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Pre-stroke frailty and stroke severity in elderly patients with acute stroke

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Running title: Pre-stroke frailty and stroke severity

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Abstract

Aim: Frailty is a major problem in super-aged societies. Because frailty assessments are largely unstudied in acute stroke settings, few reports have evaluated the association between pre-stroke frailty and stroke severity. The aim of this study was to determine the association between pre-stroke frailty and stroke severity in elderly patients with acute stroke.

Methods: This cross-sectional study enrolled consecutive elderly patients with acute stroke. We assessed stroke severity with the National Institutes of Stroke Scale (NIHSS), and pre-stroke frailty with a Frailty Screening Index in elderly patients with acute stroke. Patients were divided according to their Frailty Screening Index: the robust group, pre-frailty group, and frail group. Multiple linear regression analysis was used to determine whether pre-stroke frailty was independently associated with NIHSS score.

Results: In total, 234 elderly patients with acute stroke (age: 75.7 years; 149 men, 85 women) were enrolled in this study. Of these, the robust group comprised 76 patients, the pre-frailty group comprised 129 patients, and the frail group comprised 29 patients. The prevalence of pre-stroke frailty was 12.4%. Multiple linear regression analysis showed that pre-stroke pre-frailty and frailty were significantly associated with NIHSS score (pre-frailty; $\beta = 1.191$, $P = 0.005$, frail; $\beta = 1.708$, $P = 0.009$).

Conclusions: The present study indicated that the pre-stroke frailty was significantly associated with stroke severity in elderly patients with acute stroke. Additional study is needed to clarify the association between pre-stroke frailty and post-stroke prognosis after stroke such as that of functional outcome and stroke recovery.

Key words: elderly, frailty, risk factor, severity, stroke

1 Introduction

2
3 As the front-runner of super-aged societies, Japan is facing a fast-growing proportion of
4 elderly people.¹ According to the Japanese Stroke Databank, presently, the number of
5 elderly patients with stroke is increasing rapidly.² Because elderly people sometimes have
6 multiple morbidities and disabilities,³ strategies for preventing the onset of stroke are more
7 complex. Additionally, these people tend to have physical disfunction, cognitive
8 disfunction, and limitations in the activities of daily living before stroke onset.

9 Thus, frailty is a major problem in super-aged societies and is considered as a major
10 risk factor for disability and death.⁴ Measurement of physical function such as grip strength
11 or gait speed is crucial in determining the prevalence of frailty.⁴ However, because acute
12 stroke can often lead suddenly to physical disability, loss of consciousness, or cognitive
13 disorder, the prevalence of frailty and methods for assessing frailty have largely been
14 unstudied in the acute stroke setting.

15 There are, however, some reports about the relationship between pre-stroke physical
16 activity and stroke severity⁵ and complications.⁶ Taylor-Rowan et al. reported that frailty
17 was present in around one-quarter of all stroke patients in a UK urban hospital and that it
18 was not associated with the National Institutes of Stroke Scale (NIHSS) after adjusting for
19 confounding factors.⁷ Presently, however, knowledge of these relationships are inconsistent
20 and inconclusive.

21 Therefore, we hypothesized that pre-stroke frailty would be associated with stroke
22 severity. This study aimed to determine the association between pre-stroke frailty and

stroke severity in elderly patients with acute stroke and to evaluate characteristics of patients with pre-stroke frailty.

Materials and METHODS

Study design and participants

This cross-sectional study enrolled consecutive elderly patients with stroke within 48 hours of stroke symptom onset in Itami Kousei Neurosurgical Hospital from September 2017 to July 2019. The inclusion criterion was age ≥ 65 years. The exclusion criteria were (1) pre-stroke functional limitation (modified Rankin Scale⁸ [mRS] score ≥ 4); (2) subarachnoid hemorrhage; (3) major concurrent illness, including chronic obstructive pulmonary disease, renal failure, and active malignancy, and (4) inability to answer questionnaires because of impaired consciousness, severe cognitive dysfunction, or language disorders such as aphasia. This study was approved by the research ethics committee of Itami Kousei Neurosurgical Hospital (approval no. 690), and it conforms to the provisions of the Declaration of Helsinki (as revised in Brazil 2013). Informed consent was obtained from all patients.

