Aging Medicine and Healthcare 2019;10(2):53-61. doi:10.33879/AMH.2019.1809

Aging Medicine and Healthcare
https://www.agingmedhealthc.com

Original Article

Sarcopenia Predicts Adverse Outcomes in an Elderly Outpatient Population with New York Heart Association Class II–IV Heart Failure: A Prospective Cohort Study

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Received 13 May 2018
Accepted 15 September 2018

Keywords
Heart failure, sarcopenia, cardiac events, prospective study, elderly.

ABSTRACT

Background/Purpose: The purpose of this study was two-fold. The first was to examine the predictors of cardiac events including sarcopenia in elderly patients with heart failure (HF) and second, to determine whether the predictors of cardiac events differed between HF patients with and without any physical symptoms.

Methods: This 8-month prospective cohort study followed 191 outpatients of the Cardiovascular Medicine Department of our institution. These patients were aged 60 years and older, and had previously been admitted to hospital for the management of HF or were currently receiving pharmacological treatment for HF. The outcome measure was a cardiac event, which included cardiac death or HF-related hospitalization within an 8-month period. We measured the following as risk factors for cardiac events: age, sex, body mass index, sarcopenia, plasma brain natriuretic peptide levels, estimated glomerular filtration rate, self-care behavior, and depressive symptoms. Sarcopenia was identified using the algorithm developed by the Asian Working Group for Sarcopenia. We used the New York Heart Association (NYHA) classification to stratify patients into either the NYHA class I group (n=99) or the NYHA classes II-IV group (n=92).

Results: During the follow-up period, there were 20 (10.5%) cardiac events. Twenty patients (10.5%) had sarcopenia. Multivariate Cox proportional hazard analysis revealed that sarcopenia was significantly associated with cardiac events only in the NYHA II-IV group (hazard ratio 4.44; 95% confidence interval 1.09-18.14; P=0.04) after adjustment for sex, BNP, and eGFR.

Conclusions: Sarcopenia predicts cardiac events in patients with NYHA II-IV HF.

1. INTRODUCTION

Heart failure (HF) is a prevalent disease in elderly patients and its exacerbation results in frequent hospitalization.[1] Therefore, it is important to prevent HF exacerbation in these patients from their daily living activities. HF can be aggravated due to multiple factors and demographic (e.g., age) and biochemical influences (e.g., plasma brain natriuretic peptide [BNP] levels and renal function) have been proposed as risk factors.[2,3] Moreover, self-care behavior[4] and depression[5] have been indicated to cause severe aggravation of HF.

In addition to HF-related factors, certain geriatric conditions are also considered risk factors in elderly patients with HF. Sarcopenia, defined as an age-dependent loss of skeletal muscle mass, is currently an important topic under investigation.[6,7] The criteria recommended by the Asian Working Group for Sarcopenia (AWGS) to diagnose sarcopenia include the presence of both low muscle function and muscle mass.[8] Sarcopenia is characterized by a number of health-related issues and is associated with an increased risk of mortality,[9] disability,[10] and falls.[11]

Various factors have been proposed to be involved in the pathogenesis of sarcopenia, such as oxidative stress, inadequate nutrition, and infiltration of skeletal muscle by fat and connective tissue, and these factors may easily emerge in elderly patients.[12,13] According the results of a previous study, HF patients frequently develop skeletal muscle atrophy;[14] therefore, sarcopenia may easily occur in elderly patients with HF. Sarcopenia in elderly patients with HF may be considered a risk factor for cardiac events[15-17] and may lead to severe aggravation of HF.

We speculated that the risk factors for cardiac events differ according to the presence or absence of physical symptoms of HF. Physical symptoms of HF such as breathlessness and fatigue may greatly limit the daily living activities of elderly patients with HF.[18] The New York Heart Association (NYHA) functional classification system is based on the assessment of physical symptoms of HF at different levels of physical activity and has been widely used in many HF studies and international guidelines.[19] In a recent study, it was determined that these symptoms are associated with quality of life including a physical element in HF patients.[20] In addition, a patient's lifestyle may also influence the aggravation of HF; therefore, it is necessary to consider physical symptoms of HF when examining potential prognostic factors associated with HF.

To date, several studies have examined sarcopenia as a prognostic factor in patients with chronic HF.[15-17] However, only a few studies have examined risk factors for adverse outcomes, including sarcopenia, which is defined as presence of both low muscle mass and muscle function in patients with HF associated with physical symptoms. Thus, the purpose of this study was to examine the predictive factors for cardiac events in elderly patients with HF including sarcopenia and to determine whether the predictive factors of cardiac events differed between HF patients with and without physical symptoms.

