

ORIGINAL ARTICLE

Systemic Inflammation in the Recovery Stage of Stroke: Its Association with Sarcopenia and Poor Functional Rehabilitation Outcomes

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Objective: The aim of our study was to investigate how systemic inflammation relates to sarcopenia and its impact on functional outcomes in the recovery stages of stroke. **Methods:** A retrospective cohort study was performed in consecutive patients admitted to convalescent rehabilitation wards following stroke. Patients with acute or chronic high-grade inflammatory diseases were excluded. Systemic inflammation was evaluated using the modified Glasgow Prognostic Score (mGPS). Sarcopenia was defined as a loss of skeletal muscle mass and decreased muscle strength, with the cut-off values set by the Asian Working Group for Sarcopenia. The primary outcome was the motor domain of the Functional Independence Measure (FIM-motor). Univariate and multivariate analyses were used to determine whether mGPS was associated with sarcopenia and FIM-motor at discharge. **Results:** The study included 204 patients (mean age 74.1 years, 109 men). mGPS scores of 0, 1, and 2 were assigned to 149 (73.0%), 40 (19.6%), and 13 (6.4%) patients, respectively. Sarcopenia was diagnosed in 81 (39.7%) patients and was independently associated with stroke history (odds ratio [OR] 1.890, $P=0.027$), premorbid modified Rankin scale (OR 1.520, $P=0.040$), body mass index (OR 0.858, $P=0.022$), and mGPS score (OR 1.380, $P=0.021$). Furthermore, the mGPS score was independently associated with sarcopenia (OR 1.380, $P=0.021$) and FIM-motor at discharge ($\beta=-0.131$, $P=0.031$). **Conclusion:** Systemic inflammation is closely associated with sarcopenia and poor functional outcomes in the recovery stage of stroke. Early detection of systemic inflammation and sarcopenia can help promote both adequate exercise and nutritional support to restore muscle mass and improve post-stroke functional recovery.

Key words: nutrition; rehabilitation; sarcopenia; stroke; systemic inflammation

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.¹⁾ Furthermore, sarcopenia with disability is becoming an important concept in rehabilitation²⁾ because its prevalence is approximately 50% in hospital-based rehabilitation centers worldwide³⁾ and 53% in convalescent rehabilitation wards in Japan.⁴⁾ Sarcopenia

is associated with conditions that are major causes of disability, such as stroke, hip fractures, and hospital-associated deconditioning.²⁾ Moreover, sarcopenia can lead to poor outcomes in hospital rehabilitation settings.⁵⁾ 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,⁶⁾ and more than two-thirds of stroke survivors undergo rehabilitation after hospitalization.⁷⁾ In

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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 follows^{33,34}: 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)¹ 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 $<7.0 \text{ kg/m}^2$ and $<5.7 \text{ kg/m}^2$, respectively. The cut-off values for handgrip strength in men and women were $<26 \text{ kg}$ and $<18 \text{ kg}$, 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 ($3.4 [0.6] \text{ g/dL}$ vs. $3.6 [0.5] \text{ g/dL}$, $P=0.015$) and significantly higher CRP levels ($1.4 [1.1] \text{ mg/dL}$ vs. $1.0 [0.9] \text{ mg/dL}$, $P=0.002$) 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.

