Loss of skeletal muscle mass predicts cardiac death in heart failure with a preserved ejection fraction but not heart failure with a reduced ejection fraction

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Abstract

Aims Loss of skeletal muscle mass is an important determinant associated with poor long-term prognosis in patients with acute decompensated heart failure (ADHF). However, limited evidence is available. This study investigated the prognostic value of the psoas muscle mass index (PMI) in patients with ADHF.

Methods and results A total of 210 consecutive patients aged ≥60 years with ADHF were enrolled using a prospective database between 2015 and 2017. Primary endpoint was incidence of cardiac death. Cross-sectional psoas muscle area at the L3 vertebral level was obtained by computed tomography, and PMI was calculated by height. Reduced PMI was defined as a PMI below the 25th sex-specific percentile. Patients were also classified by their left ventricular ejection fraction (EF) as having either heart failure with a reduced ejection fraction (HFrEF, EF < 50%) or heart failure with a preserved ejection fraction (HFpEF, EF ≥ 50%). The median follow-up period was 1.8 years. There were 44 cardiac deaths (21%) during the study period. Patients with reduced PMI had significantly higher cardiac death rates than those with preserved PMI (33% vs. 17%, log-rank test P = 0.006). In subgroup analysis, HFpEF patients with reduced PMI had significantly higher cardiac death rates than those with preserved PMI (38% vs. 16%, log-rank test P = 0.006); conversely, HFrEF patients had comparable cardiac death rates regardless of their PMI group (27% for reduced PMI vs. 18% for preserved PMI, log-rank test P = 0.24). Multivariate Cox proportional hazards model revealed that patients with reduced PMI had a 2.3-fold higher risk of cardiac death compared with patients with preserved PMI (95% confidence interval 1.23–4.42, P = 0.01).

Conclusions Reduced PMI helps to predict long-term outcome in patients with HFpEF but not HFrEF.

Keywords Acute decompensated heart failure; Psoas muscle mass; Skeletal muscle

Introduction

An aging population is common in developed countries, and the increasingly common incidence of cardiovascular disease in the elderly, especially acute decompensated heart failure (ADHF), is a leading issue for public health. Despite noticeable development of diagnosis and medical therapy including interventional therapy, long-term outcome for cardiac death and heart failure rehospitalization remains unsatisfactory in elderly patients with ADHF. This may be because multidimensional factors are related to prognosis in elderly patients with ADHF, not only cardiovascular function but also a geriatric condition known as a sarcopenia, frailty, or cachexia. Although a geriatric condition that involved accurate risk stratification is crucial for providing optimal clinical management and treatment decision making in elderly patients with ADHF, it has remained unestablished.

Recently, exercise intolerance in patients with ADHF has been associated with skeletal muscle abnormalities including loss of skeletal muscle mass and skeletal muscle dysfunction rather than cardiac and pulmonary dysfunction. Risk stratification highlighting skeletal muscle abnormalities may act as a
better indicator and help prognostic prediction. Psoas muscle mass index (PMI) has received growing recognition as an objective and quantitative marker to assess loss of skeletal muscle mass and has been suggested as a useful predictive marker for long-term outcome in patients undergoing cardiovascular or oncologic surgeries.8,9 On the other hand, the prognostic implications and risk stratification capability of PMI in patients with ADHF are currently unknown. Accordingly, the purpose of the present study was to investigate the long-term prognostic value of PMI in hospitalized patients with ADHF.

Methods

Study protocol and subjects

Two hundred sixty consecutive patients aged ≥60 years who were hospitalized due to ADHF in Kansai Medical University Hospital between May 2015 and December 2017 were enrolled using a prospective database. Patients were diagnosed as having ADHF according to the Framingham criteria.10 Patients with New York Heart Association functional class III or IV on admission were included. Standard treatment strategy was performed according to 2016 European Society of Cardiology guideline.11 Additionally, multidisciplinary care management including medical treatment optimization, cardiac rehabilitation, nutritional education, and psychosocial support was provided during hospitalization. Patients with malignant disease with life expectancy ≤1 year (n = 22), end-stage renal disease on dialysis (n = 17), and loss of follow-up within 1 year (n = 11) were excluded. Thus, 210 patients were included in the final analysis. The study protocol was approved by the ethics committee of Kansai Medical University (No. 20130181) and was registered at the University Hospital Medical Information Network Clinical Trial Registry (Unique identifier: UMIN000013445). Written informed consent was obtained from all participants. The investigation conforms with the principles outlined in the Declaration of Helsinki.