2. METHODS

2.1. Patients

This prospective cohort study investigated the factors associated with cardiac events in an elderly outpatient population with HF in a community hospital setting in Shiga prefecture, Japan. The 191 study subjects included in the study were outpatients attending the Department of Cardiovascular Medicine at our institution. Patients were aged 60 years or older (mean age, 73.3±7.3 years, 136 men) who had previously been admitted to hospital for the management of HF or had already been receiving pharmacological treatment for HF. For patient recruitment, we distributed advertisements requesting patient enrollment for this study among patients visiting the community hospital for HF management. Interviews were then performed to select patients and those with the following criteria were excluded from the study: certification of artificial implants, such as cardiac pacemakers and joints, which did not allow bioimpedance testing; severe pulmonary or musculoskeletal disorders; comorbidities associated with a greater risk of falls such as Parkinson's disease and stroke; and the use of psychotropic drugs. Baseline data were collected in February 2015 and outcome data, between February and October 2015. Data analysis was carried out for all 191 patients who had undergone clinical follow-up (follow-up rate, 100.0%) for eight months after the baseline measurement. Written informed consent was obtained from each patient in accordance with the guidelines approved by the Kyoto University Graduate School of Medicine and the Declaration of Human Rights, Helsinki, 1975. The study protocol was approved by the ethics committee of the Kyoto University Graduate School of Medicine.

2.2. Study Outcome Measures

The adverse outcome was a cardiac event comprising cardiac death or HF-related hospitalization. If the death was not caused by an obvious non-cardiac cause, it was considered a cardiac death. Similarly, HF-related hospitalization was defined as an admission to the Cardiovascular Medicine Unit for worsening HF. The outcome information was collected from the medical records.

2.3. Baseline Data

2.3.1. Demographic and clinical data

Age, sex, and body mass index (BMI) were obtained as

demographic data. Data on height was self-reported by the participants. Weight was measured on a scale with patients shoeless and wearing their street clothes. Clinical data, such as the number of hospitalizations, medication history (diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers [ARB], beta-blockers, and cardiotonic agents), complications (angina, myocardial infarction, arrhythmia, cardiomyopathy, valvular heart disease, hypertension, dyslipidemia, diabetes mellitus, and chronic obstructive pulmonary disease) were obtained from the medical records. Physical therapists interviewed the patients and classified their HF according to the NYHA Functional Classification system. NYHA is divided into four classes. Patients with NYHA class I have no symptoms caused by heart disease; those in NYHA classes II, III, and IV are characterized by mild, moderate, and severe symptoms, respectively.[21]

2.3.2. Predictors of cardiac events in HF patients

We considered sarcopenia, plasma BNP levels, estimated glomerular filtration rate (eGFR), self-care behavior (self-care score), and depressive symptoms (GDS-15 score) as predictors of cardiac events. Each factor was indicated to cause severe aggravation of HF in previous studies.[2-5]

i. Sarcopenia

Patients with sarcopenia were identified using the algorithm developed and suggested by the AWGS, which assesses the presence of both low muscle function (slow walking speed or low handgrip strength) and low muscle mass.[8] A bioelectrical impedance data acquisition system (Inbody 430; Biospace Co, Ltd, Seoul, Korea) was used to perform bioelectrical impedance analysis.[22] This system uses an electric current at multiple frequencies (5, 50, 250, 500, and 1,000 kHz) to directly measure the amount of extracellular and intracellular water in the body. Using segmental body composition and muscle mass, a value for the appendicular skeletal muscle mass was determined. The skeletal muscle mass index (SMI), which has been used in several epidemiological studies,[23] was calculated by dividing the muscle mass by the square of height in meters (kg/m^2). Low muscle mass was defined as SMI less than 7.0 kg/m^2 in men and 5.7 kg/m^2 in women. To measure the usual gait speed, each patient's 10-m normal walking speed (m/s) was calculated and slow speed was defined as speed less than 0.8 m/s. Patients were asked to walk on a straight surface at a comfortable walking speed. Low handgrip strength was defined as an average of grip strength in each arm of less than 26 kg in men and 18 kg in women. Grip strength was measured in kilograms using a handheld dynamometer. Patients gripped the dynamometer with a hand using maximum effort and no other body movement was allowed. If a patient presented both low muscle function (slow walking speed or low handgrip strength) and low muscle mass, the patient was diagnosed with sarcopenia.[8]

