Title of the article:
Sarcopenia as a robust predictor of readmission within six months among individuals experiencing acute stroke

Short running title
Sarcopenia and readmission in acute stroke

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Conflicts of Interest

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Abstract

Objective: Sarcopenia negatively affects the short-term prognosis of hospitalized older adults. However, no evidence currently supports a direct relationship between sarcopenia and readmission among individuals who have experienced an acute stroke. Therefore, we investigated whether sarcopenia is associated with readmission after discharge.

Methods: This retrospective cohort study included patients who had experienced acute stroke. Sarcopenia was defined as the coexistence of low skeletal muscle mass index (SMI) and grip strength. We applied the log-rank test and Cox proportional hazards regression analysis to analyze whether sarcopenia, low SMI, and low grip strength were associated with readmission within 6 months.

Results: Among 228 included patients (mean age, 72.8 years; 146 males), the prevalence of sarcopenia was 24.6% (n=56; male, 17.8%; female, 36.6%). Cox proportional hazards regression analysis using the propensity score as a covariate revealed that sarcopenia (hazard ratio [HR] 7.21 [95% confidence interval (CI) 1.45–35.8]; p=0.016) and low skeletal muscle mass (HR 7.40 [95% CI 1.14–48.1; p=0.036), but not low grip strength (HR 1.42 [95% CI 0.281–7.21]; p=0.670), were significantly associated with readmission for stroke within 6 months.

Conclusions: Sarcopenia was negatively associated with readmission within 6 months of stroke onset in patients in Japan who had experienced an acute stroke. These findings suggest that the identification of sarcopenia may facilitate prognostic prediction from the acute stage and intervention(s) to prevent rehospitalization.

Keywords: stroke, sarcopenia, muscle mass, acute stroke, readmission, prognosis
Introduction

Sarcopenia is prevalent and associated with poor prognosis in patients with stroke (1–5). Sarcopenia is characterized by the coexistence of low muscle mass and poor muscle strength or physical function (6) and has been investigated in patients who have experienced stroke. The prevalence rates of sarcopenia in patients who have experienced stroke are 15.8–18% before onset, 28.2–30.8% during acute hospitalization, and 50–51.6% during convalescent hospitalization (1,3,5,7,8), showing increasing prevalence with each stage of stroke. In the acute phase of stroke, low muscle mass and sarcopenia are associated with poor functional prognosis, poor walking function, and limitations in activities of daily living (ADL) (3,5,9). During the convalescent phase, sarcopenia is associated with limitations in ADL, discharge to home, and independence in urination and defecation (4,10).

Individuals who experience stroke are at risk of readmission after discharge, especially community-dwelling and hospitalized older adults with sarcopenia, sepsis, heart disease, respiratory diseases, cancer, diabetes, and kidney failure (11–13). Similarly, a history of stroke, atrial fibrillation, hypertension, diabetes, hyperlipidemia, obesity, and lifestyle factors increase the risk of stroke in these populations (14,15). Readmissions of patients who have experienced stroke are often caused by recurrent stroke, infection, cardiac disease, or falls (16–18). The reported readmission rates of these patients are 24% within 180 days (19) and 24–39.1% within 1 year (20,21). The risk factors associated with readmission include older age; sex; history of stroke, cardiovascular disease, or diabetes mellitus; length of acute hospitalization; and complications during acute stays (17). Readmissions significantly contribute to the cost of inpatient care and are indicators of quality of care (16,22). Sarcopenia and low skeletal muscle mass also increase the risk of falls (23) and stroke (24) among community-dwelling adults. Furthermore, sarcopenia influences readmission rates in hospitalized older patients (12), with
probability rates of 32% at 6 months (13) and 71% at 3 years (25). Therefore, sarcopenia in patients with stroke may be associated with readmission.

However, limited evidence supports the relationship between sarcopenia and readmission among individuals who experience acute stroke. Clarifying this relationship may facilitate the early assessment of sarcopenia and its prevention and treatment. Accordingly, we aimed to determine the association of sarcopenia with readmission in patients who experienced acute stroke.

