Significance of Sarcopenia Evaluation in Acute Decompensated Heart Failure

Skeletal Muscle Mass Index versus Fat-Free Mass Index

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Summary

In patients with chronic heart failure (HF), the clinical importance of sarcopenia has been recognized in relation to disease severity, reduced exercise capacity, and adverse clinical outcome. Nevertheless, its impact on acute decompensated heart failure (ADHF) is still poorly understood. Dual-energy X-ray absorptiometry (DXA) is a technique for quantitatively analyzing muscle mass and the degree of sarcopenia. Fat-free mass index (FFMI) is a noninvasive and easily applicable marker of muscle mass.

This was a prospective observational cohort study comprising 38 consecutive patients hospitalized for ADHF. Sarcopenia, derived from DXA, was defined as a skeletal muscle mass index (SMI) two standard deviations below the mean for healthy young subjects. FFMI (kg/m^2) was calculated as $7.38 + 0.02908 \times \text{urinary creatinine (mg/day)}$ divided by the square of height (m^2).

Sarcopenia was present in 52.6% of study patients. B-type natriuretic peptide (BNP) levels were significantly higher in ADHF patients with sarcopenia than in those without sarcopenia (1666 versus 429 pg/mL , $P < 0.0001$). Receiver operator curves were used to compare the predictive accuracy of SMI and FFMI for higher BNP levels. Areas under the curve for SMI and FFMI were 0.743 and 0.717, respectively. Multiple logistic regression analysis showed sarcopenia as a predictor of higher BNP level (OR = 18.4; 95% CI, 1.86-181.27; $P = 0.013$).

Sarcopenia is associated with increased disease severity in ADHF. SMI based on DXA is potentially superior to FFMI in terms of predicting the degree of severity, but FFMI is also associated with ADHF severity.

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Key words: Acute heart failure, Skeletal muscle wasting, B-type natriuretic peptide, Disease severity

Heart failure (HF) is a major and growing healthcare issue worldwide and an important cause of hospitalization, incurring huge costs to the individual and to society.¹⁾ The management of acute decompensated heart failure (ADHF) remains challenging because of the heterogeneity of the patient population, an incomplete understanding of the pathophysiology of ADHF, and the lack of established evidence-based guidelines.²⁾ HF is characterized by sympathetic overdrive, activated immune response to systemic inflammation, and catabolism.³⁾

The combination of skeletal muscle loss, atrophy, and dysfunction is termed sarcopenia, and is defined as the age-related loss of skeletal muscle mass and strength.⁴⁾ This muscular alteration is provoked by the above-listed underlying factors of HF as a disease-specific phenomenon, distinguished from change due to aging or from mere deconditioning.^{3,5,6)} In patients with chronic HF, the clinical importance of sarcopenia has been recognized in relation

to disease severity, reduced exercise capacity, and adverse clinical outcome.⁷⁻¹⁰⁾ Sarcopenia affects approximately 20% of elderly individuals with chronic HF, which exceeds its prevalence in healthy members of the same age group.¹¹⁾ Nevertheless, the prevalence or impact of sarcopenia on ADHF is still poorly understood. Higher B-type natriuretic peptide (BNP) values ($>500 \text{ pg}/\text{mL}$) reflect severe ADHF and are associated with a grave prognosis.^{12,13)}

Several surrogate markers for sarcopenia in relation to chronic HF have been examined as potential prognostic factors. Among the classic methods for assessing muscle mass, dual-energy X-ray absorptiometry (DXA) is a standard technique for quantitatively analyzing muscle mass and the degree of sarcopenia.¹⁴⁾ However, this modality is not easily applicable to ADHF patients during the acute phase, most of whom cannot lie supine. The fat-free mass index (FFMI) is a noninvasive and easily applicable marker of muscle mass that is also used for the diagnosis

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Figure 1. Patient profile.

of sarcopenia.⁸⁾

The aim of the present study was two-fold: 1) to investigate the impact of existing sarcopenia on the disease severity of ADHF, and 2) to evaluate the utility of FFMI with reference to muscle mass measurement derived from the standard technique in patients with ADHF.