ii. Biochemical analyses

Plasma BNP levels were measured with a chemiluminescence enzyme immunoassay for human BNP using a commercial kit (Shionogi, Osaka, Japan) and a fluorescence enzyme immunoassay system (TOSOH, Tokyo, Japan). The minimum detectable concentration of human BNP using this system is 4 pg/ml. As an index of renal function, we calculated the eGFR by measuring serum creatinine levels. eGFR was calculated using a formula, which originated from the Modification of Diet in Renal Disease study group adjusted for Japanese individuals: eGFR (ml/min/1.73 m^2)=194×Scr-1.094×Age-0.287×0.739 (for women). This equation is recommended by the Japanese Society of Nephrology.[24,25]

iii. Self-care behavior

We used the Japanese version of the European Heart Failure Self-Care Behavior Scale (EHFScBS).[26,27] This self-administered 12-item questionnaire is a well-validated and reliable scale designed to assess self-care behavior.[27] The EHFScBS covers items concerning daily self-care activities of HF patients such as daily weighing, fluid restriction, medications, recognition of worsening symptoms, seeking assistance by contacting health care providers, and exercising regularly. A score for each of the EHFScBS items ranged from 1 (I completely agree) to 5 points (I do not agree at all); the sum of the individual scores was taken as the total self-care score (ranging from 12 to 60), with a higher score indicating higher levels of self-care.

iv. Depressive symptoms

We used the Geriatric Depression Scale 15-item version (GDS-15) to assess depressive symptoms. The GDS-15 is valid in elderly patients and is designed to avoid bias from somatic ailments.[28] The questionnaire comprises 15 items, and each item has two answers: yes or no. Higher GDS-15 scores represent more depressive symptoms (ranging from 0 to 15).

2.4. Statistical Analysis

The adverse outcome was a cardiac event, comprising cardiac death or HF-related hospitalization. We statistically examined the differences between patients with a cardiac event and those without a cardiac event during the clinical follow-up period using the χ^2 test or the unpaired t-test, while the Mann Whitney U-test was used to examine differences in plasma BNP levels, serum albumin, and sodium because these parameters are not normally distributed. The multivariate Cox

proportional hazard analysis was performed to investigate whether sarcopenia was associated with cardiac events after adjusting for sex, BNP, and eGFR. The hazard ratio (HR) and 95% confidence interval (CI) were estimated for evaluation. Survival time was defined as the time between the baseline measurements and either time of cardiac events or the end of the follow-up period. In addition, Kaplan-Meier survival curves were computed for patients with (sarcopenia group) and without (non-sarcopenia group) sarcopenia. In order to analyze whether association differed between HF patients with or without physical symptoms, we classified patients into two groups: NYHA I group and NYHA II-IV group. The above-mentioned statistical analyses were performed separately for both groups using SPSS Statistics for Windows version 20.0 (IBM Corp, Armonk, NY, USA). A value of P <0.05 was considered statistically significant for all analyses.

3. RESULTS

3.1. Demographic Data

The overall mean age of the cohort was 73.3±7.3 years; 136 patients were men and 55 were women. During the 8 months of this study, there were 20 (10.5%) cardiac events of worsening HF, and cardiac events were 1 hospitalization except 1 patient. Twenty patients (10.5%) had sarcopenia (Table 1). Patients who experienced cardiac events had a significantly greater number of hospitalizations (3.5±2.0 vs. 1.8±1.6 times, P <0.01) and higher incidence of angina (85.0 vs. 62.0%, P=0.04) (Table 1).

Table 1. Comparison of demographic characteristics and variables in patients with and without cardiac events.