Table 1. Baseline characteristics of study participants

	Total n=204	With sarcopenia n=123	Without sarcopenia n=81	P
Age (years)	74.1 (8.2)	74.6 (9.5)	72.27 (10.9)	0.183 ^a
Sex male n (%)	109 (53.4)	61 (49.6)	48 (59.3)	0.198 ^b
Stroke type n (%)				
Cerebral infarction	127 (62.3)	75 (61.0)	52 (64.2)	0.664 ^b
Cerebral hemorrhage	62 (30.4)	40 (32.5)	22 (27.2)	
Subarachnoid hemorrhage	15 (7.4)	8 (6.5)	7 (8.6)	
Time from onset to admission (days)	14 [9–19]	15 [9–22]	13 [10–21]	0.499 ^c
Stroke history n (%)	53 (26.0)	40 (32.5)	13 (16.0)	0.009 ^b
Premorbid mRS	0 [0–2]	0 [0–2]	0 [0–0]	0.001 ^c
Paralysis n (%)				
Right hemiplegia	83 (40.7)	49 (39.8)	34 (42.0)	0.664 ^b
Left hemiplegia	79 (38.7)	47 (38.2)	32 (39.5)	
Bilateral hemiplegia	12 (5.9)	11 (8.9)	1 (1.2)	
Brunnstrom Stage	5 [2–6]	4 [2–6]	5 [3–6]	0.01 ^c
Charlson Comorbidity Index	3 [2–4]	3 [3–5]	3 [2–4]	0.034
Food Intake LEVEL Scale	7 [6–9]	7 [2–9]	9 [7–10]	<0.001 ^c
BMI (kg/m ²)	22.1 (2.5)	20.79 (2.7)	24.1 (3.2)	<0.001 ^a
SMI (kg/m ²)	6.1 (1.3)	5.33 (1.0)	7.17 (0.8)	<0.001 ^a
Handgrip strength (kg)	16.4 (6.1)	12.27 (6.4)	22.60 (8.7)	<0.001 ^a
MNA-SF	6 [4–9]	5 [4–8]	9 [7–10]	<0.001 ^c
FIM				
Motor	38.1 (12.1)	32.6 (11.0)	45.6 (13.0)	<0.001 ^a
Cognitive	19.2 (8.2)	17.6 (8.6)	21.6 (8.5)	0.001 ^a
Total	57.1 (16.2)	50.5 (20.3)	67.4 (19.4)	<0.001 ^a
mGPS score n (%)				
0	151 (74.0)	70 (56.9)	61 (75.3)	0.041 ^b
1	40 (19.6)	33 (26.8)	12 (14.8)	
2	13 (6.4)	20 (16.3)	8 (9.9)	
Laboratory data				
Alb (g/dL)	3.5 (0.5)	3.4 (0.6)	3.6 (0.5)	0.015 ^a
Hb (g/dL)	13.1 (1.8)	12.8 (1.7)	13.61 (1.88)	0.254 ^a
CRP (mg/dL)	1.3 (0.7)	1.4 (1.1)	1.0 (0.9)	0.002 ^a

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

^at-test, ^bChi-square test, ^cMann-Whitney U test.

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 ($SE=0.543$, $\beta=-0.131$, $P=0.031$), 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

Variables	Sarcopenia			
	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
Age	1.016 (0.993, 1.039)	0.183	1.007 (0.972, 1.044)	0.060
Sex	1.478 (0.839, 2.606)	0.176	1.139 (0.498, 2.606)	0.758
Time from onset to admission	1.011 (0.990, 1.032)	0.301	1.003 (0.964, 1.044)	0.875
Stroke history	2.521 (1.248, 5.092)	0.010	1.890 (1.127, 4.110)	0.027
Premorbid mRS	1.567 (1.202, 2.041)	0.001	1.520 (1.185, 2.048)	0.040
Brunnstrom Stage	0.818 (0.707, 0.946)	0.442	0.947 (0.723, 1.242)	0.695
MNA-SF on admission	0.703 (0.609, 0.811)	<0.001	0.834 (0.663, 1.048)	0.120
BMI on admission	0.807 (0.740, 0.880)	<0.001	0.858 (0.753, 0.978)	0.022
FIM motor on admission	0.975 (0.962, 0.988)	<0.001	0.988 (0.957, 1.019)	0.438
FIM cognitive on admission	0.946 (0.914, 0.979)	0.001	1.010 (0.943, 1.083)	0.372
mGPS score	1.580 (1.214, 2.130)	0.011	1.380 (1.011, 1.960)	0.021

Multivariate analysis was performed after controlling simultaneously for potential confounders.

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

	mGPS=0 n=149	mGPS=1 n=40	mGPS=2 n=13	P
FIM-motor at discharge	75.6 (15.7)	67.2 (23.8)	52.2 (28.4)	<0.001 ^a
FIM-cognitive at discharge	26.8 (8.5)	27.3 (7.3)	23.1 (8.7)	0.091 ^a
Length of stay (days)	101.2 (39.7)	110.6 (48.6)	125.1 (42.6)	0.206 ^a
BMI at discharge (kg/m ²)	23.6 (3.2)	21.7 (4.5)	21.1 (5.1)	0.238 ^a
SMI at discharge (kg/m ²)	7.1 (1.1)	6.4 (1.4)	5.8 (0.9)	0.039 ^a
Handgrip strength at discharge (kg)	29.8 (6.1)	20.1 (7.1)	13.8 (6.2)	<0.001 ^a
CCI on admission	3 [2–4]	3 [3–4]	4 [3–4]	0.044 ^b
Alb at discharge (g/dL)	4.0 (0.5)	3.8 (0.6)	3.6 (0.9)	0.037 ^a
MNA-SF at discharge	11 [10–12]	10 [8–12]	10 [8–11]	0.379 ^b

