel blocker	59 (50%)	39 (48%)	20 (54%)	
ACEI or ARB	85 (71%)	63 (77%)	22 (54%)	
β-blocker	64 (54%)	46 (56%)	18 (49%)	
Diuretics	47 (39%)	36 (44%)	11 (30%)	
Etiology				
Ischemia heart disease	39 (33%)	30 (37%)	9 (24%)	
Hypertensive heart disease	16 (13%)	12 (15%)	4 (11%)	
Dilated cardiomyopathy	8 (7%)	6 (7%)	2 (5%)	
Valvular heart disease	20 (17%)	13 (16%)	7 (19%)	
Other causes	36 (30%)	21 (25%)	15 (40%)	

Data are mean ± SD, number (percentage) or (interquartile range).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; hs-TnT, high-sensitivity cardiac troponin T; LVEF, left ventricular ejection fraction; LVDd, left ventricular end-diastolic diameter.

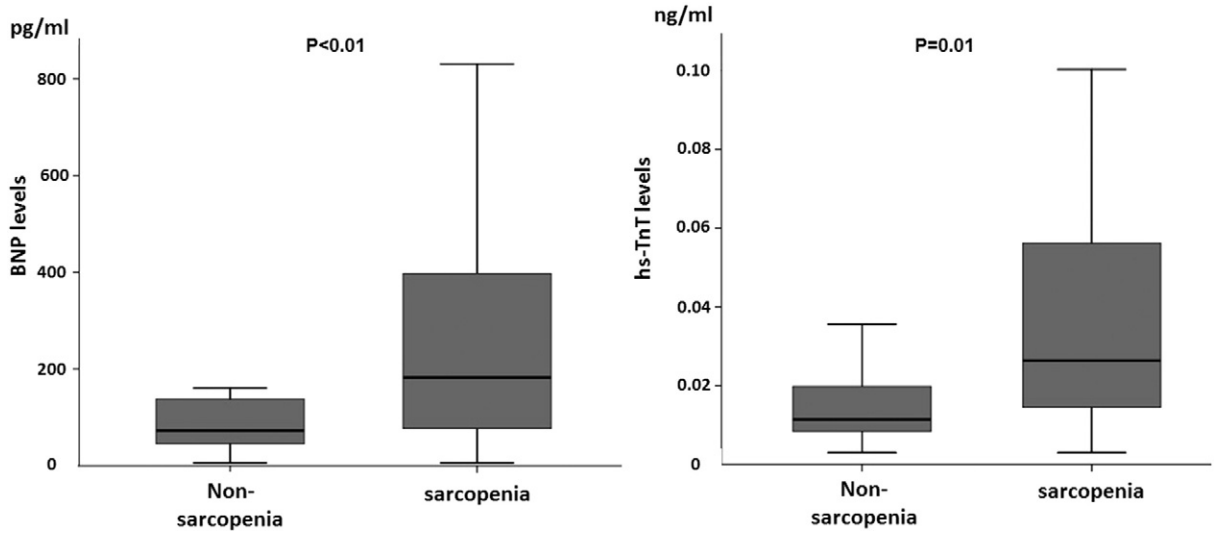

Fig. 1. Box-and-whisker plots of B-type natriuretic peptide (BNP) and high-sensitivity cardiac troponin T (hs-TnT) in the sarcopenia and non-sarcopenia groups. The cutoff point for sarcopenia was 105 points for males and 120 points for females. In BNP and hs-TnT plots, lines within the boxes represent median values; the upper and lower lines of the boxes represent the 25th and 75th percentiles, respectively; and the upper and lower bars outside the boxes represent the 90th and 10th percentiles, respectively.

analyses. Multivariate Cox proportional hazards analysis were performed using the forced entry method. Age and sex were excluded from the forced entry parameter, because they were used for calculating the sarcopenia score. All data were analyzed using SPSS v17.0J for Windows (SPSS Japan, Tokyo).

3. Results

Table 1 lists the patients' characteristics. The study consisted of 73 males (61%), the mean age was 76.1 ± 6.2 years and the mean sarcopenia screening score was 130.5 points. Thirty 9 % of all study