Analysis of psoas muscle mass index

Plain abdominal computed tomography (CT) with 5 mm slice imaging was performed during hospitalization using an 80 multidetector CT (Aquilion Prime, Canon, Japan). Cross-sectional psoas muscle area (mm²) and CT value (Hounsfield units) were measured using a dedicated workstation (Virtual Place, AZE Ltd, Japan). Both left and right cross-sectional areas of the psoas muscle at the L3 vertebral level were traced semi-automatically by a physician who was blinded to the clinical history. PMI was obtained by cross-sectional psoas muscle area divided by height: PMI (mm²/m²) = [right psoas muscle mass (mm²) + left psoas muscle mass (mm²)]/height (m) × height (m)]. Reduced PMI was defined as a PMI below the 25th sex-specific percentile according to previous reports.12,13

Data collection

Patient characteristics, vital signs on admission, and past medical history were extracted from the medical records. Laboratory parameters were collected on admission. Echocardiography was performed by a cardiologist on admission using Vivid 7 or Vivid E9 (GE Healthcare, Marlborough, MA, USA). Standard transthoracic and Doppler echocardiographic parameters were examined. Left ventricular ejection fraction (EF) was measured by Simpson method, and all patients were classified according to their EF as having heart failure with a reduced ejection fraction (HFrEF, EF < 50%) or heart failure with a preserved ejection fraction (HFnEF, EF ≥ 50%). Oral medication at discharge including loop diuretics, angiotensin converting enzyme inhibitor or angiotensin II receptor blocker, beta blocker, spironolactone, and sodium glucose cotransporter 2 inhibitor was extracted from medical records for patients without in-hospital death.

Endpoint and follow-up

Primary endpoint was cardiac death. Secondary endpoint was heart failure rehospitalization. The incidence of events was identified from the medical records or mailed questionnaire to the follow-up hospitals. The death certificate was prepared by two experienced physicians using medical records or mailed questionnaire who were blinded to the endpoint classification. If the reviewing physicians disagreed in the event classification, they were arbitrated by a third party.

Estimation of Get With the Guidelines-Heart Failure risk score

The Get With the Guidelines-Heart Failure (GWTG-HF) risk score was established as an assessment tool to predict in-hospital mortality in patients with ADHF, besides it was possible to provide a long-term prognosis.14–16 This risk score consists of seven predictor variables (age, systolic blood pressure, heart rate, blood urea nitrogen, sodium, chronic obstructive pulmonary disease, and race). Patient’s score was calculated by summing points assigned to the value of each predictor, and the values were between 0 and 100. Additionally, a modified GWTG-HF model had been proposed to improve predictive value of long-term prognosis.15 This modified score added the following variables to the GWTG-HF score: New York Heart Association classification, anaemia, EF, and B-type natriuretic peptide. PMI was added
to the modified GWTG-HF model to clarify the discrimination capability of PMI. The risk stratification capability of PMI was evaluated using the GWTG-HF risk score as well as a modified GWTG-HF model.

Statistical analysis

Results are presented as means ± standard deviations or medians with interquartile ranges. Categorical variables were presented as number of total (percentages). Comparisons of differences between the groups were made by unpaired Student t-test or Mann–Whitney U-test for continuous variables and χ² square test for categorical variables. Cardiac death and heart failurerehospitalization were compared by Kaplan–Meier survival analysis and log-rank test. Multivariate Cox proportional hazards models were conducted according to AHEAD risk score (age, atrial fibrillation, diabetes mellitus, anaemia, and serum creatinine), which was established to predict long-term mortality in patients with ADHF. When the optimal cut-off value of PMI for predicting cardiac death was analysed by the receiver operating characteristic curve analysis, net reclassification improvement and integrated discrimination index were calculated to evaluate the quality of improvement of the PMI to the GWTG-HF score and modified GWTG-HF model. The JMP 14.2.0 software (SAS Institute Inc., Cary, NC, USA) and R 3.6.3 with additional packages, including Rcmdr, Epi, pROC, and Predict ABEL were used for all statistical analyses. A P value < 0.05 was considered significant.

