INTRODUCTION

Sarcopenia is the loss of muscle mass, strength, and physical function and largely accounts for physical frailty. It also increases the risk of adverse outcomes such as physical disability, poor quality of life, and death. Furthermore, sarcopenia with disability is becoming an important concept in rehabilitation because its prevalence is approximately 50% in hospital-based rehabilitation centers worldwide and 53% in convalescent rehabilitation wards in Japan. Sarcopenia is associated with conditions that are major causes of disability, such as stroke, hip fractures, and hospital-associated deconditioning. Moreover, sarcopenia can lead to poor outcomes in hospital rehabilitation settings. Therefore, in rehabilitation settings, early detection and appropriate management of sarcopenia, i.e., prevention and treatment, are very important.

Stroke is one of the leading causes of morbidity and mortality worldwide, and more than two-thirds of stroke survivors undergo rehabilitation after hospitalization. In...
geriatric medicine, stroke-related sarcopenia is an emerging concept that has garnered much interest.8–10 Although it has recently been reported that up to 50% of older post-stroke patients are diagnosed with sarcopenia as defined by the Asian Working Group for Sarcopenia,11,12 there is little information about the pathology and clinical impact of stroke-related sarcopenia.

Systemic inflammation plays an important role in sarcopenia. Chronic low-grade inflammation and changes in body composition are interconnected phenomena that characterize the aging process, leading to sarcopenia.13–15 The association between inflammation and muscle wasting as well as impairment of physical function has been known for many years.16–18 Nevertheless, few studies have attempted to evaluate the relationship between systemic inflammation and sarcopenia or to evaluate the adverse effects of sarcopenia on health-related outcomes in rehabilitation settings. Furthermore, to the best of our knowledge, no studies have reported the associations between systemic inflammation and functional rehabilitation outcomes in the recovery stages of stroke.

Therefore, the aim of this study was to determine how systemic inflammation relates to sarcopenia and its impact on functional outcomes in the recovery stages in post-stroke patients.

MATERIALS AND METHODS

This was a retrospective cohort study conducted at a 225-bed hospital that provides convalescent rehabilitation in Kumamoto, Japan, and where 28% of the residents are more than 65 years old. Because of the retrospective nature of the study, an opt-out procedure for recruitment was instituted allowing the patients to withdraw from the study at any time. The study was approved by the Institutional Review Board of Kumamoto Rehabilitation Hospital and adhered to the tenets of the Declaration of Helsinki.

Participants

The present study examined data from 262 consecutive stroke patients admitted to the convalescent rehabilitation wards at the Kumamoto Rehabilitation Hospital between June 2015 and December 2017. The following patients were excluded: (1) those with disturbance of consciousness, (2) those for whom bioelectrical impedance analysis (BIA) was not applicable because of restlessness, implanted metallic devices, or use of other medical equipment, (3) those with acute or chronic high-grade inflammatory diseases, and (4) those who were medically unstable.

Participant characteristics including age, sex, stroke type, body mass index (BMI), nutritional status (the Mini Nutritional Assessment-Short Form [MNA-SF]),19,20 dysphagia using the Food Intake Level Scale (FILS),21) comorbidity severity (the Charlson Comorbidity Index [CCI]),22) premorbid activities of daily living (ADL) (the modified Rankin scale [mRS]),23) time from stroke onset, the presence of paralysis (if present, Brunnstrom stage (BRS) of the paralyzed lower limb),24) and stroke history were all recorded at the time of admission. Within 3 days of admission, the skeletal muscle mass was assessed using BIA, the patient’s physical and cognitive functions were assessed using the Functional Independence Measure (FIM),25) and the handgrip strength was measured. Trained nurses evaluated the BMI, and trained physical and occupational therapists assessed BIA, handgrip strength, and FIM. Handgrip strength was measured using a Smedley hand-dynamometer (TTM, Tokyo, Japan) in the non-dominant hand (or in case of hemiparesis, in the non-paralyzed hand), with the patient in a standing or seated position, depending on their ability, and with arms straight at their side; the higher value from two measurements was recorded.

Systemic Inflammation Assessment

We evaluated low-grade systemic inflammation using the modified Glasgow Prognostic Score (mGPS), which is calculated using serum levels of C-reactive protein (CRP) and albumin (Alb). The mGPS has been validated as an independent prognostic factor in patients with various conditions,26,27 including dependence on parenteral nutrition,28 gastric cancer,29 lung cancer,30 soft tissue sarcoma,31 and chemotherapy.32

The mGPS was calculated as follows33,34): patients with high CRP levels (>1.0 mg/dL) and low Alb levels (<3.5 g/dL) were assigned a score of 2. Patients with high CRP levels (>1.0 mg/dL) were assigned a score of 1, and patients with CRP levels of ≤1.0 mg/dL were assigned a score of 0; albumin levels do not affect a score of 1 or 0. The mGPS for all patients was determined at the time of their admission to the convalescent rehabilitation wards.