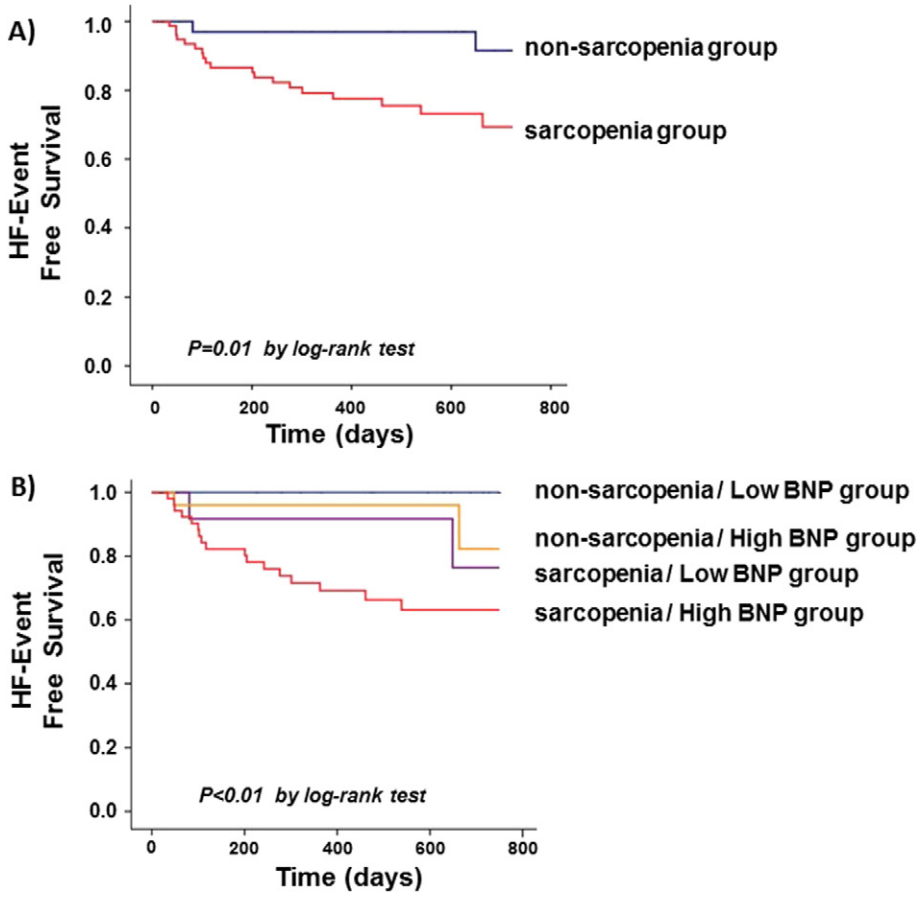

Fig. 2. Kaplan–Meier analysis for the probability of heart failure events in A) patients with and without sarcopenia, B) patients with and without sarcopenia and high and low B-type natriuretic peptide (BNP) level. The cutoff point for sarcopenia was 105 points for males and 120 points for females, while that of BNP was 100 pg/ml.

Table 2
Results of univariate and multivariate Cox proportional hazard analyses for heart failure events.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)	1.06 (0.99–1.15)	0.12	Not selected	
Sex (male)	1.39 (0.56–3.44)	0.48	Not selected	
BMI (kg/m^2)	0.87 (0.76–0.99)	0.03	Not selected	
NYHA functional class	3.64 (1.82–7.28)	<0.01	Not selected	
Sarcopenia score	1.03 (1.01–1.04)	<0.01	1.031(1.01–1.05)	<0.01
Coronary artery disease	0.88 (0.35–2.23)	0.77	Not selected	
Hypertension	0.49 (0.21–1.16)	0.11	Not selected	
Dyslipidemia	0.88 (0.36–2.15)	0.78	Not selected	
Diabetes mellitus	1.83 (0.78–4.31)	0.17	Not selected	
Current smoker	0.62 (0.08–4.61)	0.64	Not selected	
Hemoglobin (g/dl)	0.75 (0.59–0.94)	0.01	Not selected	
Albumin (g/dl)	0.57 (0.26–1.27)	0.17	Not selected	
eGFR (ml/min/1.73 m^2)	0.97 (0.95–0.99)	0.01	Not selected	
ln (BNP)	2.17 (1.53–3.07)	<0.01	1.58 (1.09–2.29)	0.02
ln (hs-TnT)	1.36 (1.05–1.75)	0.02	Not selected	
ln (hs-CRP)	1.62 (1.26–2.10)	<0.01	1.82 (1.23–2.68)	<0.01
LVEF (%)	0.96 (0.93–0.99)	<0.01	Not selected	
LVDd (mm)	1.03 (0.98–1.08)	0.31	Not selected	
E/e′	1.01 (0.96–1.05)	0.80	Not selected	

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; hs-TnT, high-sensitivity cardiac troponin T; ln, logarithm; LVEF, left ventricular ejection fraction; LVDd, left ventricular end-diastolic diameter; NYHA, New York Heart Association.

population had coronary artery diseases. With regard to the risk factors of cardiovascular diseases, 65% had hypertension, 39% had diabetes mellitus, 42% had dyslipidemia, and 6% were current smokers. During follow-up, there were 28 events, including 4 deaths due to HF and 24 HF-related hospitalization.