Methods

Study design and data collection: This study was a prospective observational cohort study, and 96 consecutive patients hospitalized for ADHF from June 2015 to January 2016 were selected. Patients with severe dependence, severe dementia, indwelling metallic devices, acute coronary syndrome, or in-hospital death were excluded; finally, 38 patients were eligible. ADHF was assessed using clinical observation and diagnosed when a patient manifested S3 gallop and pulmonary rales or when alveolar and/or interstitial edema was present by chest radiograph, based on the Framingham criteria.¹⁵⁾

The patient flow diagram is depicted in Figure 1. Any baseline demographics were confirmed from medical charts. All the admission plasma BNP levels were measured in patients presenting with ADHF on hospital arrival. A BNP level > 500 pg/mL was deemed an indicator of severe ADHF, for which physicians might pursue more aggressive patient management.^{12,13)} Therefore, we used BNP levels as a surrogate marker for disease severity in ADHF. Individual comorbid conditions were evaluated using the Charlson Comorbidity Index and higher scores (≥ 3) indicated greater comorbidity.¹⁶⁾ Anemia was defined using the World Health Organization criteria (hemoglobin < 13.0 g/dL for males and hemoglobin < 12.0 g/dL for females).¹⁷⁾ The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee.

A DXA system (Hologic, Inc., Marlborough, MA, USA) was used to determine the skeletal muscle mass index (SMI: skeletal muscle mass/height²). SMI is one of the useful measures to determine sarcopenia. Baumgartner, *et al.* summed the muscle masses of the four limbs from a DXA scan to calculate the appendicular skeletal muscle mass (ASM) and defined SMI as ASM/height² (kg/m²).¹⁸⁾

DXA is a nearly noninvasive method, except for slight radiation exposure. In the present study, sarcopenia was defined as an SMI two or more standard deviations below the mean for healthy, young Japanese subjects (< 6.87 kg/m² in males and < 5.46 kg/m² in females).¹⁹⁾ The study patients underwent DXA when they were able to maintain a supine position after sufficient decongestion was achieved at the earliest possible date. We then categorized the study patients into the binary groups of sarcopenia versus non-sarcopenia.

Fat-free mass (FFM) can be measured or calculated using several methods. We adopted the following formula to measure FFM: $7.38 + 0.02908 \times \text{urinary creatinine (mg/day)}$. Urinary creatinine (mg/day) was computed as $2.04 \times \text{age} + 14.89 \times \text{body weight (kg)} + 16.14 \times \text{height (cm)} - 2244.45$.^{20,21)} FFM was then divided by the square of the patient height in meters to obtain FFMI.

Statistical analysis: Continuous variables are expressed as the mean $\pm$ SD or the median with 25th and 75th percentiles, and frequency is expressed as a percentage for descriptive purposes. For continuous variables, comparisons between groups were performed using either Student's *t* test or the Mann-Whitney *U* test. Frequency analysis was made using the χ^2 test or Fisher's exact test. To provide factors associated with ADHF severity as odds ratios (ORs) with 95% confidence intervals (CIs), variables that achieved statistical significance ($P < 0.05$) in univariate analyses were subsequently induced in a multivariate analysis using a stepwise logistic regression procedure. Receiver operating characteristic (ROC) curves were used to compare the performance and predictive accuracy of SMI and FFMI for admission plasma BNP levels. $P < 0.05$ was considered significant, and all *P* values were two-sided. Analyses were performed with PASW Statistics version 18 software (SPSS Inc., Chicago, IL, USA).

Results

Table I shows the baseline characteristics of the study patients. The mean age was 75.0 ± 11.4 years and 65.8% were male. Sarcopenia was present in 52.6% (20/38). The median FFMI was 18.6 kg/m² (interquartile range [IQR], 16.3-19.9). The comorbidity burden was high given that the incidence of Charlson index ≥ 3 was 34.2%. Medications were well balanced between groups. Sarcopenia was associated with body mass index (BMI) ($r = -0.53$; $P = 0.001$), diastolic blood pressure ($r = 0.35$; $P = 0.036$), serum albumin ($r = -0.40$; $P = 0.015$), and BNP levels ($r = 0.53$; $P = 0.001$). BNP levels were significantly higher in ADHF patients with sarcopenia than in those without sarcopenia (1666 [IQR, 611-1998] versus 429 [IQR, 260-651] pg/mL; $P < 0.0001$).