Sarcopenia Definition

Sarcopenia was defined as a low skeletal muscle mass index (SMI), as assessed using BIA, and decreased muscle strength (handgrip strength)9 using cut-off values specific to the elderly Asian population.12 A multi-frequency validated BIA instrument (InBody S10; InBody, Tokyo, Japan) was
used for the patients in the present study, many of whom were unable to stand independently. The body composition was measured with patients in the supine position. The measurements were performed by experienced physical therapists in the evenings 1 h before dinner and after more than 1 h of rest following rehabilitation. A correction for dehydration caused by exercise was applied when applicable. The SMI was calculated as the measured skeletal muscle mass divided by the squared body height in meters. The cut-off values for SMI in men and women were <7.0 kg/m² and <5.7 kg/m², respectively. The cut-off values for handgrip strength in men and women were <26 kg and <18 kg, respectively.12)

Main Outcomes

The primary outcome was the FIM score25) at discharge. The FIM score is one of the most common measurement tools for assessing ADLs. The FIM is divided into the motor domain (FIM-motor) with 13 sub-items and the cognitive domain (FIM-cognitive) with 5 sub-items. Tasks are rated on a seven-point ordinal scale that ranges from total assistance to complete independence. The total FIM score ranges from 18 to 126 points; FIM-motor ranges from 13 to 91 points; and FIM-cognitive from 5 to 35 points. Lower scores indicate lower abilities regarding ADLs.

The secondary outcomes included SMI, handgrip strength, and Alb level at discharge.

Statistical Analysis

This study was powered to detect an effect size of a score of 15 in FIM-motor.35) Assuming an alpha error of 0.05 and a two-sided effect, a sample size of 23 per group provided 80% power to observe the effect, implying that a minimum of 46 participants with or without sarcopenia were needed. Statistical analyses were performed using IBM SPSS Statistics (version 21, Armonk, New York). Continuous variables were reported as means (standard deviation, SD) for parametric data or medians (25th–75th percentiles, IQR) for non-parametric data. The t-test, chi-squared test, and the Mann-Whitney U test were used to examine differences between groups with and without sarcopenia. One-way ANOVA for parametric data and the Kruskal-Wallis test for non-parametric data were used for comparing the three independent samples based on the mGPS score. Univariate and multivariate logistic analyses were used to examine which variables were associated with sarcopenia after adjusting for confounders while excluding CCI owing to multicollinearity with mGPS. Multiple linear regression analysis was used to examine which variables were independently associated with FIM-motor at discharge as a functional rehabilitation outcome. Covariates selected to adjust for bias included age, sex, length of stay, time from onset, premorbid mRS, BRS, FILS, MNA-SF, sarcopenia, mGPS, FIM-motor, and FIM-cognitive, all of which were considered to be clinically associated with ADL at discharge, while excluding CCI owing to multicollinearity with mGPS. P values <0.05 were considered statistically significant.

Ethics

We conducted the study in accordance with the Declaration of Helsinki, and the study was approved by the ethics committee of Kumamoto Rehabilitation Hospital. We supplied information regarding the study to all patients, and patients were informed that withdrawal from the study was always possible.

RESULTS

The present study included 204 patients (mean age 74.1 years, 109 men, and 95 women) for analysis. Patients with missing data (n=11) and those with disturbed consciousness (n=19), those not able to undergo BIA (n=14), those with other acute disease (s) or chronic high-grade inflammation (n=12), and those in a medically unstable condition (n=2) were all excluded from the study.