Results

During the median follow-up of 1.8 years (interquartile range, 1.1–2.9 years), 44 patients (21%) had cardiac death, 14 (6.7%) had in-hospital death, 75 (36%) had all-cause death, and 86 (44%) had heart failure rehospitalization.

Psoas muscle assessment

Cross-sectional psoas muscle area, PMI, and CT value were significantly lower in patients with cardiac death compared with those without (Table 2). The 25th sex-specific percentile of PMI was 409 mm²/m² in men and 317 mm²/m² in women. According to these PMI cut-off values, patients were divided into two groups: a reduced PMI group (n = 52) and a preserved PMI group (n = 158). Figure 1 shows representative CT imaging for each group.

Patient characteristics

Baseline patient characteristics are shown in Table 2. There were no significant differences between our patient groups in age, sex, vital signs, past medical history, laboratory parameters, New York Heart Association classification, or EF, except for body mass index and B-type natriuretic peptide levels. Oral medication on hospital discharge in patients without in-hospital death was shown (Supporting Information, Table S2). Patients with reduced PMI had a higher rate of loop diuretic administration compared with patients with preserved PMI. The administration of other standard heart failure treatments including angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, spironolactone, and sodium glucose cotransporter 2 inhibitors was comparable between groups.

Prognostic value of psoas muscle mass index

Kaplan–Meier survival analysis illustrated that reduced PMI was associated with significantly higher cardiac death rates compared with preserved PMI (33% vs. 17%, log-rank test P = 0.006, Figure 1). In patients with HFpEF, those with reduced PMI had significantly higher cardiac death rates compared with those with preserved PMI (38% vs. 16%, log-rank test P = 0.006); in contrast, there was no difference in the incidence of cardiac death regardless of PMI in patients with HFrEF (27% for reduced PMI vs. 18% for preserved PMI, log-rank test P = 0.24, Figure 2). Patients with reduced PMI had a significantly higher rate of heart failure rehospitalization compared with patients with preserved PMI (50% vs. 38%, log-rank test P = 0.04, Figure 3). However, patients with reduced PMI experienced no difference in the incidence of heart failure rehospitalization compared with those with preserved PMI in either the HFpEF subgroup (50% for reduced PMI vs. 37% for preserved PMI, log-rank test P = 0.15) or the HFrEF subgroup (50% for reduced PMI vs. 39% for preserved PMI, log-rank test P = 0.14).

Table 1  Psoas muscle assessment

| Variable                        | Cardiac death (+) (n = 44) | Cardiac death (–) (n = 166) | P value |
|--------------------------------|-----------------------------|-----------------------------|---------|
| Cross-sectional psoas muscle area (mm²) | 947 ± 311                   | 1156 ± 403                  | 0.002   |
| PMI (mm²/m²)                    | 398 ± 103                   | 467 ± 137                   | 0.002   |
| CT value (Hounsfield unit)      | 27.3 ± 10.0                 | 33.1 ± 10.0                 | <0.001  |

CT, computed tomography; PMI, psoas muscle mass index. Data presented as mean ± standard deviation.
The multivariate Cox proportional hazard model revealed that patients with reduced PMI had a 2.3-fold higher risk of cardiac death compared with those with preserved PMI after adjusting for covariates within the AHEAD risk model (95% confidence interval 1.23–4.42, \( P = 0.01 \), Table 3). The optimal PMI cut-off value for predicting cardiac death was determined to be 524 mm\(^2\)/m\(^2\) (sensitivity, 95%; specificity, 31%; positive predictive value, 27%; and negative predictive value, 96%). Discrimination capability was evaluated with the addition of PMI < 524 mm\(^2\)/m\(^2\) to the modified GWTG-HF model. Net reclassification improvement and integrated discrimination index were significantly improved by adding PMI < 524 mm\(^2\)/m\(^2\) to the modified risk model (Table 4).