Clinical characteristics

Patient clinical characteristics including age, sex, body mass index (BMI), stroke type (ischemic or hemorrhage), affected side, NIHSS score,⁹ premorbid mRS score, comorbidities or risk factors for stroke (hypertension, diabetes mellitus, dyslipidemia,

previous stroke, ischemic heart disease, atrial fibrillation, and smoking) were obtained from the patients' electronic medical records. The NIHSS is a valid, reliable, and reproducible scale for assessing neurologic severity, and it is also widely used in the clinical setting for acute stroke.¹⁰ The main outcome was the NIHSS score, which was assessed by physical therapists at 3 days after admission.

Measurement of frailty

To clarify the prevalence of pre-stroke frailty, patients were asked to complete the Frailty Screening Index within 7 days of admission.¹¹ This index includes simple yes/no questions concerning nutrition/loss of weight, physical function, physical activity, forgetfulness, and emotions/exhaustion.¹¹ The index consisted of 5 items, which are rated as 0 or 1 by the participants. The 5 items are as follows: 1) "Have you lost 2 kg or more in the past 6 months?", Yes = 1; 2) "Do you think you walk slower than before?", Yes = 1; 3) "Do you go for a walk for your health at least once a week?", No = 1; 4) "Can you recall what happened 5 minutes ago?", No = 1; and 5) "In the past 2 weeks, have you felt tired without a reason?", Yes = 1.

Statistical analysis

The results are shown as median (interquartile range) or ordinal variables and counts (%) for categorical variables. Patients were divided according to their Frailty Screening Index: the robust group comprised patients with score = 0, the pre-frailty group comprised patients with score = 1 or 2, and the frail group comprised patients with score ≥ 3 .

One-way analysis of variance, Bonferroni post-hoc test, and χ^2 test were used to clarify clinical characteristics between the groups. Multiple linear regression analysis was used to determine whether the pre-stroke frailty status was independently associated with the NIHSS score. We selected the following relevant confounding variables: age, sex, BMI, stroke type, affected side, premorbid mRS, and comorbidities or risk factors for stroke (hypertension, diabetes mellitus, dyslipidemia, previous stroke, ischemic heart disease, atrial fibrillation, and smoking history). Multicollinearity was assessed using the Variance Inflation Factor (VIF): a VIF value between 1–10 was considered to indicate the absence of multicollinearity. A *P* value of < 0.05 was considered to indicate statistical significance. Statistical analyses were performed with IBM SPSS 25.0 statistical software (IBM SPSS Japan, Inc., Tokyo, Japan).

Results

In total, 478 elderly patients with stroke were hospitalized during the study inclusion period. Of these, 244 patients were excluded from the study, and thus, 234 patients were included the study (Figure 1). Of these, the robust group comprised 76 patients, the pre-frailty group comprised 129 patients, and the frail group comprised 29 patients. The prevalence of pre-stroke frailty was 12.4%. The patients' clinical characteristics are shown in Table 1. The frail group was significantly older than the other two groups (*P* < 0.01). The pre-frailty group and frail group had significantly higher NIHSS scores than the robust

group (both, $P < 0.01$). Comorbidities or risk factors for stroke were not different between the three groups.

Results of multiple linear regression analysis for potential confounders including pre-stroke frailty are shown in Table 2. The VIF value was <10 ; therefore, there was no multicollinearity in the model. After adjustments for confounding variables, pre-stroke pre-frailty and frailty were significantly associated with NIHSS score (pre-frailty: $\beta = 1.191$, $P = 0.005$; frail: $\beta = 1.708$, $P = 0.009$).

Discussion

The findings of the present study show that the prevalence of pre-stroke frailty was 12.4%, as indicated by the Frailty Screening Index, and pre-stroke frailty level was significantly associated with NIHSS score in the elderly patients with acute stroke. A meta-analysis showed that the prevalence of physical frailty is 7.4% in Japan.¹² Thus, elderly people who are at high risk of stroke might have a high prevalence of frailty. Recently, Taylor-Rowan et al.⁷ investigated the prevalence of frailty among acute stroke patients using the Frailty Index and frailty phenotype approach. Both approaches resulted in prevalence rates of 28% in their study.⁷ Although these prevalence rates vary depending on the report or measurement of frailty, the prevalence of frailty in the present study was slightly lower than that reported by Taylor-Rowan et al. This discrepancy might have occurred because they included more severely affected patients (pre-stroke mRS ≥ 2 : 41%) than the present study (pre-stroke mRS ≥ 2 : 9.4%).