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

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

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,^{36–39} loss of muscle strength,⁴⁰ weight loss,^{41,42} 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,⁵¹ 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*

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 and sarcopenia 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.

REFERENCES

1. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, Topinková E, Vandewoude M, Zamboni M, European Working Group on Sarcopenia in Older People: Sarcopenia: European consensus on definition and diagnosis. *Age Ageing* 2010;39:412–423. PMID:20392703, DOI:10.1093/ageing/afq034
2. Wakabayashi H, Sakuma K: Rehabilitation nutrition for sarcopenia with disability: a combination of both rehabilitation and nutrition care management. *J Cachexia Sarcopenia Muscle* 2014;5:269–277. PMID:25223471, DOI:10.1007/s13539-014-0162-x
3. Sánchez-Rodríguez D, Calle A, Contra A, Ronquillo N, Rodríguez-Marcos A, Vázquez-Ibar O, Colominas M, Inzitari M: Sarcopenia in post-acute care and rehabilitation of older adults: A review. *Eur Geriatr Med* 2016;7:224–231. DOI:10.1016/j.eurger.2015.11.001
4. Yoshimura Y, Wakabayashi H, Bise T, Tanoue M. Prevalence of sarcopenia and its association with activities of daily living and dysphagia in convalescent rehabilitation ward inpatients. *Clin Nutr*. 2017 Sep 23. pii: S0261-5614(17)31341–9.
5. Morandi A, Onder G, Fodri L, Sanniti A, Schnelle J, Simmons S, Landi F, Gentile S, Trabucchi M, Bellelli G: The association between the probability of sarcopenia and functional outcomes in older patients undergoing in-hospital rehabilitation. *J Am Med Dir Assoc* 2015;16:951–956. PMID:26089115, DOI:10.1016/j.jamda.2015.05.010
6. Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, Deruyter F, Eng JJ, Fisher B, Harvey RL, Lang CE, MacKay-Lyons M, Ottenbacher KJ, Pugh S, Reeves MJ, Richards LG, Stiers W, Zorowitz RD, American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research: Guidelines for adult stroke rehabilitation and recovery. *Stroke* 2016;47:e98–e169. PMID:27145936, DOI:10.1161/STR.0000000000000098
7. Buntin MB, Colla CH, Deb P, Sood N, Escarce JJ: Medicare spending and outcomes after postacute care for stroke and hip fracture. *Med Care* 2010;48:776–784. PMID:20706167, DOI:10.1097/MLR.0b013e3181e359df
8. Scherbakov N, Sandek A, Doehner W: Stroke-related sarcopenia: specific characteristics. *J Am Med Dir Assoc* 2015;16:272–276. PMID:25676847, DOI:10.1016/j.jamda.2014.12.007
9. Scherbakov N, von Haehling S, Anker SD, Dirnagl U, Doehner W: Stroke induced sarcopenia: muscle wasting