	All (n=191)	Event-Free (n=171)	Cardiac Event (n=20)	P value
Age, year[b]	73.3±7.3	73.2±7.5	74.4±5.7	0.49
Male sex (n)[a]	136 (71.2%)	120 (70.2%)	16 (80.0%)	0.36
BMI, kg/m^2 [b]	23.5±3.1	23.6±3.1	22.5±3.3	0.13
Hospitalizations, times[b]	1.9±1.7	1.8±1.6	3.5±2.0	<0.01[#]
Sarcopenia (n)[a]	20 (10.5%)	16 (9.4%)	4 (20.0%)	0.14
Self-care score[b]	35.0±8.0	35.2±8.1	32.9±7.3	0.22
GDS-15 score[b]	4.2±3.2	4.2±3.3	3.8±2.6	0.61
Blood samples				
BNP, pg/ml[c]	74.9±113.7	76.3±118.2	63.1±64.6	0.83
eGFR, ml/min/1.73m^2 [b]	58.0±17.3	57.9±17.6	59.4±15.1	0.72
Serum albumin, g/dl[c]	4.0±0.3	4.0±0.3	4.1±0.3	0.36
Sodium, mEq/l[c]	140.1±3.0	140.1±2.9	140.2±3.4	0.85
Hemoglobin, g/dl[b]	13.2±1.5	13.2±1.5	13.3±1.3	0.93
Complication (n)[a]				
Angina	123 (64.4%)	106 (62.0%)	17 (85.0%)	0.04*
Myocardial infarction	50 (26.2%)	45 (26.3%)	5 (25.0%)	0.90
Arrhythmia	37 (19.4%)	33 (19.3%)	4 (20.0%)	0.94
Cardiomyopathy	7 (3.7%)	6 (3.5%)	1 (5.0%)	0.74
Valvular heart disease	20 (10.5%)	19 (11.1%)	1 (5.0%)	0.40
Hypertension	90 (47.1%)	83 (48.5%)	7 (35.0%)	0.25
Dyslipidemia	65 (34.0%)	58 (33.9%)	7 (35.0%)	0.92
Diabetes mellitus	38 (19.9%)	34 (19.9%)	4 (20.0%)	0.99
COPD	4 (2.1%)	4 (2.3%)	0 (0.0%)	0.49
Medication (n)[a]				
Diuretic	39 (20.4%)	35 (20.5%)	4 (20.0%)	0.96
ACE inhibitor	23 (12.0%)	21 (12.3%)	2 (10.0%)	0.77
ARB	68 (35.6%)	63 (36.8%)	5 (25.0%)	0.30
Beta-blocker	61 (31.9%)	54 (31.6%)	7 (35.0%)	0.76
Cardiotonic agent	8 (4.2%)	8 (4.7%)	0 (0.0%)	0.32

BMI, body mass index; GDS-15, Geriatric Depression Scale (15-item); BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; COPD, chronic obstructive pulmonary disease; ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NYHA, New York Heart Association; AWGS, Asian Working Group for Sarcopenia.
A cardiac event was defined as cardiac death or re-hospitalization for worsening heart failure. Sarcopenia was defined according to the AWGS-recommended diagnostic algorithm. Self-care score was measured with the European Heart Failure Self-care Behavior scale.
*P <0.05; [#]P <0.01. [a]Assessed by χ^2 test; [b]Assessed by unpaired t-test; [c]Assessed by Mann Whitney U-test.

Ninety-nine patients (51.8%) were classified as NYHA class I, whereas 92 patients (48.2%) satisfied NYHA classes II-IV criteria (Tables 2, 3). There were 9 (9.1%) cardiac events and cardiac events were 1 hospitalization except 1 patient, while 10 patients (10.1%) had sarcopenia in the NYHA I group (Table 2). Conversely, 11 (12.0%) cardiac events occurred and all cardiac events were 1 hospitalization, and 10 patients (10.9%) experienced sarcopenia in the NYHA II–IV group (Table 3). In the NYHA I group, the patients who experienced cardiac events had a significantly greater number of hospitalizations (3.4±1.7 vs. 1.7±1.6 times, P <0.01) and a higher prevalence of prescription of ARB (33.3 vs. 0.0%, P=0.04) and beta-blockers (66.7 vs. 26.3%, P=0.02) than those who did not experience any cardiac events (Table 2). In the NYHA II–IV group, the number of hospitalizations among patients with cardiac events was significantly higher than patients without any cardiac events (3.4±1.7 vs. 1.7±1.6 times, P <0.01) (Table 3).