The patients in the frailty group were significantly older than those in the other two groups and had a higher NIHSS score than that of the robust group. With regard to age, the prevalence of frailty increasing with age was consistent with a report by Yamada and Arai.¹¹ With regard to physical function and physical activity, Reinholdsson et al.⁵ and Wen et al.⁶ indicated that higher pre-stroke physical activity could result in lower stroke severity. The frail population tends toward a low physical activity level and excessive sedentary behavior.^{13,14} Because the Frailty Screening Index is partly comprised of items related to physical function and physical activity, the score might be associated with stroke severity as it relates to pre-stroke physical activity. Premorbid frailty also impacts disease severity and health outcomes.¹⁵ Therefore, further studies are needed to clarify whether other items of the Frailty Screening Index (nutrition/weight loss, forgetfulness, and emotions/exhaustion) are also associated with stroke severity.

There are many reports indicating an association between comorbidities (diabetes mellitus,¹⁶ history of heart failure,¹⁷ coronary heart disease,¹⁸ and atrial fibrillation¹⁷ or risk factors for stroke (smoking history)¹⁸ and stroke severity, fatality, functional status, or some combination of these outcomes. However, these factors were not significantly associated with the NIHSS score after adjusting for these confounding factors in the present study. Although the mechanism has not been elucidated, pre-stroke physical activity and exercise could play a role in neuroprotection and neuroplasticity.¹⁹ Winovich et al.²⁰ suggested that the frailty status and markers of physical function may indicate vulnerability to poor recovery after ischemic stroke. Pre-stroke frailty might indicate decreased physiological resilience to stroke events. For these reasons, pre-stroke frailty levels were significantly associated with the NIHSS score. From our results, physicians will need to consider the

negative effects of pre-stroke frailty on stroke severity when evaluating it in the acute phase in these patients. Because frailty or pre-frailty status is modifiable,^{21,22} specific approaches to improve these conditions in the primary prevention of stroke need to be considered.

This study has some limitations. First, we diagnosed pre-stroke frailty using a questionnaire, and only half of the patients could be assessed with this questionnaire in this study. Additionally, recall bias might somehow have influenced frailty status. Second, the Frailty Screening Index cannot evaluate social frailty and oral frailty. Therefore, we cannot know whether these aspects of frailty are associated with stroke severity. Finally, we did not evaluate the association of pre-stroke frailty with functional outcomes or stroke recovery.²⁰ As stroke severity depends on pre-stroke frailty, these outcomes might have varied depending on the patient's frailty status.

In conclusion, the present study indicated that pre-stroke frailty was significantly associated with stroke severity in elderly patients with acute stroke. Additional study is needed to clarify the association between pre-stroke frailty and post-stroke prognosis after stroke such as that of functional outcome and stroke recovery.

Disclosure statement

The authors declare no potential conflicts of interest.

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212 **Figure legend**

213

214 **Figure 1.** Participant flow in the present study.