The patients in HF group were divided into two groups based on the presence or absence of sarcopenia using the male and female cutoff scores. There were no significant differences in the percentage of patients with hypertension, diabetes mellitus, dyslipidemia and coronary artery disease between the two groups. LVEF was significantly lower in the sarcopenia group than the non-sarcopenia group (53.8 ± 12.3 vs 58.8 ± 11.8%, p = 0.04). As shown in Fig. 1, patients of the sarcopenia group had significantly higher BNP (median 182.6, IQR [77.1–419.2] vs 72.7, [42.3–139.6] pg/ml, p < 0.01) and hs-TnT (median 0.026, IQR [0.014–0.058] vs 0.011, [0.008–0.022] ng/ml, p = 0.01) than the non-sarcopenia group. Kaplan–Meier curve indicated that the HF event-free survival rates were significantly lower in the sarcopenia group (Fig. 2A). The combination of sarcopenia and high BNP (cut-off value: 100 pg/ml) was associated with higher probability of HF events (log-rank test, P < 0.01; Fig. 2B).

As shown in Table 2, univariate Cox proportional hazards analysis demonstrated that BMI, NYHA functional class, eGFR, BNP, hs-TnT, hs-CRP, LVEF and sarcopenia score correlated significantly with future HF-events. The stepwise multivariate COX proportional hazard analysis identified BNP (ln[BNP]) (hazard ratio [HR]: 1.58; 95% CI: 1.09–2.29, p = 0.02), hs-CRP (ln[CRP]) (HR: 1.82; 95% CI: 1.23–2.68; p < 0.01) and sarcopenia score (HR: 1.03; 95% CI: 1.01–1.05, p < 0.01) as independent and significant predictors of future HF-events. Furthermore, multivariate Cox proportional hazards analysis by forced entry method were performed to adjust factors suspected for association with HF or nutrition (Table 3). In these four models, the sarcopenia score was significant predictor of future HF events.

In receiver operating characteristic (ROC) analysis, the sarcopenia score had an area under the curve (AUC) of 0.77 (95% CI: 0.67–0.86) and BNP had an AUC of 0.82 (95% CI: 0.73–0.92) (Fig. 3). The combination of these factors increased an AUC to 0.89 (95% CI: 0.83–0.96) and this increasing of an AUC was statistically significant (net reclassification improvement [NRI]: 0.001, integrated discrimination improvement [IDI]: 0.012). ROC analysis was also performed in male and female patients separately to find the cut-off value of the sarcopenia score for future HF events. These analyses identified that the cut-off value was 136.9 for male (sensitivity 93%, specificity 66%) and 159.6 for female (sensitivity 57%, specificity 82%). The forced entry multivariate COX analysis identified the presence of sarcopenia defined using this cut-off value (136.9 for male, 159.6 for female) as independent and strong predictor of future HF-events (Table. 4).

4. Discussion

Considerable attention has been paid in recent years to sarcopenia because it could be used as an independent risk factor for mortality in patients with cardiovascular diseases. The main findings of the present study were: 1) In HF patients, HF event-free survival rate was significantly lower in the sarcopenia group defined by the sarcopenia score. 2) The sarcopenia score was an independent predictor of future HF events. These findings indicate that this easily obtainable screening test could be used for risk stratification of patients with HF.

To date, there are no established criteria for the diagnosis of sarcopenia. However, evaluation of sarcopenia generally requires the assessment of muscle mass by using specific modalities, such as CT scan and/or MRI, and either muscle strength or physical performance [15]. Although these measurements are important for precise evaluation of sarcopenia, they are difficult to perform routinely in daily clinical setting. The simple screening test for sarcopenia employed in this study is based on age, grip strength and calf circumference [16]. The important point of this index is measuring calf circumference as a marker of muscle mass, because it is easy to perform even in the outpatient clinic. It has been shown that calf circumference could be used as a surrogate marker of muscle mass for the diagnosis of sarcopenia [18].

In the present study, HF was defined as the typical symptoms and signs, not LVEF. Therefore, this study included both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). Most of the previous clinical trials of HF, HF was

Table 3
Forced entry multivariate COX proportional hazard analyses for heart failure events.

	Forced entry model-1		Forced entry model-2		Force entry model-3		Force entry model-4	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)	1.04 (0.96–1.12)	0.39	–					
Sarcopenia score	1.02 (1.00–1.04)	0.01	1.023 (1.01–1.04)	<0.01	1.02 (1.01–1.04)	<0.01	1.04 (1.02–1.05)	<0.01
Hemoglobin (g/dl)			0.89 (0.70–1.14)	0.35				
Albumin (g/dl)			0.72 (0.29–1.79)	0.72				
eGFR (ml/min/1.73 m^2)					0.98 (0.96–1.00)	0.12		
ln BNP	1.95 (1.33–2.84)	<0.01						
ln hs-TnT							1.00 (0.71–1.41)	0.99
ln hs-CRP							1.94 (1.29–2.93)	<0.01
LVEF (%)			–		0.99 (0.95–1.02)	0.50		

BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; hs-TnT, high-sensitivity cardiac troponin T; ln, logarithm; LVEF, left ventricular ejection fraction.