3.2. Cox Proportional Hazards Model

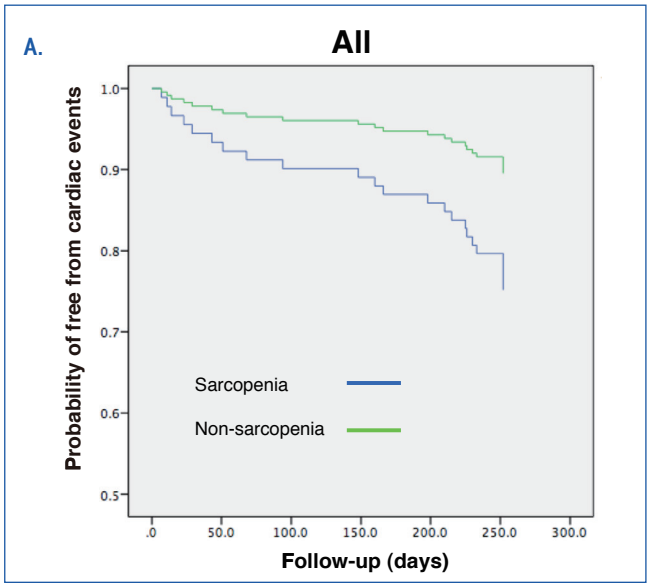
The multivariate Cox proportional hazard analysis revealed that sarcopenia was significantly associated with a cardiac event only in the NYHA II–IV group (HR, 4.44; 95% CI, 1.09-18.14; P=0.04) after adjusting for sex, BNP, and eGFR (Table 4). Figure 1 shows the Kaplan-Meier survival curves during the 8-month follow-up according to the probability of experiencing a cardiac event, with the patients stratified into the sarcopenia and non-sarcopenia groups. Among the NYHA II-IV patients, 3 (27.3%) patients in the sarcopenia group and 7 (8.6%) patients in the non-sarcopenia group experienced a cardiac event during the 8-month period (Figure 1-C).

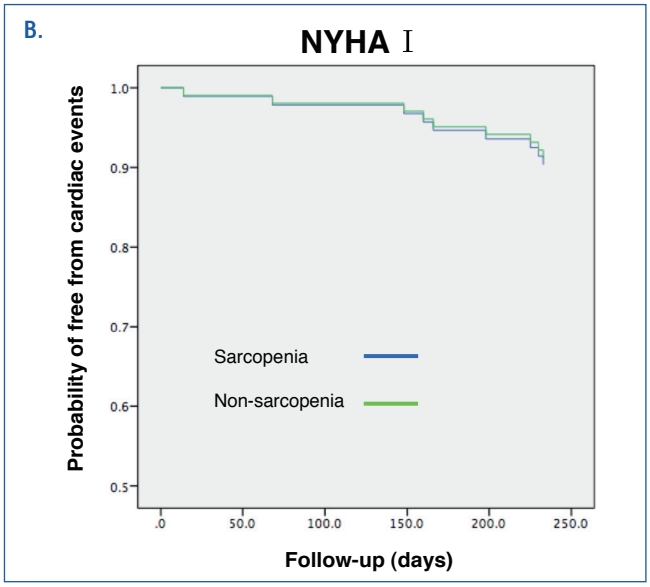
4. DISCUSSION

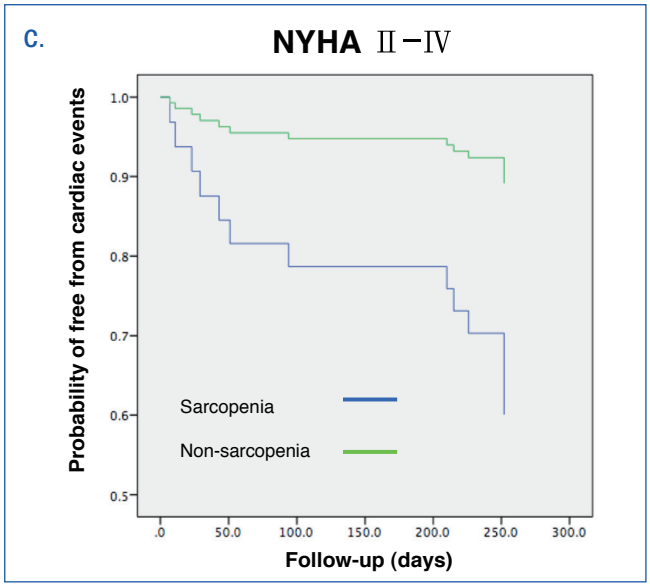
We analyzed whether the risk factors of cardiac events including sarcopenia differed between HF patients based on the presence or absence of physical symptoms. Sarcopenia could be considered a risk factor for cardiac events only in patients with HF belonging to the NYHA II–IV group. Many studies have identified numerous factors that influence the aggravation of HF (e.g., age, plasma BNP level, renal function);[2-5] however, few reports examining these factors have included sarcopenia after having considered physical symptoms. Interestingly, this finding suggests that prevention and treatment of sarcopenia may prevent the aggravation of HF in elderly patients with symptomatic HF.