Methods

Participants

This single-center, retrospective cohort study was conducted at the authors’ 454-bed acute-care hospital in Niigata, Japan, between August 2020 and March 2022. All patients admitted within 48 h of stroke onset during the study period were enrolled. Patients diagnosed with subarachnoid hemorrhage were excluded because they require different treatment and management approaches from those for other patients with stroke. The inclusion criterion was evidence of stroke supported by computed tomography or magnetic resonance imaging findings. Individuals with metal implants, those who died in hospital or after discharge, or those with missing data were excluded from the study.

Definition of sarcopenia

Sarcopenia was defined as the co-existence of low muscle mass (skeletal muscle mass index [SMI]: males <7.0 kg/m², females <5.7 kg/m²) and muscle strength (low grip strength: males <28 kg, females <18 kg) (1,6). Body composition was measured using a portable, noninvasive, multifrequency bioimpedance device (InBody S10, InBody, Tokyo, Japan). This device can be conveniently used on patients who cannot remain in a standing or sitting position because of
hemiplegia or those who are bedridden. Measurements were performed after the patients had rested for 15 min in the supine position and were avoided within 3 h of eating. The electrodes were placed on the thumb, third finger, and ankle on both sides. SMI was calculated as the appendicular skeletal muscle mass divided by height squared (kg/m²). Handgrip strength was defined as the highest of two measures using a Smedley hand dynamometer (TKK 5401; Takei Scientific Instruments Co., Ltd., Tokyo, Japan) on the patient's non-paralyzed side while in a supine position (5,7,26). Sarcopenia was assessed within 5 days of admission.

**Data collection**

The data were collected retrospectively. Basic data, including age, sex, body mass index (BMI), and clinical details at the time of stroke onset were collected within 48 h of admission. Stroke severity was assessed according to the National Institutes of Health Stroke Scale (NIHSS) score, pre-stroke physical function using the pre-stroke modified Rankin Scale (mRS) score, laboratory data (albumin and hemoglobin levels), stroke type, paralysis, infarct location, comorbidities, nutritional status using the Geriatric Nutritional Risk Index (GNRI), average daily energy intake, Functional Independence Measure (FIM) score, and outcomes at discharge. The GNRI was calculated using the following equation: \( (1.489 \times \text{albumin [g/dL]}) + (41.7 \times [\text{weight/ideal weight}]) \) (26). The ideal body weight was defined as the weight of the patient at a BMI of 22.0 kg/m². Average daily energy intake was determined as previously described (28). Dietary records were reviewed to quantify the mean daily nutritional intake during the first week after admission to the acute-care hospital. Experienced nurses measured patient oral intake using visual estimation. The energy content of enteral and parenteral nutrition was collected from medical records.

**Outcome**
The endpoint of this study was readmission within 6 months of stroke onset. A self-administered questionnaire was sent to patients 6 months after stroke onset. Information regarding first readmission after discharge, date of readmission, and reasons for readmission were collected. From the questionnaire results, data regarding readmissions due to stroke at the authors’ hospital or other hospitals and all readmissions, including those for other diseases, were collected.

**Ethical approval**

This retrospective cohort study was approved by the ethics committee of the authors’ hospital (approval no.: 02-024) and conducted in accordance with the principles of the Declaration of Helsinki. Owing to the retrospective nature of the study and use of anonymized data, the requirement for informed written consent was waived. Instead, the patients were offered an opt-out option with the opportunity to withdraw from the study at any time.

**Statistical analysis**

Continuous data are expressed as means (SD) or medians (interquartile range [IQR], i.e., 25th–75th percentile). Categorical data are expressed as numbers (%) of participants. We compared the sarcopenia and non-sarcopenia groups using the chi-square test, unpaired t-test, and Mann–Whitney U test. Using the log-rank test, we evaluated the effects of sarcopenia, low skeletal muscle mass, and low grip strength on readmission within 6 months and reported the results using Kaplan–Meier survival curves. We applied Cox proportional hazards regression analysis to analyze whether sarcopenia, low SMI, and low grip strength were associated with readmission within 6 months, after adjusting for confounders. In this study, because the number of patients was low relative to the number of confounders, we used propensity scores to control for confounding factors. The propensity score, as a single summary of all covariates included in the
propensity score model, can be included as a covariate in the treatment regression model (29). First, we performed logistic regression analysis with sarcopenia or low SMI and grip strength as the objective variables and each covariate as the explanatory variable, and the propensity score was calculated. Next, we performed Cox proportional hazards regression analysis with propensity score, sarcopenia or low SMI, and grip strength as explanatory variables and readmission within 6 months as the objective variable. The adjusted covariates were age; sex; BMI; premorbid mRS score; NIHSS score; stroke type; GNRI; hemoglobin level; atrial fibrillation; history of stroke, diabetes, dyslipidemia, and hypertension; FIM score at admission; and average daily energy intake.