Participant Characteristics

Table 1 compares the characteristics of study participants with and without sarcopenia. Stroke types included cerebral infarction (n=127, 62.3%), cerebral hemorrhage (n=62, 30.4%), and subarachnoid hemorrhage (n=15, 7.4%). Of the 204 patients included in the current study, 81 (39.7%) were diagnosed with sarcopenia. mGPS scores of 0, 1, and 2 were assigned to 151 (74.0%), 40 (19.6%), and 13 (6.4%) patients, respectively. Sarcopenic patients exhibited significantly lower Alb levels (3.4 [0.6] g/dL vs. 3.6 [0.5] g/dL, P=0.015) and significantly higher CRP levels (1.4 [1.1] mg/dL vs. 1.0 [0.9] mg/dL, P=0.002) compared with those without sarcopenia, leading to significant differences in the mGPS scores between the two groups. Moreover, patients with sarcopenia had a significantly higher CCI score compared to those without sarcopenia (3 [3–5] vs. 3 [2–4], P=0.034). However, there was no difference in the frequency of sarcopenia based on the stroke type.
Clinical Outcomes Associated with Systemic Inflammation and Sarcopenia

Univariate and multivariate regression analyses showed that sarcopenia is independently associated with stroke history (odds ratio [OR] 1.890, P=0.027), premorbid mRS (OR 1.520, P=0.040), BMI (OR 0.858, P=0.022), and mGPS score (OR 1.380, P=0.021) (Table 2). Comparisons of the outcomes at discharge based on the mGPS scores are given in Table 3. FIM-motor, SMI, handgrip strength, and Alb level at discharge showed significant differences among patients with different mGPS scores.

Factors Associated with Functional Rehabilitation Outcomes

Table 4 shows the results of multiple regression analysis for FIM-motor at discharge after adjusting simultaneously for potential confounders. No multicollinearity was found between the included variables. The results showed that the mGPS score was independently associated with FIM-motor at discharge (SE=0.543, β=−0.131, P=0.031), suggesting that systemic inflammation is negatively associated with functional rehabilitation outcomes. FIM-motor on admission was also independently associated with FIM-motor at discharge.
Table 2. Univariate and multivariate logistic analyses of sarcopenia using variables recorded at the time of admission

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis</th>
<th>Sarcopenia</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Age</td>
<td>1.016 (0.993, 1.039)</td>
<td>0.183</td>
<td>1.007 (0.972, 1.044)</td>
</tr>
<tr>
<td>Sex</td>
<td>1.478 (0.839, 2.606)</td>
<td>0.176</td>
<td>1.139 (0.498, 2.606)</td>
</tr>
<tr>
<td>Time from onset to admission</td>
<td>1.011 (0.990, 1.032)</td>
<td>0.301</td>
<td>1.003 (0.964, 1.044)</td>
</tr>
<tr>
<td>Stroke history</td>
<td>2.521 (1.248, 5.092)</td>
<td>0.010</td>
<td>1.890 (1.127, 4.110)</td>
</tr>
<tr>
<td>Premorbid mRS</td>
<td>1.567 (1.202, 2.041)</td>
<td>&lt;0.001</td>
<td>0.834 (0.663, 1.048)</td>
</tr>
<tr>
<td>BMI on admission</td>
<td>0.807 (0.740, 0.880)</td>
<td>&lt;0.001</td>
<td>0.858 (0.753, 0.978)</td>
</tr>
<tr>
<td>FIM motor on admission</td>
<td>0.975 (0.962, 0.988)</td>
<td>&lt;0.001</td>
<td>0.988 (0.957, 1.019)</td>
</tr>
<tr>
<td>FIM cognitive on admission</td>
<td>0.946 (0.914, 0.979)</td>
<td>0.001</td>
<td>1.101 (0.943, 1.083)</td>
</tr>
<tr>
<td>mGPS score</td>
<td>1.580 (1.214, 2.130)</td>
<td>0.011</td>
<td>1.380 (1.011, 1.960)</td>
</tr>
</tbody>
</table>

Multivariate analysis was performed after controlling simultaneously for potential confounders.

Table 3. Comparisons of clinical outcomes based on the mGPS score

<table>
<thead>
<tr>
<th></th>
<th>mGPS=0 n=149</th>
<th>mGPS=1 n=40</th>
<th>mGPS=2 n=13</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIM-motor at discharge</td>
<td>75.6 (15.7)</td>
<td>67.2 (23.8)</td>
<td>52.2 (28.4)</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>FIM-cognitive at discharge</td>
<td>26.8 (8.5)</td>
<td>27.3 (7.3)</td>
<td>23.1 (8.7)</td>
<td>0.091a</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td>101.2 (39.7)</td>
<td>110.6 (48.6)</td>
<td>125.1 (42.6)</td>
<td>0.206a</td>
</tr>
<tr>
<td>BMI at discharge (kg/m²)</td>
<td>23.6 (3.2)</td>
<td>21.7 (4.5)</td>
<td>21.1 (5.1)</td>
<td>0.238a</td>
</tr>
<tr>
<td>SMI at discharge (kg/m²)</td>
<td>7.1 (1.1)</td>
<td>6.4 (1.4)</td>
<td>5.8 (0.9)</td>
<td>0.039a</td>
</tr>
<tr>
<td>Handgrip strength at discharge (kg)</td>
<td>29.8 (6.1)</td>
<td>20.1 (7.1)</td>
<td>13.8 (6.2)</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>Alb at discharge (g/dL)</td>
<td>4.0 (0.5)</td>
<td>3.8 (0.6)</td>
<td>3.6 (0.9)</td>
<td>0.037b</td>
</tr>
</tbody>
</table>

