**Title:** Improved systemic inflammation is associated with functional prognosis in post-stroke patients

**Running title:** Systemic Inflammation Impact on Stroke Prognosis

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Abstract

Background: Systemic inflammation is associated with poor functional outcomes. However, the effects of improved inflammation on functional indicators remain unclear. This study aimed to clarify the relationship between improvements in systemic inflammation and activities of daily living (ADL) in patients after stroke.

Methods: This retrospective cohort study included patients post stroke with systemic inflammation upon admission. Systemic inflammation was defined as a modified Glasgow Prognostic Score (mGPS) score of 1–2. Improvement in systemic inflammation was defined as a reduction in mGPS score or blood C-reactive protein (CRP) levels during hospitalization. The primary outcomes were the motor items of the Functional Independence Measure (FIM-motor) at discharge. We applied multiple linear regression analysis to examine whether reduced systemic inflammation was associated with outcomes after adjusting for confounding factors.
**Results:** Of the 1490 patients recruited, 158 (median age, 79 years; 88 men) had systemic inflammation on admission and were included in the study. Among these patients, 131 (82.9%) and 147 (93.0%) exhibited reduced mGPS and CRP levels, respectively. The median change in CRP was 2.1 [1.1, 3.8] mg/dL. Multivariate analysis revealed that improvements in mGPS ($\beta = 0.125$, $p = 0.012$) and CRP levels ($\beta = 0.108$, $p = 0.108$) were independently and positively associated with FIM-motor at discharge.

**Conclusions:** Improvement in systemic inflammation was positively associated with functional outcomes in patients post stroke. Early detection and therapeutic intervention for systemic inflammation may further improve outcomes in these patients.

**Keywords:** systemic inflammation, modified Glasgow Prognostic Score, inflammation improvement, sarcopenia, functional outcomes
Introduction

Systemic inflammation is negatively associated with patient outcomes [1]. Inflammation occurs in response to infection, injury, or other stimuli, and triggers the release of inflammatory mediators throughout the body [2]. These mediators can induce widespread inflammation, leading to organ dysfunction and failure [3]. For instance, the activation of macrophages in the lungs can affect body function owing to systemic inflammation [4], whereas neuroinflammation can result in structural and functional brain damage [5,6]. Patients who are critically ill commonly develop systemic inflammation, particularly those with sepsis or other infections. Moreover, systemic inflammation is linked to chronic inflammatory conditions including diabetes, obesity, and cardiovascular disease [7,8], is a significant predictor of mortality in patients with critical illness [9,10], and is associated with an unfavorable prognosis in individuals with chronic inflammatory diseases [2,11].

Reducing systemic inflammation may lead to favorable outcomes. Controlling systemic inflammation in combination with interventions to improve grip strength demonstrated significant benefits in activities of daily living (ADL) in older Chinese adults [12]. Additionally, physical function, systemic inflammation, and dietary intake indicated associations in older adults receiving convalescent care [13]. In patients with cachexia, the modified Glasgow Prognostic Score [mGPS] is associated with prognosis and is considered an indicator of systemic
inflammation [14]

However, few studies have demonstrated an association between improvements in systemic inflammation and improvements in functional impairment. Therefore, this study aimed to clarify the relationship between improvements in systemic inflammation and ADL indicators in patients with systemic inflammation recovering from stroke events.

Materials and Methods

Participants and setting

This retrospective cohort study was conducted in a 225-bed rehabilitation hospital in Japan using an opt-out method that allowed patients to withdraw from the study at any time. The study was approved by the internal ethics committee of Kumamoto Rehabilitation Hospital and was conducted in accordance with the tenets of the Declaration of Helsinki.

Convalescent rehabilitation

Various specialists conducted convalescent rehabilitation programs, which lasted for up to three hours per day. The content was determined according to the functional abilities or disabilities of each patient and included physical, occupational, speech, and hearing therapies. These programs also included nutritional therapy [15], oral therapy [16], and medication management [17].
Eligible patients

This study included patients recovering from stroke who also had systemic inflammation and were consecutively admitted to the Recovery Rehabilitation Unit of Kumamoto Rehabilitation Hospital between 2015 and 2022. We excluded the following patients: 1) those with impaired consciousness and 2) those who were unsuitable for bioelectrical impedance analysis (BIA) because of agitation, the presence of metals in the body, or the use of other medical devices.

We recorded patient information including age, sex, stroke type, history of stroke, mRS score before stroke onset [18], number of days between stroke onset and hospitalization, presence and stage of paralysis (Brunnstrom stage [BRS]) [19], and Charlson Comorbidity Index (CCI) [20]. Within three days of admission, physical function, cognitive function, and grip strength were assessed using the Functional Independence Measure (FIM) [21].