- and disability after stroke. *Int J Cardiol* 2013;170:89–94. PMID:24231058, DOI:10.1016/j.ijcard.2013.10.031
10. Hunnicutt JL, Gregory CM: Skeletal muscle changes following stroke: a systematic review and comparison to healthy individuals. *Top Stroke Rehabil* 2017;24:463–471. PMID:28251861, DOI:10.1080/10749357.2017.1292720
 11. Shiraishi A, Yoshimura Y, Wakabayashi H, Tsuji Y. Prevalence of stroke-related sarcopenia and its association with poor oral status in post-acute stroke patients: implications for oral sarcopenia. *Clin Nutr*. 2016 Dec 10. pii: S0261-5614(16)31343–7.
 12. Chen LK, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, Chou MY, Chen LY, Hsu PS, Kairait O, Lee JS, Lee WJ, Lee Y, Liang CK, Limpawattana P, Lin CS, Peng LN, Satake S, Suzuki T, Won CW, Wu CH, Wu SN, Zhang T, Zeng P, Akishita M, Arai H: Sarcopenia in Asia: Consensus Report of the Asian Working Group for Sarcopenia. *J Am Med Dir Assoc* 2014;15:95–101. PMID:24461239, DOI:10.1016/j.jamda.2013.11.025
 13. Buford TW, Lott DJ, Marzetti E, Wohlgemuth SE, Vandenborne K, Pahor M, Leeuwenburgh C, Manini TM: Age-related differences in lower extremity tissue compartments and associations with physical function in older adults. *Exp Gerontol* 2012;47:38–44. PMID:22015325, DOI:10.1016/j.exger.2011.10.001
 14. Hughes VA, Frontera WR, Roubenoff R, Evans WJ, Singh MA: Longitudinal changes in body composition in older men and women: role of body weight change and physical activity. *Am J Clin Nutr* 2002;76:473–481. PMID:12145025, DOI:10.1093/ajcn/76.2.473
 15. Marzetti E, Landi F, Marini F, Cesari M, Buford TW, Manini TM, Onder G, Pahor M, Bernabei R, Leeuwenburgh C, Calvani R. Patterns of circulating inflammatory biomarkers in older persons with varying levels of physical performance: a partial least squares-discriminant analysis approach. *Front Med (Lausanne)*. 2014; 1;1:27.
 16. Jo E, Lee SR, Park BS, Kim JS: Potential mechanisms underlying the role of chronic inflammation in age-related muscle wasting. *Aging Clin Exp Res* 2012;24:412–422. PMID:22717404
 17. De Martinis M, Franceschi C, Monti D, Ginaldi L: Inflammation markers predicting frailty and mortality in the elderly. *Exp Mol Pathol* 2006;80:219–227. PMID:16460728, DOI:10.1016/j.yexmp.2005.11.004
 18. Peterson MJ, Thompson DK, Pieper CF, Morey MC, Kraus VB, Kraus WE, Sullivan P, Fillenbaum G, Cohen HJ: A novel analytic technique to measure associations between circulating biomarkers and physical performance across the adult life span. *J Gerontol A Biol Sci Med Sci* 2016;71:196–202. PMID:25745025, DOI:10.1093/gerona/glv007
 19. Vellas B, Villars H, Abellan G, Soto ME, Rolland Y, Guigoz Y, Morley JE, Chumlea W, Salva A, Rubenstein LZ, Garry P: Overview of the MNA – its history and challenges. *J Nutr Health Aging* 2006;10:456–463, discussion 463–465. PMID:17183418
 20. Rubenstein LZ, Harker JO, Salvà A, Guigoz Y, Vellas B: Screening for undernutrition in geriatric practice: developing the short-form mini-nutritional assessment (MNA-SF). *J Gerontol A Biol Sci Med Sci* 2001;56:M366–M372. PMID:11382797, DOI:10.1093/gerona/56.6.M366
 21. Kunieda K, Ohno T, Fujishima I, Hojo K, Morita T: Reliability and validity of a tool to measure the severity of dysphagia: the Food Intake LEVEL Scale. *J Pain Symptom Manage* 2013;46:201–206. PMID:23159683, DOI:10.1016/j.jpainsymman.2012.07.020
 22. Charlson ME, Pompei P, Ales KL, MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–383. PMID:3558716, DOI:10.1016/0021-9681(87)90171-8
 23. Banks JL, Marotta CA: Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. *Stroke* 2007;38:1091–1096. PMID:17272767, DOI:10.1161/01.STR.0000258355.23810.c6
 24. Brunnstrom S: Motor testing procedures in hemiplegia: based on sequential recovery stages. *Phys Ther* 1966;46:357–375. PMID:5907254, DOI:10.1093/ptj/46.4.357
 25. Ottenbacher KJ, Hsu Y, Granger CV, Fiedler RC: The reliability of the functional independence measure: a quantitative review. *Arch Phys Med Rehabil* 1996;77:1226–1232. PMID:8976303, DOI:10.1016/S0003-9993(96)90184-7
 26. Proctor MJ, McMillan DC, Horgan PG, Fletcher CD, Talwar D, Morrison DS: Systemic inflammation predicts all-cause mortality: a Glasgow inflammation outcome study. *PLoS One* 2015;10:e0116206. PMID:25730322, DOI:10.1371/journal.pone.0116206