ROC curves were used to compare the predictive accuracy of SMI and FFMI for higher BNP levels (Figure 2). Areas under the curves for SMI and FFMI were 0.743 and 0.717, respectively. The optimal cutoff value of FFMI to discriminate severe ADHF was 18.7 kg/m² (sensitivity/specificity = 75.0%/71.4%).

On univariate analysis, sarcopenia (OR = 2.69; 95% CI, 1.36-5.32; $P = 0.006$), anemia (OR = 3.00; 95% CI, 1.06-8.46; $P = 0.029$), and absence of atrial fibrillation

Table I. Baseline Characteristics of the Study Patients

	Total (n = 38)	Non-sarcopenia (n = 18)	Sarcopenia (n = 20)	P
Age mean, years	75.0 ± 11.4	72.0 ± 13.1	77.9 ± 9.1	0.116
Body weight, kg	61.5 ± 17.6	68.2 ± 20.6	55.5 ± 11.9	0.030
Body mass index, mean kg/m ²	24.1 ± 5.0	26.9 ± 5.4	21.7 ± 3.1	0.001
Body surface area, mean, m ²	1.62 ± 0.25	1.69 ± 0.31	1.56 ± 0.19	0.138
Male, n (%)	25 (65.8)	9 (50.0)	16 (80.0)	0.052
NYHA Class	3.6 ± 0.6	3.6 ± 0.5	3.6 ± 0.7	0.758
Clinical scenario 1, n (%)	21 (55.3)	8 (44.4)	13 (65.0)	0.203
Prior HF hospitalization, n (%)	13 (34.2)	6 (33.3)	7 (35.0)	1.000
Hypertension, n (%)	26 (68.4)	14 (77.8)	12 (60.0)	0.307
Diabetes, n (%)	13 (34.2)	8 (44.4)	5 (25.0)	0.307
COPD, n (%)	1 (2.6)	1 (5.5)	0	0.474
Atrial fibrillation, n (%)	16 (42.1)	10 (55.6)	6 (30.0)	0.188
Charlson index	2.2 ± 0.9	2.0 ± 0.8	2.4 ± 0.9	0.232
Etiology of HF				
Ischemic n (%)	15 (39.5)	6 (33.3)	9 (45.0)	0.522
Dilated cardiomyopathy, n (%)	7 (18.4)	3 (16.6)	4 (20.0)	1.000
Valvular/structural, n (%)	6 (15.8)	1 (5.6)	5 (25.0)	0.184
Arrhythmias, n (%)	5 (13.2)	4 (22.2)	1 (5.0)	0.170
Others, n (%)	4 (10.5)	2 (11.1)	2 (10.0)	1.000
Systolic BP, mmHg	146.9 ± 31.8	139.0 ± 33.4	154.0 ± 29.3	0.149
Diastolic BP, mmHg	87.0 ± 18.3	80.2 ± 13.3	92.8 ± 20.3	0.036
Heart rate, beats/minute	105.0 ± 31.4	103.8 ± 37.6	106.0 ± 25.4	0.835
LVEF, %	47.6 ± 15.3	49.6 ± 16.9	45.6 ± 13.8	0.425
LVEF ≤ 40%, n (%)	23 (60.5)	11 (61.1)	12 (60.0)	1.000
BNP, pg/mL	682 [376, 1748]	429.0 [260, 651]	1666 [661, 1998]	< 0.0001
Hemoglobin, g/dL	12.32 ± 2.36	12.24 ± 2.94	12.38 ± 1.76	0.862
Serum BUN, mg/dL	26.08 ± 10.92	26.37 ± 12.01	25.81 ± 10.16	0.874
Serum creatinine, mg/dL	1.25 ± 0.54	1.27 ± 0.66	1.23 ± 0.42	0.812
CrCl, mL/minute	59.77 ± 29.03	60.77 ± 29.70	58.89 ± 29.38	0.863
Total protein, g/dL	7.18 ± 0.40	7.21 ± 0.40	7.16 ± 0.41	0.670
Serum albumin, g/dL	3.60 ± 0.35	3.75 ± 0.33	3.48 ± 0.33	0.015
ChE, IU/L	252.92 ± 93.89	279.2 ± 111.6	229.4 ± 69.5	0.113
Plasma glucose, mg/dL	177.9 ± 79.5	179.2 ± 61.7	176.9 ± 92.0	0.932
HbA1c, %	6.0 ± 0.8	6.0 ± 0.4	6.0 ± 1.1	0.868
FFMI, kg/m ²	18.66 ± 2.45	19.61 ± 2.85	17.80 ± 1.68	0.027
Medications				
Loop diuretics, n (%)	38 (100)	18 (100)	20 (100)	1.000
ACE inhibitors/ARBs, n (%)	29 (76.3)	15 (83.3)	14 (70.0)	0.454
Beta-blockers, n (%)	33 (86.8)	16 (88.9)	17 (85.0)	1.000
Thiazide diuretics, n (%)	11 (28.9)	4 (22.2)	7 (35.0)	0.458
Aldosterone antagonists, n (%)	17 (44.7)	7 (38.9)	10 (50.0)	0.532
Statins, n (%)	19 (50.0)	11 (61.1)	8 (40.0)	0.330
Tolvaptan, n (%)	2 (5.3)	1 (5.6)	1 (5.0)	1.000
Carperitide, n (%)	7 (18.4)	3 (16.7)	4 (20.0)	1.000