Assessment of systemic inflammation

The presence of systemic inflammation was assessed using mGPS. This test is used to assess inflammation in patients with various cancers and inflammatory bowel disease [22,23]. The mGPS score was calculated as follows: patients with high C-reactive protein (CRP) (>1.0 mg/dL) and low albumin (Alb) (<3.5 g/dL) were assigned a score of 2, those with high (>1.0 mg/dL) were
assigned a score of 1, and patients with CRP ≤1.0 mg/dL were assigned a score of 0. Alb levels did not affect scores of 1 or 0 [24,25]. We calculated the mGPS for all patients using data from admission to the rehabilitation unit. Systemic inflammation was defined as an mGPS of 1–2.

Improvement in systemic inflammation was defined as a decrease in the CRP level at discharge compared to the level at admission. The mGPS was used to assess the presence of systemic inflammation; however, an improvement in mGPS was not necessarily defined as an improvement in inflammation as the mGPS also includes Alb and CRP levels. Thus, improved mGPS was defined as a decrease in mGPS at discharge compared with that at admission. In the acute phase, a decrease in CRP of 0.31 mg/dL is associated with a good prognosis in sepsis [26]. Although no clear criteria exist regarding chronic inflammation in cardiovascular disease, an improvement in CRP levels may indicate a reduction in systemic inflammation [27]. Using individual-level standard deviation (SD) estimates, the reported mean monthly SD of CRP level variation is 0.063 mg/dL, corresponding to a CRP risk threshold of 0.2 mg/dL [28]. A change in CRP of approximately 0.2–0.3 mg/dL is likely to be due to inflammation. As even relatively small changes in CRP levels may occur due to inflammation, we defined an improvement in systemic inflammation as any decrease in CRP level at discharge from the hospital compared with the level at admission.

Outcomes
The primary outcome was the FIM-motor score, which is one of the most widely used tools for measuring ADL, at discharge. It is divided into 13 motor (FIM-motor) and five cognitive (FIM-cognitive) domain sub-items. Each ADL was rated on a seven-point ordinal scale ranging from fully assisted to fully independent, with total FIM, FIM-motor, and FIM cognitive scores ranges of 18–126, 13–91, and 5–35, respectively.

The secondary endpoint was the FIM-cognitive score at discharge.

Sample size calculation

Data from a previous study conducted under the same circumstances [29] reported that patients' admission FIM-motor scores were normally distributed, with an SD of 23.4. We used these data to determine the sample size in the present study. In addition, inflammatory response in sepsis increased again in approximately 25% of patients after 3 months [30]; however, as patients in the convalescent ward are considered to be in a less inflammatory state, we expected approximately five times more patients in the improved inflammation group. To reject the null hypothesis with a power of 0.8 and an alpha error of 0.05, we calculated that a minimum of 19 patients would be required in the non-improved inflammation group if the true difference between the means of improved and unimproved systemic inflammation scores during hospitalization was 17, with a median frequency cutoff [31].
**Statistical analysis**

We performed the statistical analyses using IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA). As all continuous variables were nonparametric, medians (25th and 75th interquartile [IQR] percentiles) were reported. We used the χ² and Mann–Whitney U tests to examine differences between groups according to the presence or absence of improvement in systemic inflammation and mGPS. Univariate and multivariate logistic analyses were used to examine the association of improvements in systemic inflammation and mGPS with FIM motor status after adjusting for confounders. We performed a multiple regression analysis to examine whether mGPS was independently associated with the discharge FIM-motor score as a functional outcome of rehabilitation medicine. The covariates selected to adjust for confounding variables were age [1,29,32,33], sex [1,29,32], rehabilitation time [33], length of hospital stay [1,29,32], CCI [29], premorbid mRS [1,29], admission FIM-motor score [1,32], admission FIM-cognitive score [1,32] and admission mGPS score based on earlier studies and the clinical expertise of the co-authors of the present study. All patients were assessed for their ability to perform ADLs at the time of discharge. Statistical significance was set at p < 0.05.

**Ethical considerations**
This study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Kumamoto Rehabilitation Hospital. All patients were informed of the study and could withdraw at any time.

**Results**

Of the 1490 patients who recovered from stroke and were consecutively hospitalized during the study period, 128 who were deemed ineligible for BIA, 48 with a severely impaired level of consciousness (as judged by the three-digit Japan Coma Scale), and 401 with missing data were excluded from this analysis. Finally, this study included 158 patients (median age 80 years; 88 males and 70 females) with systemic inflammation (Figure 1).