It is certain that the pathophysiology of HF and sarcopenia share common elements. Various factors have been proposed to be involved in the pathogenesis of sarcopenia, such as oxidative stress, inadequate nutrition, and infiltration of skeletal muscle by fat and connective tissue.[12,13] Furthermore,

Figure 1-A, B, C. Kaplan-Meier survival curves illustrating the probability of the absence of cardiac events.







pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6, in particular, have been reported to be responsible for causing skeletal muscle wasting and reduced muscle function in HF patients.[29,30] In fact, it has been indicated that the production of these cytokines is increased in these patients and that TNF-α induced loss of protein in muscle cells, leading to abnormal expression of muscle proteins.[31-33] Unfortunately, we were unable to collect data relative to pro-inflammatory cytokines in the present study. Thus, it may be postulated that in terms of potential underlying mechanisms, HF may be related to sarcopenia, although we could not collect data regarding pro-inflammatory cytokines in the present study.

This study indicated that sarcopenia predicts cardiac events in HF patients of NYHA classes II-IV. HF patients with sarcopenia induced by overactivation of pro-inflammatory cytokines not only have a slower walking speed or low handgrip strength but also demonstrate deterioration in exercise tolerance.[34] HF patients of NYHA classes II-IV develop common HF symptoms such as breathlessness, fatigue, and palpitation when they perform physical activities. It seems that the deterioration in exercise function and common HF symptoms limit physical activities further. It is possible that the reduced muscle function in sarcopenia combined with HF symptoms and the limited physical activity of HF patients are associated with an increased risk of physical disability, which subsequently lead to cardiac events. Moreover, a previous study has suggested that limited physical activity resulted in increased production of pro-inflammatory cytokines.[35]

Table 2. Comparison of demographic characteristics and measurements in patients of NYHA I group with and without cardiac events.

	NYHA I (n=99)	Event-Free (n=90)	Cardiac Event (n=9)	P value
Age, year[b]	72.8±6.8	72.8±7.0	73.0±4.7	0.93
Male sex (n)[a]	76 (76.8%)	69 (76.7%)	7 (77.8%)	0.94
BMI, kg/m^2 [b]	23.3±2.8	23.4±2.9	23.1±2.0	0.75
Hospitalizations, times[b]	1.9±1.6	1.7±1.6	3.4±1.7	<0.01[#]
Sarcopenia (n)[a]	10 (10.1%)	9 (10.0%)	1 (11.1%)	0.92
Self-care score[b]	36.4±8.3	36.6±8.2	34.2 ± 9.2	0.41
GDS-15 score[b]	3.8±3.3	3.9±3.4	2.3±2.2	0.18
Blood samples				
BNP, pg/ml[c]	78.0±141.8	78.8±147.1	70.0±74.1	0.44
eGFR, ml/min/1.73m^2 [b]	60.5±15.8	60.2±16.1	63.7±13.2	0.53
Serum albumin, g/dl[c]	4.0±0.3	4.0±0.3	4.0±0.3	0.62
Sodium, mEq/l[c]	140.5±2.7	140.6±2.6	139.1±3.3	0.16
Hemoglobin, g/dl[b]	13.4±1.4	13.4±1.4	13.6±1.0	0.66
Complication (n)[a]				
Angina	70 (70.7%)	62 (68.9%)	8 (88.9%)	0.21
Myocardial infarction	29 (29.3%)	26 (28.9%)	3 (33.3%)	0.78
Arrhythmia	15 (15.2%)	14 (15.6%)	1 (11.1%)	0.72
Cardiomyopathy	4 (4.0%)	3 (3.3%)	1 (11.1%)	0.26
Valvular heart disease	5 (5.1%)	5 (5.6%)	0 (0.0%)	0.47
Hypertension	52 (52.5%)	50 (55.6%)	2 (22.2%)	0.06
Dyslipidemia	44 (44.4%)	40 (44.4%)	4 (44.4%)	1.00
Diabetes mellitus	20 (20.2%)	17 (18.9%)	3 (33.3%)	0.30
COPD	2 (2.0%)	2 (2.2%)	0 (0.0%)	0.65
Medication (n)[a]				
Diuretic	13 (13.1%)	12 (13.3%)	1 (11.1%)	0.85
ACE inhibitor	10 (10.1%)	9 (10.0%)	1 (11.1%)	0.92
ARB	30 (30.3%)	30 (33.3%)	0 (0.0%)	0.04*
Beta-blocker	32 (32.3%)	26 (26.3%)	6 (66.7%)	0.02*
Cardiotonic agent	3 (3.0%)	3 (3.3%)	0 (0.0%)	0.58