ACE indicates angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; ChE, cholinesterase; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; FFMI, fat-free mass index; HF, heart failure; LVEF, left ventricular ejection fraction; and NYHA, New York Heart Association.

(OR = 2.20; 95% CI, 1.06-4.60; $P = 0.047$) were associated with higher (≥ 500 pg/mL) BNP levels. FFMI < 18.7 kg/m² did not correlate with higher BNP (OR = 1.91; 95% CI, 1.03-3.52; $P = 0.091$). Finally, when these three parameters selected in the univariate analysis were induced in a stepwise logistic regression analysis, sarcopenia (OR = 18.4; 95% CI, 1.86-181.27; $P = 0.013$), and anemia (OR = 12.2; 95% CI, 1.25-119.15; $P = 0.032$) were predictive of higher BNP (Table II).

Discussion

The major findings of the present study are summarized as follows: 1) sarcopenia is frequently observed in ADHF patients and is associated with increased disease severity of ADHF; and 2) SMI is superior to FFMI as a predictor of the degree of severity, but FFMI also has good discriminatory power for severe ADHF cases.

The hallmarks of HF are sympathetic overdrive, activated immune response to systemic inflammation, and catabolism.³⁾ The degree of these neurohormonal derangements is potentially related to HF severity and subsequent

Figure 2. Receiver operating characteristics curves to compare the performance and predictive accuracy of SMI (left panel) and FFMI (right panel) for higher (≥ 500 pg/mL) BNP level in ADHF. FFMI indicates fat-free mass index; and SMI, skeletal muscle mass index.

Table II. Logistic Regression Model to Identify the Variables Associated with Higher (≥ 500 Pg/mL) BNP Level

	Univariate analysis			Multivariate analysis		
	Odds ratio	P	95% CI	Odds ratio	P	95% CI
Age ≥ 75 years	1.50	0.311	0.69-3.24			
Male gender	1.11	1.000	0.28-4.43			
New-onset HF	1.34	0.205	0.08-1.73			
Ischemic	0.86	0.717	0.36-2.00			
Dilated cardiomyopathy	0.28	0.171	0.38-2.13			
Valvular disease	0.85	0.846	0.18-4.09			
Hypertension	1.07	0.761	0.69-1.65			
Diabetes	1.07	0.881	0.44-2.64			
Systolic BP ≥ 140 mmHg	0.89	1.000	0.24-3.35			
Heart rate ≥ 100 /minute	3.00	0.179	0.76-11.81			
Anemia	3.00	0.029	1.06-8.46	12.2	0.032	1.25-119.15
Clinical scenario 1	1.06	0.859	0.59-1.89			
Atrial fibrillation	0.50	0.047	1.06-4.60	0.31	0.185	0.05-1.76
LVEF $< 40\%$	1.51	0.108	0.93-2.47			
CrCl < 30 mL/minute	1.33	0.067	1.00-1.68			
Sarcopenia	2.69	0.006	1.36-5.32	18.4	0.013	1.86-181.27
FFMI < 18.7 kg/m ²	4.17	0.050	1.00-17.30			