### Table 2: Patient characteristics at admission

| Characteristic                        | Reduced PMI (n = 52)       | Preserved PMI (n = 158) | \( P \) value |
|---------------------------------------|---------------------------|-------------------------|---------------|
| Age (years)                           | 80 (70–86)                | 79 (72–85)              | 0.53          |
| Male                                  | 25 (48)                   | 82 (52)                 | 0.63          |
| Body mass index (kg/m\(^2\))          | 19.0 (16.6–21.3)          | 21.2 (19.3–24.7)        | <0.0001       |
| Systolic BP (mm Hg)                   | 144 (127–166)             | 137 (120–159)           | 0.22          |
| Diastolic BP (mm Hg)                  | 84 (69–92)                | 78 (66–96)              | 0.87          |
| Heart rate (beats/min)                | 101 (86–114)              | 94 (77–114)             | 0.09          |
| Hypertension                          | 28 (54)                   | 81 (51)                 | 0.75          |
| Diabetes mellitus                     | 14 (27)                   | 64 (41)                 | 0.08          |
| Atrial fibrillation                   | 20 (38)                   | 75 (47)                 | 0.26          |
| Past smoking                          | 23 (44)                   | 80 (51)                 | 0.42          |
| Prior myocardial infarction           | 9 (17)                    | 39 (25)                 | 0.27          |
| Prior heart failure hospitalization   | 17 (33)                   | 51 (32)                 | 0.96          |
| Laboratory parameters                 |                           |                         |               |
| Haemoglobin (g/dL)                    | 11.1 (10.0–13.2)          | 11.1 (9.6–13.1)         | 0.88          |
| Serum creatinine (mg/dL)              | 1.0 (0.8–1.5)             | 1.3 (0.9–1.7)           | 0.11          |
| Serum sodium (mEq/L)                  | 140 (136–142)             | 140 (136–142)           | 0.36          |
| Serum albumin (g/dL)                  | 3.4 (3.0–3.8)             | 3.5 (3.2–3.9)           | 0.32          |
| BNP (pg/mL)                           | 1042 (644–1976)           | 746 (395–1325)          | 0.02          |
| High-sensitive CRP (mg/dL)            | 0.41 (0.19–2.09)          | 0.84 (0.28–2.69)        | 0.10          |
| NYHA classification IV                | 29 (56)                   | 108 (68)                | 0.10          |
| LVEF (%)                              | 52 (26–66)                | 46 (31–63)              | 0.89          |
| LVEF < 50%                            | 26 (50)                   | 85 (54)                 | 0.63          |

BNP, B-type natriuretic peptide; BP, blood pressure; CRP, C-reactive protein; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Data presented as median (25th to 75th percentiles), or number (%).

The main findings of this observational study were as follows. First, during the median follow-up of 1.8 years, 44 (21%) of 210 patients had cardiac death. Cross-sectional psoas muscle area, PMI, and CT value were significantly lower in patients...
with cardiac death as compared with those without cardiac death. Second, the patients with reduced PMI, defined as a PMI less than the 25th sex-specific percentile, had a significantly higher incidence of cardiac death than those with preserved PMI among the patients with HFpEF but not among patients with HFrEF. Third, patients with a reduced PMI had a 2.3-fold increase in the risk of cardiac death compared with those with a preserved PMI after adjusting for covariates. Fourth, when adding PMI < 524 mm$^2$/m$^2$ to the modified GWTG-HF model, PMI improved discrimination capability for predicting cardiac death. To the best of our knowledge, this is the first observational study identifying the prognostic value of PMI in patients aged ≥60 years with ADHF.
Loss of skeletal muscle is more prevalent in patients with heart failure compared with healthy age-matched controls, and it is not only a condition of the elderly but also a result of physical inactivity, malnutrition, and chronic illness.\textsuperscript{18,19} Importantly, declining skeletal muscle mass is a progressive syndrome, and skeletal muscle is lost earlier than body weight. As a result, skeletal muscle loss precedes frailty and cachexia.\textsuperscript{20} Loss of skeletal muscle occurs predominantly in postural rather than non-postural muscles and develops earlier in life.\textsuperscript{21} Likewise, psoas muscle mass declines significantly in healthy individuals ≥50 years of age compared with younger individuals.\textsuperscript{22} Earlier detection of skeletal muscle loss, especially postural muscles, in patients with ADHF, is important for early treatment before cachexia manifests and is detectable.\textsuperscript{5}