BMI, body mass index; GDS-15, Geriatric Depression Scale (15-item); BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; COPD, chronic obstructive pulmonary disease; ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NYHA, New York Heart Association; AWGS, Asian Working Group for Sarcopenia.
A cardiac event was defined as cardiac death or re-hospitalization for worsening heart failure. Sarcopenia was defined according to the AWGS-recommended diagnostic algorithm. Self-care score was measured with the European Heart Failure Self-care Behavior scale.
*P <0.05; [#]P <0.01. [a]Assessed by χ^2 test; [b]Assessed by unpaired t-test; [c]Assessed by Mann Whitney U-test.

Table 3. Comparison of demographic characteristics and measurements in patients with NYHA II-IV groups with and without cardiac events.

	NYHA II-IV (n=92)	Event-Free (n=81)	Cardiac Event (n=11)	P value
Age, year[b]	73.9±7.8	73.7±8.0	75.6±6.3	0.46
Male sex (n)[a]	60 (65.2%)	51 (55.4%)	9 (81.8%)	0.22
BMI, kg/m^2 [b]	23.7±3.4	23.9±3.3	22.1±4.1	0.09
Hospitalizations, times[b]	2.0±1.8	1.8±1.7	3.6±2.3	<0.01[#]
Sarcopenia (n)[a]	10 (10.9%)	7 (8.6%)	3 (27.3%)	0.06
Self-care score[b]	33.4±7.4	33.6±7.7	31.7±5.6	0.44
GDS-15 score[b]	4.6±3.0	4.5±3.1	5.0±2.3	0.62
Blood samples				
BNP, pg/ml[c]	71.5±73.1	73.4±74.9	57.3±58.9	0.57
eGFR, ml/min/1.73m^2 [b]	55.4±18.6	55.3±18.9	55.8±16.2	0.93
Serum albumin, g/dl[c]	4.0±0.3	4.0±0.3	4.2±0.2	0.11
Sodium, mEq/l[c]	139.7±3.2	139.5±3.2	141.0±3.3	0.11
Hemoglobin, g/dl[b]	13.1±1.6	13.1±1.6	13.0±1.5	0.87
Complication (n)[a]				
Angina	53 (57.6%)	44 (54.3%)	9 (81.8%)	0.08
Myocardial infarction	21 (22.8%)	19 (23.5%)	2 (18.2%)	0.70
Arrhythmia	22 (23.9%)	19 (23.5%)	3 (27.3%)	0.78
Cardiomyopathy	3 (3.3%)	3 (3.7%)	0 (0.0%)	0.52
Valvular heart disease	15 (16.3%)	14 (17.3%)	1 (9.1%)	0.49
Hypertension	38 (41.3%)	33 (40.7%)	5 (45.5%)	0.77
Dyslipidemia	21 (22.8%)	18 (22.2%)	3 (27.3%)	0.71
Diabetes mellitus	18 (19.6%)	17 (21.0%)	1 (9.1%)	0.35
COPD	2 (2.2%)	2 (2.5%)	0 (0.0%)	0.60
Medication (n)[a]				
Diuretic	26 (28.3%)	23 (28.4%)	3 (27.3%)	0.94
ACE inhibitor	13 (14.1%)	12 (14.8%)	1 (9.1%)	0.61
ARB	38 (41.3%)	33 (40.7%)	5 (45.5%)	0.77
Beta-blocker	29 (31.5%)	28 (34.6%)	1 (9.1%)	0.09
Cardiotonic agent	5 (5.4%)	5 (6.2%)	0 (0.0%)	0.40

BMI, body mass index; GDS-15, Geriatric Depression Scale (15-item); BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; COPD, chronic obstructive pulmonary disease; ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NYHA, New York Heart Association; AWGS, Asian Working Group for Sarcopenia.
A cardiac event was defined as cardiac death or re-hospitalization for worsening heart failure. Sarcopenia was defined according to the AWGS-recommended diagnostic algorithm. Self-care score was measured with the European Heart Failure Self-care Behavior scale.
*P <0.05; [#]P <0.01. [a]Assessed by χ^2 test; [b]Assessed by unpaired t-test; [c]Assessed by Mann Whitney U-test.