The patient characteristics are presented in Table 1. The stroke types included cerebral infarction (105 patients, 66.5%), cerebral hemorrhage (43 patients, 27.2%), and subarachnoid hemorrhage (10 patients, 6.3%). The median patient age was 80 years (IQR: 70, 85 years), and 55.7% were male. Patients with a history of stroke accounted for 31.6% of the study population, with a median premorbid mRS score of 0 (IQR: 0, 2) and a median CCI of 3 (IQR: 3, 4). The median baseline FIM scores were 35 (IQR: 21–60), 20 (IQR: 12, 43), and 13 (IQR: 7, 20), respectively. Of the 158 subjects, 131 (82.9%) demonstrated an improvement in mGPS, and 147 (93.0%) indicated an improvement in CRP. The median change in CRP was 2.1 mg/dL (IQR: 1.1,
Tables 2 and 3 outline the results of univariate analyses assessing the associations of improvements in mGPS and CRP levels with discharge FIM motor and cognitive scores, respectively. Improvements in mGPS were significantly associated with discharge FIM motor scores (62 [IQR: 29–84] vs. 24 [IQR: 13, 42], p < 0.001) and cognitive scores (24 [IQR: 16, 30] vs. 17 [IQR: 11, 21], p < 0.001). Similarly, improvements in CRP levels were significantly associated with FIM motor (59 [IQR: 24, 82] vs. 24 [IQR: 15, 34], p = 0.016) and cognitive (23 [IQR: 16, 29] vs. 13 [IQR: 12, 19], p = 0.015) functions at discharge.

Tables 4 and 5 present the multivariate analyses assessing the associations of improvements in mGPS and CRP levels with discharge FIM-motor and FIM-cognitive scores, respectively. Improvements in mGPS were independently associated with FIM-motor (β = 0.125, p = 0.013) but not with FIM-cognitive (β = 0.088, p = 0.069) at discharge, while improvements in CRP levels were independently associated with both FIM-motor (β = 0.108, p = 0.028) and FIM-cognitive (β = 0.099, p = 0.035) at discharge.

Discussion

We investigated the association between improvements in systemic inflammation and functional outcomes in patients undergoing convalescent rehabilitation after stroke. Our results
revealed two novel findings: 1) improvements in systemic inflammation and reductions in mGPS were positively associated with ADL recovery, and 2) improvements in systemic inflammation were positively associated with cognitive recovery, whereas reductions in mGPS were not.

In the present study, improvements in systemic inflammation and reductions in mGPS were positively associated with ADL recovery in patients with systemic inflammation recovering from stroke. Our findings highlight the importance of addressing systemic inflammation to improve the functional and cognitive outcomes in these patients. Systemic inflammation adversely affects life and functional prognosis in several diseases; however, amelioration of inflammation may improve prognosis [1,2,9,11]. The results of the present study suggest that the effects of systemic inflammation are reversible in some patients. Rehabilitation and nutrition are important for functional improvement. Anti-inflammatory interventions should be considered in patients with systemic inflammation [34-36].

In our patient cohort, improvements in systemic inflammation were positively associated with cognitive recovery, whereas reductions in mGPS did not show a significant association. Systemic inflammation affects cognitive function and may contribute to cognitive decline and dementia [37,38]. The markers of inflammation are also associated with rates of cognitive decline [39,40]. In Alzheimer's disease, systemic inflammation may exacerbate neuroinflammation. Thus, the association between systemic inflammation and neuroinflammation may explain the association
between systemic inflammation and cognitive function [29]. Improvements in mGPS were not significantly related to cognitive function in this study, although further evaluation using different sample sizes is warranted to definitively determine whether a significant relationship exists.

Exercise and diet are important for improving systemic inflammation. Moderate physical activity and exercise exert anti-inflammatory effects and prevent chronic inflammation-related diseases [31,34,35]. Nutrient content indicative of anti-inflammation, such as ω3 fatty acid levels, have also demonstrated similar effects [36]. The results of the present study suggest that improving inflammation is directly related to ADL and that comprehensive interventions such as exercise and nutrition therapies are needed to improve outcomes by reducing systemic inflammation.

This study has several limitations. First, we conducted this study in a single hospital in Japan and limited the study population to patients with systemic inflammation upon admission, which reduced the number of patients included in the analysis and may have limited the generalizability of our results. Moreover, the sample size was adequate for mGPS but was insufficient for CRP. Further multicenter studies are required to verify whether similar results can be obtained in different populations. Second, we were unable to evaluate the factors that contributed to the change in inflammation. Therefore, future studies should evaluate the association between rehabilitation therapies such as aerobic exercise and resistance training, and
nutritional therapies such as ω3 fatty acid and branched-chain amino acid (BCAA) intake, and reductions in inflammation. Third, we did not assess the causes of inflammation in our patients; thus, we could not determine whether the reduced inflammation differed depending on the underlying cause.

Conclusions

Improvement in systemic inflammation may be positively correlated with functional outcomes in patients post stroke with systemic inflammation. In the presence of systemic inflammation, inflammation control should be targeted as improvement in inflammation may be directly related to functional outcomes.