Data are expressed as means (standard deviation) or medians [interquartile range].

aone-way ANOVA, bKruskal-Wallis test.

Table 4. Multiple regression analysis of FIM-motor at discharge

<table>
<thead>
<tr>
<th></th>
<th>B (95%CI)</th>
<th>SE</th>
<th>β</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>−0.055 (−0.273, 0.164)</td>
<td>0.111</td>
<td>−0.126</td>
<td>0.122</td>
</tr>
<tr>
<td>Sex</td>
<td>−2.04 (−7.08, 2.99)</td>
<td>2.547</td>
<td>0.042</td>
<td>0.423</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>0.070 (−0.002, 0.141)</td>
<td>0.036</td>
<td>0.128</td>
<td>0.257</td>
</tr>
<tr>
<td>Time from onset to admission</td>
<td>−0.026 (−0.204, 0.152)</td>
<td>0.090</td>
<td>−0.015</td>
<td>0.776</td>
</tr>
<tr>
<td>Premorbid mRS</td>
<td>−3.361 (−5.121, −1.600)</td>
<td>0.890</td>
<td>−0.205</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Brunnstrom Stage</td>
<td>−1.987 (−5.201, 1.227)</td>
<td>1.225</td>
<td>0.264</td>
<td>0.124</td>
</tr>
<tr>
<td>Food Intake LEVEL Scale</td>
<td>0.026 (−1.074, 0.925)</td>
<td>0.556</td>
<td>0.103</td>
<td>0.163</td>
</tr>
<tr>
<td>MNA-SF</td>
<td>1.141 (0.003, 2.278)</td>
<td>0.575</td>
<td>0.142</td>
<td>0.109</td>
</tr>
<tr>
<td>Sarcopenia</td>
<td>−1.635 (−5.553, −0.284)</td>
<td>1.992</td>
<td>−0.132</td>
<td>0.046</td>
</tr>
<tr>
<td>mGPS score</td>
<td>−0.891 (−4.944, −0.162)</td>
<td>0.543</td>
<td>−0.131</td>
<td>0.031</td>
</tr>
<tr>
<td>FIM-motor on admission</td>
<td>0.673 (0.484, 0.863)</td>
<td>0.096</td>
<td>0.586</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FIM-cognitive on admission</td>
<td>0.382 (−0.037, 0.800)</td>
<td>0.212</td>
<td>0.134</td>
<td>0.074</td>
</tr>
</tbody>
</table>

Multivariate analysis was performed after controlling simultaneously for potential confounders.
FIM-motor on admission had a smaller standard error (SE) and larger absolute value of β (SE=0.096, β=0.586, P<0.001) than those of the mGPS score. A smaller SE value is associated with less variation in statistics, and a larger absolute value of β is associated with a greater effect on outcome.

**DISCUSSION**

To the best of our knowledge, this retrospective cohort study was the first to evaluate the association of systemic inflammation and sarcopenia with clinical outcomes among patients in the recovery stage of stroke. This study highlights two important clinical findings. First, systemic inflammation in the recovery stage of stroke is associated with sarcopenia. Second, systemic inflammation is independently and negatively associated with functional rehabilitation outcomes among these patients.

Although we found that systemic inflammation is associated with sarcopenia in the recovery stage of stroke, the mechanisms by which post-stroke patients develop systemic inflammation are not fully understood. The presence of systemic inflammation, however, is closely associated with complications that affect prognosis, such as loss of skeletal muscle mass,46 loss of muscle strength,47 weight loss,41 cachexia,43-45 and all-cause mortality.46 Although the current study was not designed to address mechanistic hypotheses, it may be speculated that the relationship between systemic inflammation and sarcopenia could reflect the involvement of underlying diseases. Indeed, in the current study, the CCI score and severity of comorbidities were significantly different for patients with different mGPS scores. Patients with sarcopenia had a higher CCI score than those without sarcopenia. Here, we hypothesize that sarcopenia prior to stroke onset may be associated with, and possibly caused by, systemic inflammation driven by underlying diseases, including chronic heart failure, diabetes, peripheral artery disease, and chronic kidney disease. Therefore, the inflammatory responses driven by underlying diseases are thought to have a prominent role in sarcopenia. Further studies, however, are needed to investigate the influence of underlying diseases on the progression of sarcopenia.