Table 4. Cox proportional hazards model showing the impact of sarcopenia on cardiac events for each group.

	All (n=191)		NYHA I (n=99)		NYHA II–IV (n=92)	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Sarcopenia	2.59 (0.85-7.88)	0.10	1.10 (0.13-9.08)	0.93	4.44 (1.09-18.14)	0.04*
Sex (male=1)	0.59 (0.19-1.79)	0.35	0.83 (0.16-4.40)	0.83	0.45 (0.10-2.12)	0.31
BNP	1.00 (0.99-1.00)	0.65	1.00 (1.00-1.01)	0.95	1.00 (0.98-1.01)	0.52
eGFR	1.01 (0.98-1.03)	0.70	1.02 (0.97-1.06)	0.51	1.00 (0.96-1.04)	0.94

BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; AWGS, Asian Working Group for Sarcopenia; HR, hazard ratio; CI, confidence interval. Sarcopenia was defined according to the AWGS-recommended diagnostic algorithm.
Confounders like sex, BNP, and eGFR were adjusted for in the multivariate analyses.
*P <0.05.

Therefore, it is likely that these various factors associated with sarcopenia may result in further deterioration of elderly patients with HF.

In the NYHA I group, we found no significant association between cardiac events and other variables. HF patients with NYHA I did not present any physical symptoms and this might have influenced the present results. Low left ventricular ejection fraction, atrial fibrillation, and causative diseases of HF are leading examples of factors and prognosticators of HF, although we could not measure these in the present study.[36,37] It would be important to investigate prognosticators of HF patients classified as NYHA I by including HF itself as a potential factor.

Based on the results of this study, prevention and treatment of sarcopenia in elderly patients with HF are quite important. First, early detection of sarcopenia using the algorithm developed by the AWGS is beneficial in elderly patients with HF. Next, a combination of physical exercise and nutritional supplements containing proteins,[38] amino acids[39] and vitamin D[40] may effectively improve sarcopenia.[41] In terms of exercise, it may be beneficial for symptomatic HF patients to increase their level of physical activity using appropriate exercises of strength. It is necessary to devise interventions that a physical therapist or managerial dietician can easily introduce into clinical practice.

This study had several limitations. The first limitation consisted in the inclusion criteria used for this study. We recruited patients who had previously been admitted to hospital for the management of HF or who were receiving prescription medication for HF only at our institution. Furthermore, studies using gold standards for the diagnosis of HF, such as the Framingham Heart Study HF criteria[42] or standardized and detailed inclusion criteria are needed. Second, we did not include HF patients with artificial implants such as cardiac pacemakers or joints, as they could not undergo bioimpedance testing. These patients had comorbidities associated with a greater risk of falls. Furthermore, we did not include HF patients who did not consent to participate in this study. This sampling bias might introduce some errors of inference and limit the generalizability of the results. Third, we did not collect data regarding cardiac cachexia, fluid status that might be associated with measurements of bioelectrical impedance analysis, cardiac output data such as left ventricular ejection fraction, levels of pro-inflammatory cytokines, detailed data regarding medication history such as dosage, exercise tolerance, or information about physical activity. Moreover, we did not include NYHA and medications as predictive factors of cardiac events in our analysis. Therefore, the relationship between sarcopenia and cardiac events remains unclear. Further studies are needed using these data for a more comprehensive assessment of predictive factors of cardiac events. Fourth, the classification of patients into two groups (NYHA I group and NYHA II–IV group), our limited sample size (n=99 patients in the NYHA I group and n=92 patients in the NYHA II–IV group), and low rate of overall events (10.5%), as well as the short follow-up period (eight months) might have affected the results, reduced the power of the analysis, and limited the generalizability of the results. A fifth limitation was the method used for the measurement of demographic data. Self-reported body height might have influenced the diagnosis of sarcopenia and might have affected influences the results.

5. CONCLUSION

In the present study, we investigated the potential risk factors of cardiac events in elderly patients with HF, including sarcopenia. We demonstrated that sarcopenia predicts cardiac events in HF patients belonging to NYHA classes II-IV. Intervention studies are necessary in the future to explore whether prevention and treatment of sarcopenia may prevent cardiac events in HF patients.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

Acknowledgements

The authors acknowledge the clinicians of the Department of Cardiovascular Medicine at the Koto Memorial Hospital for their help with the recruitment of patients and the students of the Human Health Sciences at Kyoto University for their help with data collection.

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