BNP indicates B-type natriuretic peptide; BP, blood pressure; CrCl, creatinine clearance; FFMI, fat-free mass index; HF, heart failure; and LVEF, left ventricular ejection fraction.

unfavorable outcome. Skeletal muscle wasting in HF is a complex process integrating failing heart, skeletal muscle, fat and bone tissue, and is likely to be caused by the above-mentioned core components of HF.^{6,22,23)}

Several possible explanations could account for our finding that existing sarcopenia potentially aggravates ADHF. There is increasing evidence for crosstalk between the heart and adipose tissue, although precise mechanisms remain undefined. Recent studies suggest that the failing heart acts on fat metabolism by inducing adiponectin secretion and lipolytic actions through the secretion of natriuretic peptides (atrial natriuretic peptide and BNP).²⁴⁾ At the same time, soluble myostatin released from the failing heart may induce skeletal muscle wasting in HF.²⁵⁾ However, a direct natriuretic peptide-mediated interaction be-

tween the failing heart and muscle has not been clarified. The BNP level inversely correlates with BMI or fat mass.²⁶⁾ We found that patients with sarcopenia had significantly higher BNP levels than those without sarcopenia. Admission plasma BNP levels provide prognostic information in patients with ADHF.^{27,28)} Given that both SMI and FFMI are independent markers of fat mass, the present study provides important information on the significance of index skeletal muscle mass degree in relation to cardiac load status, severity level, and prognosis of ADHF. Our results also may complement the view indicating that skeletal myopathy in HF is, in part, disease-specific, not a result of deconditioning.

The imaging technologies used to detect sarcopenia include DXA, magnetic resonance imaging, computed to-

mography, and ultrasonography. Among these methods, DXA is a standard technique for quantitatively analyzing muscle mass and the degree of sarcopenia.¹⁴⁾ However, this modality is not easily applicable to ADHF patients during the acute phase, most of whom cannot lie supine. FFMI is a noninvasive and easily applicable marker of muscle mass, even in the acute phase, and can also be used for the diagnosis of sarcopenia.⁸⁾ The prognostic significance of FFMI in chronic HF has been reported.⁸⁾ The present study demonstrated that FFMI had identical detection power for severity level of ADHF compared with SMI. Although no cutoff value diagnosing sarcopenia has been established in FFMI, our present results indicate that this noninvasive method can be useful to identify sarcopenia and to predict any subsequent adverse future outcome of HF management at an earlier stage.

The present study has several limitations. First, this was a single-center study. Second, the study population was small and, because no power or sample size calculation was performed, the possibility of a type II error should be considered. Third, the duration of bed rest might affect the SMI results because the timing of DXA examination differed among study patients, although patients underwent DXA at the earliest possible date. Finally, some patients with ADHF, such as those experiencing acute exacerbation of chronic HF, may have persistently elevated BNP levels regardless of treatment, and such levels may not be of prognostic importance.

In conclusion, sarcopenia evaluation in ADHF is important to identify high-risk patients. Although DXA is a standard technique for screening sarcopenia, FFMI is a simple and easily applicable method, even in the acute phase of ADHF. Meanwhile, the mechanism behind the relationship between skeletal muscle loss and failing heart remains elusive. Further studies are needed to investigate whether sarcopenia can be a potential therapeutic target to improve the outcome of ADHF patients.²⁹⁾

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Disclosures

Conflicts of interest: None declared.

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