All analyses were performed using EZR in R Commander, version 1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (30). Differences with p < 0.05 were considered statistically significant.

Results

A flow diagram illustrating patient inclusion and exclusion criteria is shown in Figure 1. We initially considered data from 435 individuals who experienced a stroke and were hospitalized during the study period. Of these, we excluded 114 patients for metal implants in the body (n = 11), death in the hospital or after discharge (n = 18), and missing data (n = 85), resulting in 321 patients. The response rate to the questionnaire was 71% (n = 228); thus, data from 228 patients were included in the study (Figure 1).

The patient characteristics are summarized in Table 1. Sarcopenia was identified in 24.6% (n = 56) of patients (male, 17.8%; female, 36.6%). The patients in the sarcopenia group were significantly older; predominantly female; and had lower BMI, GMRI, FOIS, and FIM total scores on admission than those in the non-sarcopenia group. The overall readmission rate was
16.1% (n = 9) in the sarcopenia group and 6.4% (n = 11) in the non-sarcopenia group (p = 0.052), whereas the readmission rates due to stroke were 8.9% (n = 5) and 2.3% (n = 4), respectively (p = 0.042) (Table 2). The reasons for readmission other than stroke were gastrointestinal disease (n = 5), fall (n = 1), and other unknown causes (n = 5).

Kaplan–Meier curves illustrating the effects of sarcopenia, low skeletal muscle mass, and low grip strength on the duration of readmission within 6 months are presented in Figure 2. For stroke readmission within 6 months, we observed significant differences in patients with sarcopenia (p = 0.026) and low skeletal muscle mass (p = 0.009), but not in those with low grip strength (p = 0.397). For all readmissions within 6 months, we observed significant differences for patients with sarcopenia (p = 0.023) and low skeletal muscle mass (p = 0.006) but not for those with low grip strength (p = 0.260).

The results of the Cox proportional hazards regression analysis, with propensity score as a covariate, are summarized in Table 3. Sarcopenia (hazard ratio [HR] 7.21 [95% confidence interval (CI) 1.45–35.8]; p = 0.016) and low skeletal muscle mass (HR 7.40 [95% CI 1.14–48.1]; p = 0.036) were significantly associated with readmission for stroke within 6 months, whereas low grip strength was not (HR 1.42 [95% CI 0.281–7.21]; p = 0.670). Low skeletal muscle mass (HR 3.88 [95% CI 1.17–12.8]; p = 0.026) was significantly associated with all readmissions within 6 months, whereas sarcopenia (HR 3.26 [95% CI 0.96–11.0]; p = 0.058) and low grip strength (HR 1.14 [95% CI 0.372–3.49]; p = 0.815) were not.

**Discussion**

In this study, we aimed to determine whether sarcopenia at admission was associated with readmission within 6 months among individuals who had experienced an acute stroke. Our results yielded two important findings: first, sarcopenia and low muscle mass at admission were
negatively associated with readmission within 6 months; second, 16.1% of patients with stroke and sarcopenia were readmitted for any reason within 6 months.

Sarcopenia and low muscle mass at admission were negatively associated with stroke readmission within 6 months of admission. The potential mechanism underlying this association lies in the decrease in muscle mass and strength, which are crucial for physical function and recovery after stroke. Sarcopenia and low muscle mass can lead to increased risks of cerebral infarction (24) and hypertension (31,32), thus increasing the risk of stroke readmission. Although associations between sarcopenia and readmission in patients with cardiovascular disease (33) and older adults (34) have been reported, to the best of our knowledge, the present study is the first to examine the association between sarcopenia and readmission in patients who had experienced acute stroke.