27. McMillan DC: The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer. *Cancer Treat Rev* 2013;39:534–540. [PMID:22995477](#), [DOI:10.1016/j.ctrv.2012.08.003](#)
28. Llop-Talaveron J, Badia-Tahull MB, Leiva-Badosa E. An inflammation-based prognostic score, the C-reactive protein/albumin ratio predicts the morbidity and mortality of patients on parenteral nutrition. *Clin Nutr*. 2017 Aug 21. pii: S0261–5614(17)30296–0.
29. Powell AG, Parkinson D, Patel N, Chan D, Christian A, Lewis WG: Prognostic significance of serum inflammatory markers in gastric cancer. *J Gastrointest Surg*. Epub 2017 Oct 4. 2018;22:595–605. [PMID:29234999](#), [DOI:10.1007/s11605-017-3597-5](#)
30. Zhu L, Chen S, Ma S, Zhang S: Glasgow prognostic score predicts prognosis of non-small cell lung cancer: a meta-analysis. *Springerplus* 2016;5:439. [PMID:27104127](#), [DOI:10.1186/s40064-016-2093-9](#)
31. Liang Y, Xiao W, Guan YX, Wang W, Chen HY, Fang C, Zhang X, Zhou ZW: Prognostic value of the C-reactive protein/albumin ratio (CAR) in patients with operable soft tissue sarcoma. *Oncotarget* 2017;8:98135–98147. [PMID:29228679](#), [DOI:10.18632/oncotarget.20990](#)
32. Kasuga A, Okano N, Naruge D, Kitamura H, Takasu A, Nagashima F, Furuse J: Retrospective analysis of fixed dose rate infusion of gemcitabine and S-1 combination therapy (FGS) as salvage chemotherapy in patients with gemcitabine-refractory advanced pancreatic cancer: inflammation-based prognostic score predicts survival. *Cancer Chemother Pharmacol* 2015;75:457–464. [PMID:25547407](#), [DOI:10.1007/s00280-014-2665-8](#)
33. McMillan DC: An inflammation-based prognostic score and its role in the nutrition-based management of patients with cancer. *Proc Nutr Soc* 2008;67:257–262. [PMID:18452641](#), [DOI:10.1017/S0029665108007131](#)
34. Ishihara H, Kondo T, Omae K, Takagi T, Iizuka J, Kobayashi H, Tanabe K: Sarcopenia and the modified Glasgow prognostic score are significant predictors of survival among patients with metastatic renal cell carcinoma who are receiving first-line sunitinib treatment. *Target Oncol* 2016;11:605–617. [PMID:27023922](#), [DOI:10.1007/s11523-016-0430-0](#)
35. Shiraishi A, Yoshimura Y, Wakabayashi H, Tsuji Y: Poor oral status is associated with rehabilitation outcome in older people. *Geriatr Gerontol Int* 2017;17:598–604. [PMID:27150279](#), [DOI:10.1111/ggi.12763](#)
36. Hida T, Imagama S, Ando K, Kobayashi K, Muramoto A, Ito K, Ishikawa Y, Tsushima M, Nishida Y, Ishiguro N, Hasegawa Y: Sarcopenia and physical function are associated with inflammation and arteriosclerosis in community-dwelling people: the Yakumo study. *Mod Rheumatol* 2018;28:345–350. [PMID:28741974](#)
37. Visser M, Pahor M, Taaffe DR, Goodpaster BH, Simon-sick EM, Newman AB, Nevitt M, Harris TB: Relationship of interleukin-6 and tumor necrosis factor- α with muscle mass and muscle strength in elderly men and women: the Health ABC Study. *J Gerontol A Biol Sci Med Sci* 2002;57:M326–M332. [PMID:11983728](#), [DOI:10.1093/gerona/57.5.M326](#)
38. Schaap LA, Pluijm SM, Deeg DJ, Visser M: Inflammatory markers and loss of muscle mass (sarcopenia) and strength. *Am J Med* 2006;119:526.e9–526.e17. [PMID:16750969](#), [DOI:10.1016/j.amjmed.2005.10.049](#)
39. Bano G, Trevisan C, Carraro S, Solmi M, Luchini C, Stubbs B, Manzato E, Sergi G, Veronese N: Inflammation and sarcopenia: a systematic review and meta-analysis. *Maturitas* 2017;96:10–15. [PMID:28041587](#), [DOI:10.1016/j.maturitas.2016.11.006](#)
40. Granic A, Davies K, Martin-Ruiz C, Jagger C, Kirkwood TB, von Zglinicki T, Aihie Sayer A: Grip strength and inflammatory biomarker profiles in very old adults. *Age Ageing* 2017;46:976–982. [PMID:28541423](#), [DOI:10.1093/ageing/afx088](#)
41. de Godoy I, Donahoe M, Calhoun WJ, Mancino J, Rogers RM: Elevated TNF- α production by peripheral blood monocytes of weight-losing COPD patients. *Am J Respir Crit Care Med* 1996;153:633–637. [PMID:8564110](#), [DOI:10.1164/ajrccm.153.2.8564110](#)
42. Eid AA, Ionescu AA, Nixon LS, Lewis-Jenkins V, Matthews SB, Griffiths TL, Shale DJ: Inflammatory response and body composition in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;164:1414–1418. [PMID:11704588](#), [DOI:10.1164/ajrccm.164.8.2008109](#)
43. Seelaender M, Laviano A, Busquets S, Püschel GP, Margaria T, Batista ML Jr: Inflammation in cachexia. *Mediators Inflamm* 2015;2015:1–2. [PMID:26523095](#), [DOI:10.1155/2015/536954](#)
44. Leibel A, Muzes G, Feher J: Current perspectives of catabolic mediators of cancer cachexia. *Med Sci Monit* 2007;13:RA168–RA173. [PMID:17767131](#)
45. Morley JE, Thomas DR, Wilson MM: Cachexia: pathophysiology and clinical relevance. *Am J Clin Nutr* 2006;83:735–743. [PMID:16600922](#), [DOI:10.1093/ajcn/83.4.735](#)