Although several methods have been proposed for the quantitative assessment of skeletal muscle mass, a gold standard has not been established. Imaging techniques including dual energy X-ray absorptiometry, bioelectrical impedance analysis, CT, and magnetic resonance imaging have become useful for assessing the loss of skeletal muscle mass in certain circumstances.\textsuperscript{6,23} However, an accurate assessment of skeletal muscle mass has proven elusive for hospitalized patients with ADHF. Clinical assessment of sarcopenia using symptom-based assessments such as questionnaires and symptom scoring is susceptible to being erroneously linked with the severity of heart failure in cases of ADHF because fatigue, variations in body weight, and decreased exercise tolerance are common heart failure-related symptoms. Therefore, using symptom-based assessments of sarcopenia for ADHF may be misleading to evaluate the clinical definition of sarcopenia.\textsuperscript{24}

Assessment of PMI using CT imaging has been advocated for as an objective and quantitative method for assessing sarcopenia. The psoas muscle provides postural support to the lumbar spine as well as the sacroiliac and hip joint, and it is the main flexor of the hip; as a result, it is strongly linked with physical performance in daily life. Furthermore, low PMI is strongly associated with poor short-term and long-term outcomes in cardiac and oncologic surgeries.\textsuperscript{8} A systematic review suggests that psoas muscle mass is more strongly related to short-term prognosis than total skeletal muscle mass according to CT-based assessments in patients who underwent oncologic surgery.\textsuperscript{8} Evaluation of PMI derived by CT is a useful objective and quantitative method for patients with ADHF. In our study, calculation of cross-sectional psoas muscle area was traced semi-automatically, though automated analysis can be performed for a quicker and easier assessment of psoas muscle area.\textsuperscript{25}

Several models for long-term risk stratification in patients with ADHF have been advocated. In our study, AHEAD score and GWTG-HF risk score were utilized to evaluate prognostic capability collaborated with PMI. AHEAD score consists of five variables, namely, atrial fibrillation, anaemia, elderly, renal impairment, and diabetes mellitus and estimates the short-term and long-term prognosis.\textsuperscript{17} We conducted multivariate analysis including PMI in addition to those five variables and found that PMI was the strongest variable in predicting long-term cardiac death. GWTG-HF score can estimate not only in the acute phase but also long-term prognostic score in patients with ADHF.\textsuperscript{14–16} More recently, the modified GWTG-HF model has been reported with improved long-term prognostic value as compared with the previous GWTG-HF model. Thus, we investigated further the risk stratification capability when PMI was added to those models and found that PMI significantly improved long-term prognostic value for cardiac death in elderly patients with ADHF.

In our study, the CT value of the psoas muscle was significantly lower in patients with cardiac death than in those without cardiac death. Skeletal muscle CT value reflects muscle fat infiltration, which relates to skeletal muscle quality. Although the clinical implication of muscle fat infiltration in patients with ADHF is not well established, greater muscle fat infiltration is associated with diminished skeletal muscle strength in the general population.\textsuperscript{26} Additionally, a decrease in skeletal muscle CT value was reported to involve poor long-term prognosis in the general population. Therefore, decreased psoas muscle CT value may be a marker of muscle function impairment including muscle metabolism.