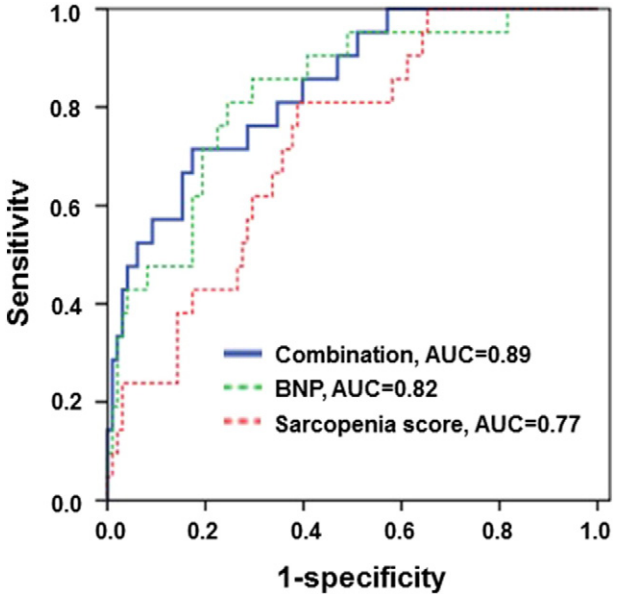

Fig. 3. Receiver operating characteristic curves for the sarcopenia score, BNP and a combination of these two factors of the future HF-events. AUC, area under the curve.

divided into HFrEF and HFpEF depending on the LVEF. However, the terms of HFrEF and HFpEF do not show the causes of HF, thus using the LVEF for diagnosing and dividing patients with HF is controversial [19]. On the other hand, their etiology and neurohormonal activation are overlap, and it is thought that the treatment for HF with ACE inhibitors, ARBs, beta blockers and aldosterone antagonists should be dependent on their etiology, regardless of HFrEF or HFpEF [20]. Thus, there are similarities between HFrEF and HFpEF, and we consider that the sarcopenia screening test also can be applied equally well in HFpEF and HFrEF.

BNP correlates negatively with body mass index or fat mass [21]. Such relation is considered to relate to the increased clearance receptor or high lipolytic action in adipose tissue [22]. In the present study, we detected a significant relation between the presence of sarcopenia and BNP levels. Because the test used in this study is independent of fat mass, our results suggest that reduced muscle mass and function affect the status of cardiac load. In this regard, we have demonstrated previously that various cardio-protective factors secreted from the muscle tissue attenuate cardiac detrimental remodeling using transgenic mouse model, in which functional skeletal muscle growth could be induced by genetic manipulation [23–26]. Therefore, it is possible that interventions that promote the growth or maintenance of skeletal muscle mass, which result in reduction of sarcopenia score, decrease the risk of HF-events in HF patients.

5. Conclusions

In conclusion, the sarcopenia screening test could be used to predict future HF events in patients with HF. This simple and easy to conduct screening test could be applied in daily clinical setting, especially in patients with muscle wasting disease such as HF, CKD and COPD.

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Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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Table 4
COX proportional hazard analyses for future heart failure events.

	Univariate analysis	
	HR (95% CI)	P value
Presence of sarcopenia new cut-off[a]	8.87 (2.97–26.52)	<0.01

	Forced entry model-1		Forced entry model-2		Forced entry model-3		Forced entry model-4	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)	1.02 (0.95–1.11)	0.56	–					
Presence of sarcopenia new cut-off[a]	4.74 (1.42–15.77)	0.01	8.50 (2.76–26.23)	<0.01	6.78 (2.04–22.54)	<0.01	11.63 (3.08–43.88)	<0.01
Hemoglobin (g/dl)			0.89 (0.71–1.12)	0.33				
Albumin (g/dl)			0.67 (0.26–1.74)	0.41				
eGFR (ml/min/1.73 m^2)					0.99 (0.97–1.01)	0.37		
ln BNP	1.83 (1.26–2.66)	<0.01						
ln hs-TnT							1.15 (0.78–1.68)	0.49
ln hs-CRP							1.73 (1.17–2.55)	<0.01
LVEF (%)			–		0.99 (0.95–1.02)	0.40		

BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; hs-TnT, high-sensitivity cardiac troponin T; ln, logarithm; LVEF, left ventricular ejection fraction.
[a] The presence of sarcopenia as the sarcopenia score > 136.9 for male and >159.6 for female.

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