46. Proctor MJ, McMillan DC, Horgan PG, Fletcher CD, Talwar D, Morrison DS: Systemic inflammation predicts all-cause mortality: a Glasgow inflammation outcome study. *PLoS One* 2015;10:e0116206. [PMID:25730322](#), [DOI:10.1371/journal.pone.0116206](#)
47. Xia Z, Cholewa J, Zhao Y, Shang HY, Yang YQ, Araújo Pessôa K, Su QS, Lima-Soares F, Zanchi NE: Targeting inflammation and downstream protein metabolism in sarcopenia: a brief up-dated description of concurrent exercise and leucine-based multimodal intervention. *Front Physiol* 2017;8:434. [PMID:28690550](#), [DOI:10.3389/fphys.2017.00434](#)
48. Sakuma K, Aoi W, Yamaguchi A: Current understanding of sarcopenia: possible candidates modulating muscle mass. *Pflugers Arch* 2015;467:213–229. [PMID:24797147](#), [DOI:10.1007/s00424-014-1527-x](#)
49. Dong B, Sun B: Inflammatory markers and disability in Chinese older adults. *J Gerontol Geriatr Res* 2016;05:275. [DOI:10.4172/2167-7182.1000275](#)
50. Yoshimura Y, Wakabayashi H, Yamada M, Kim H, Harada A, Arai H: Interventions for treating sarcopenia: a systematic review and meta-analysis of randomized controlled studies. *J Am Med Dir Assoc* 2017;18:553.e1–553.e16. [PMID:28549707](#), [DOI:10.1016/j.jamda.2017.03.019](#)
51. Schoenfeld BJ, Grgic J, Ogborn D, Krieger JW: Strength and hypertrophy adaptations between low- vs. high-load resistance training. *J Strength Cond Res* 2017;31:3508–3523. [PMID:28834797](#), [DOI:10.1519/JSC.0000000000002200](#)
52. Sakuma K, Yamaguchi A: Recent advances in pharmacological, hormonal, and nutritional intervention for sarcopenia. *Pflugers Arch* 2018;470:449–460. Epub 2017 Oct 18. [Epub ahead of print]. [PMID:29043432](#), [DOI:10.1007/s00424-017-2077-9](#)
53. Wakabayashi H: Rehabilitation nutrition in general and family medicine. *J Gen Fam Med* 2017;18:153–154. [PMID:29264014](#), [DOI:10.1002/jgf2.116](#)