A recent systematic review by Bano et al.39 found that sarcopenia is associated with higher serum CRP levels and moderate serum levels of interleukin-6 (IL6) or tumor necrosis factor alpha (TNF-alpha). It has also been shown that depletion of muscle mass with aging is caused by inflammatory cytokines produced by chronic low-grade inflammation.47 Inflammatory cytokines suppress protein synthesis pathways including that of the mammalian target of rapamycin. Inflammatory cytokines also activate the ubiquitin–proteasome pathway (UPP) which promotes the breakdown of muscle proteins.47 This inflammation-driven mechanism is believed to partly explain the age-related decrease in muscle mass. Decreases in growth hormones, indirectly caused by inflammation, are also negatively associated with skeletal muscle metabolism.48 However, uncovering the specific molecular mechanisms by which inflammation interacts with muscle protein metabolism remains a challenge.

The finding that systemic inflammation is associated with poor functional rehabilitation outcome in post-stroke patients is consistent with a recent study by Petersen et al.18 They reported age-dependent patterns of association between inflammatory cytokines and physical function. Furthermore, a significant relationship between higher levels of pro- and anti-inflammatory mediators (including IL6, IL10, and TNF-alpha) and Short Physical Performance Battery scores has been reported in older adults with disabilities.49 This finding can be largely explained by the mechanism of muscle protein breakdown, i.e., the progression of sarcopenia.47 We hypothesize that pre-existing sarcopenia caused partly by systemic inflammation might have meaningful effects on rehabilitation outcomes, even though a causal relationship between systemic inflammation and sarcopenia was not clear in the current study because of its design. We believe that it is important to be aware of the influence of systemic inflammation on functional outcomes in the relevant study fields. Therefore, special attention and measures are needed to tackle with systemic inflammation as well as sarcopenia in rehabilitation settings.

Sarcopenia treatment should include resistance training and sufficient protein intake to maintain skeletal muscle mass and function as well as measures to reduce chronic low-grade inflammation.47,50 In a recent meta-analysis,53 it was clarified that low-intensity resistance training sufficiently enhances the synthesis of muscle proteins, and is therefore recommended for maintaining skeletal muscle mass in the frail and elderly. Furthermore, low and/or moderate intensity aerobic training seems to be effective in reducing inflammation and restoring muscle protein.47 However, nutritional support is needed to make these exercises multimodal. It is well accepted that individuals performing aerobic or resistance training require adequate protein intakes, and older adults may benefit from increasing their consumption of branched-amino acids (BCAAs), especially leucine.52 “Rehabilitation nutrition,” a concept combining both rehabilitation and nutrition care management (as presented by Wakabayashi et

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al.2,53) can, therefore, further improve outcomes in the disabled elderly with malnutrition and sarcopenia. Additional studies on rehabilitation nutrition are required to elucidate the multimodal treatment responses. This area of research will become increasingly important, because the number of elderly with disabilities is expected to increase.

Although we have reported novel findings, our study has some limitations. First, a causal relation between systemic inflammation and sarcopenia was unclear because of the study design. Second, the mGPS score could have been influenced by acute inflammation prior to admission to the convalescent wards, even though the patients had no symptoms of an acute infection. To increase the reliability of evaluating systemic inflammation at baseline, we may need to measure high-sensitivity CRP or carry out a more in-depth examination of the patients’ medical history. Third, the effect of various interventions, e.g., rehabilitation treatment and nutrition therapy, and the state of inflammation during the hospital stay were not investigated. Future studies should investigate the clinical effects of physical rehabilitation (including aerobic or resistance training) and nutritional support (including the intake of high levels of protein, BCAAs, or leucine) on systemic inflammation, sarcopenia, and physical function in the recovery stage of stroke.

In conclusion, systemic inflammation is closely associated with sarcopenia and poor functional outcomes in the recovery stage of stroke. The present study showed that both mGPS and sarcopenia can be easily evaluated without any additional cost or effort, because both are quantifiable using a blood test and BIA. Early detection of systemic inflammation at baseline can help promote both adequate exercise and nutritional support to restore muscle mass and improve functional recovery in post-stroke patients. Further studies are, however, needed to validate our findings.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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