Sarcopenia was not significantly associated with readmission rates in the present study. Sarcopenia can lead to decreased overall physical performance (3,5), hindering rehabilitation and increasing the risk of readmission. In addition, a decline in physical function in patients with stroke is associated with a risk for readmission within 1 year (20,35,36). In this study, sarcopenia may not have been significantly associated with all readmissions because of the short observation period (6 months).

We also observed no significant association between low grip strength and readmission rates. Grip strength was assessed at the early stage of disease onset, wherein the patients were in a supine position for rest during treatment, and they showed varying degrees of cognitive decline and impaired consciousness due to stroke. Our findings suggest the need to evaluate sarcopenia and muscle mass in addition to the current prognostic evaluations.

In the present study, 16% of patients with stroke and sarcopenia were readmitted for any reason within 6 months. The reported readmission rates of patients with stroke are 24% within 180 days.
(19), 24–39.1% within 1 year (20,21), and 24.7% within 1 year among patients with stroke admitted to convalescent rehabilitation wards (37), with most hospitalizations occurring within 100 days of discharge (35). The factors contributing to the lower readmission rate in the present study compared with those in previous studies include regional differences in the indications for thrombolysis or surgery as well as the length of hospitalization and rehabilitation (38,39). Additionally, the present investigation included patients in the acute phase of stroke; thus, the patient background differed from those of studies that targeted patients in the convalescent phase. Evaluations of low skeletal muscle mass and sarcopenia in patients with acute stroke and providing interventions for prevention and improvement are important. Falls, as a factor in readmission, are associated with decreased balance and walking speed, suggesting the importance of improving physical function (40). Regarding rehabilitation load, while previous research has shown that more hours of exercise can reduce the risk of readmission (41), opinions regarding these findings are mixed in Japan (37). During the short-term acute phase, sufficient exercise and nutrition cannot be guaranteed owing to the bed rest associated with treatment; therefore, improving sarcopenia is difficult. However, future studies should identify patients at a high risk of readmission due to sarcopenia at an early stage and investigate interventions to prevent readmission from the acute phase. Measurement of lower leg circumference should be considered an alternative assessment for sarcopenia, enabling a more comprehensive and precise evaluation of the patient's condition (5,42). As pre-sarcopenia and low skeletal muscle mass can lead to decreased physical function (3,9) and an increased risk of readmission (24), preventing sarcopenia before stroke onset is important. Furthermore, behaviors such as the intake of high-quality protein (43) and resistance training such as standing exercises (44) may help prevent and improve sarcopenia after the acute phase of stroke. Maintaining skeletal muscle mass and preventing sarcopenia are critical during the acute phase, whereas interventions to improve these conditions
are important after the recovery phase.

The present study has several limitations. The first was its single-center design (i.e., one hospital in Japan); moreover, 41% of the participants were excluded, which may have limited the generalizability of the results. Second, owing to the retrospective study design, we were unable to fully adjust for the impact of confounding factors such as genetic, social, and clinical factors on readmission. To enhance the robustness of our findings, future prospective studies with rigorous methodologies, high quality, adequate sample sizes, and strong statistical analyses are needed. Third, because this study was based on data from a questionnaire survey, it may have included cases in which it was difficult to respond to the questionnaire owing to a lack of support. Fourth, although we used propensity scores to assess the impact of sarcopenia on readmission, the specific effects of other covariates remain unclear. Fifth, this study was relatively short-term as it targeted patients within 6 months of stroke onset.

In conclusion, among patients who experienced acute stroke in Japan, sarcopenia was negatively associated with stroke readmission within 6 months of stroke onset but was not significantly associated with readmission rates. Our findings suggest that the identification of sarcopenia or low muscle mass may facilitate prognostic prediction based on the acute stage and intervention(s) to prevent rehospitalization.
Figure legends

Figure 1. Flow diagram illustrating participant inclusion and exclusion.

Figure 2. Kaplan–Meier curves demonstrating the association between stroke readmission and sarcopenia (A); all readmissions and sarcopenia (B); stroke readmission and low SMI (C); all readmissions and low SMI (D); stroke readmission and low grip strength (E); and all readmissions and low grip strength using the log-rank test (F). SMI, skeletal muscle index.