### Table 3: Multivariate Cox proportional hazards model for cardiac death

| Characteristic       | Hazard ratio | 95% CI          | P value |
|----------------------|--------------|-----------------|---------|
| Age (years)          | 1.08         | 1.04–1.13       | <0.001  |
| Atrial fibrillation  | 1.40         | 0.74–2.64       | 0.31    |
| Diabetes mellitus    | 1.67         | 0.84–3.31       | 0.15    |
| Haemoglobin (g/dL)   | 1.03         | 0.88–1.21       | 0.70    |
| Serum creatinine (mg/dL) | 1.29     | 1.02–1.62       | 0.03    |
| Reduced PMI          | 2.33         | 1.23–4.42       | 0.01    |

CI, confidence interval; PMI, psoas muscle mass index.

### Table 4: Effect of adding psoas muscle mass index to predict cardiovascular event

|                      | C-statistics | 95% CI          | P value | NRI | 95% CI          | P value | IDI | 95% CI          | P value |
|----------------------|--------------|-----------------|---------|-----|-----------------|---------|-----|-----------------|---------|
| GWTG-HF risk score   | 0.68         | 0.58–0.78 Ref.  |         |     | Ref.            |         |     | Ref.            |         |
| Modified GWTG-HF model\textsuperscript{a} | 0.71         | 0.61–0.81 0.13  | 0.245–0.085–0.574 | 0.15  | 0.020 0.003–0.03 | 0.02    |     | 0.001 0.007–0.048 | 0.000  <0.009 | 0.001 |
| Modified GWTG-HF model\textsuperscript{a} + PMI < 524 mm\textsuperscript{2}/m\textsuperscript{2} | 0.77         | 0.69–0.86 <0.001 0.646 | 0.381–0.910 <0.001 0.074 | 0.048–0.009 | <0.001 |

BNP, B-type natriuretic peptide; CI, confidence interval; GWTG-HF, Get With the Guidelines-Heart Failure; IDI, integrated discrimination improvement; NYHA, New York Heart Association classification; PMI, psoas muscle mass index.

\textsuperscript{a}GWTG-HF risk score plus NYHA class, anaemia, LVEF, and BNP.
Therapeutic approaches for ADHF patients with sarcopenia remain poorly defined, but multidimensional approaches including guideline-recommended doses of heart failure therapies, exercise, and nutritional support have been recommended.\textsuperscript{11} Standard heart failure treatments including angiotensin converting enzyme inhibitors, beta-blockers, and spironolactone should be administrated because these therapies not only improve long-term prognosis but also provide favourable effects to counteract loss of skeletal muscle mass. Cardiac rehabilitation with aerobic and resistance exercise training can reduce mortality and heart failure rehospitalization as well as improve functional capacity and quality of life. Additionally, anabolic agents might improve loss of skeletal muscle mass.\textsuperscript{27} Nutritional treatment is generally supported by poor evidence, but omega-3 polyunsaturated fatty acids, protein-rich and calorie-rich nutritional supplements, and essential amino acids may be helpful.\textsuperscript{5} In our study, patients with ADHF received multidisciplinary treatment including standard heart failure drugs, cardiac rehabilitation, and nutritional education during their hospitalization. These therapeutic approaches may be continued after hospital discharge, and further study is required to determine whether these interventional approaches beneficially impact PMI and long-term prognosis.

**Limitations**

The current study has several limitations. First, this study was conducted in a single-centre registry and had a small sample size. Therefore, limiting the ability to generalize the findings. Nonetheless, this is the first study to elucidate the prognostic value of PMI in patients with ADHF. Second, the cut-off value of PMI obtained by the receiver operative characteristic curve analysis were based on this present study. We do not have data regarding the validity of the cut-off value, and there may be a better cut-off value that should be used. Third, our study had the potential for patient treatment bias because treatment strategy was at the discretion of the attending physician. Older patients with greater comorbidities might have avoided interventional treatment. However, the percentage of patients who developed in-hospital death was only 6.7%, which was not a high incidence. Therefore, patients are most likely to have received adequate treatments.

**Conclusions**

Reduced PMI predicts long-term outcome in patients with HFpEF but not with HFrEF.

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**Conflict of interest**

None declared.

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**Supporting information**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Oral medication at hospital discharge in patients without in-hospital death.

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