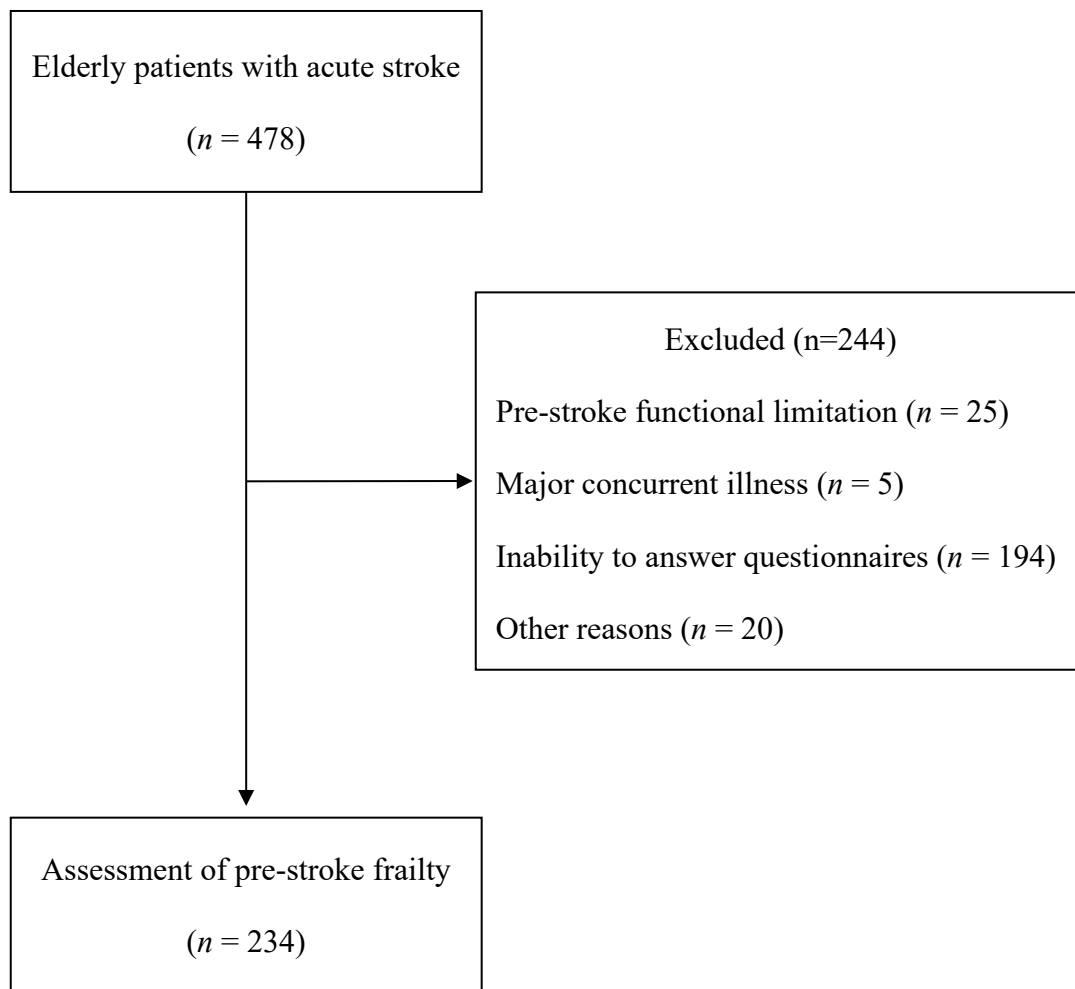


Figure 1

Table 1 Clinical characteristics patients with stroke according to pre-stroke frailty status

	Robust (<i>n</i> = 76)	Pre-frailty (<i>n</i> = 129)	Frail (<i>n</i> = 29)
Age (years)	73.0 (68.8-78.0)*	76.0 (70.0-81.0)*	81.0 (75.0-86.0)
Sex (male/female)	54/22	81/48	14/15
Body mass index (kg/m ²)	22.6 (21.2-24.7)	22.6 (21.2-25.7)	22.4 (20.8-24.4)
Stroke type (lacunar/atherosclerotic/cardio- embolic/hemorrhage/unknown)	38/20/3/2/13	60/34/11/2/22	15/5/4/1/4
Affected side (right/left/bilateral/unknown)	36/35/3/2	64/63/2/0	11/16/1/1
NIHSS (score)	1.0 (0-3.0)*†	2.0 (1.0-4.0)	3.0 (2.0-6.0)
Premorbid mRS (0/1/2/3)	64/8/3/1	93/24/9/3	20/3/2/4
Comorbidities or risk factors for stroke (%)			
Hypertension	38 (50.0)	66 (51.2)	18 (62.1)
Diabetes mellitus	21 (27.6)	26 (20.2)	7 (24.1)
Dyslipidemia	15 (19.7)	21 (16.3)	4 (13.8)
Previous stroke	23 (30.2)	36 (27.9)	12 (41.4)
Ischemic heart disease	8 (10.5)	8 (6.2)	1 (3.4)
Atrial fibrillation	7 (9.2)	11 (8.5)	5 (17.2)
Smoking history	16 (21.1)	29 (22.5)	5 (17.2)

NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.

Values are shown as median (interquartile range), or ordinal variables and counts (%) for categorical variables.

**P* < 0.01 (vs. frail), †*P* < 0.01 (vs. pre-frailty).

Table 2 Multivariate regression analysis for predicting stroke severity

	β	<i>P</i> value
Presence of frailty		
Robust	Reference	
Pre-frailty	1.191	0.005
Frail	1.708	0.009
Hypertension	0.144	0.709
Diabetes mellitus	0.798	0.084
Dyslipidemia	-0.441	0.386
Previous stroke	0.661	0.115
Ischemic heart disease	-0.551	0.458
Atrial fibrillation	0.366	0.650
Smoking history	-0.413	0.390
Adjusted $R^2 = 0.151$		

Adjusted by confounding factors of age, sex body mass index, stroke type, affected side, and premorbid modified Rankin Scale.