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Functional Recovery in Acute and Subacute Stroke Patients With or Without Post-stroke Fatigue

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HIGHLIGHTS

- Post-stroke fatigue (PSF) prevalence in acute/subacute stroke patients was 52.5%.
- PSF negatively impacts activities of daily living recovery.
- PSF can affect the motor and cognitive functions.
- PSF management is crucial for improving stroke rehabilitation outcomes.
- Study uses validated scales for comprehensive functional assessment.

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The authors have no potential conflicts of interest to disclose.

Author Contributions
Conceptualization: Lee J, Kim G; Data curation: Lee J; Methodology: Lee J, Kim G; Supervision: Kim G; Writing - original draft: Lee J; Writing - review & editing: Kim G.

ABSTRACT

This study analyzed the impact of post-stroke fatigue (PSF) on functional recovery in acute and subacute stroke patients during inpatient rehabilitation. Medical records of 177 patients were retrospectively reviewed. PSF was assessed using the Fatigue Severity Scale (FSS)-9. Patients were classified into two groups: a PSF group (mean FSS ≥ 4) and a non-PSF group (mean FSS < 4). Stroke severity was measured with the National Institutes of Health Stroke Scale, and functional outcomes were evaluated using Functional Ambulation Category (FAC), Berg Balance Test, Korean version of the Modified Barthel Index (K-MBI), and Mini-Mental State Examination-Korean version (MMSE-K). Statistical significance was set at $p < 0.05$. The prevalence of PSF was 52.5%. The repeated measures of analysis of variance showed significant "time" effects on FAC ($F = 29.726$, $p < 0.001$) and K-MBI ($F = 15.348$, $p < 0.001$). A significant "group" effect was observed on MMSE-K ($F = 4.571$, $p = 0.035$), and a "time × group" interaction on only K-MBI ($F = 4.284$, $p = 0.041$). Multivariable logistic regression analysis showed that improvements in K-MBI scores were independent of initial severity, depression, and age ($p = 0.043$). PSF affects the recovery of activities of daily living (ADL) in stroke patients, suggesting that regulating early fatigue after stroke positively affects functional recovery.

Keywords: Stroke; Fatigue; Activities of Daily Living; Prospective Study

INTRODUCTION

Stroke, recognized as a formidable global health concern, is currently ranked as the second leading cause of death and the third leading cause of death and disability worldwide according to the Global Burden of Disease, Injuries, and Risk Factors Study [1-3]. In Korea, stroke is the fifth leading cause of death, with a mortality rate of 49.6% [4]. Despite the decline in mortality rates attributable to advancements in acute stroke care, the incidence of stroke is increasing, resulting in an increasing number of survivors experiencing disabilities after stroke [5]. Stroke leads to variable sequelae, including physical disability, cognitive impairment, speech disorders, and psychological disorders, which significantly impact survivors' quality of life (QOL) and daily functioning [6]. Among the numerous sequelae of stroke, psychological symptoms, including fatigue, pain, mood disturbances, and sleep disturbances, are considered the least understood, most challenging to manage, and significantly disruptive to daily living [2,7].

Fatigue is a complex and multidimensional symptom characterized by a lack of mental and/or physical energy, feelings of exhaustion, and weariness [2,8]. This condition diminishes patient engagement in social and professional activities, leading to a marked decline in overall QOL [9]. Notably, post-stroke fatigue (PSF) differs from physiological fatigue in that it persists even at rest [2,10]. Moreover, PSF includes a lack of interest or poor motivation, resulting in interference with participation in rehabilitation, and has been reported to be related to mortality, poor functional recovery, and QOL [9-13]. PSF is a common symptom of stroke with reported prevalence rates estimated at 40%, ranging from 25% to 85% [10,12,14]. A previous prospective study reported that 41% of all post-stroke patients complained of early fatigue after stroke, and 51% experienced fatigue six months after stroke [15]. Despite its high prevalence and clinical importance, PSF remains a neglected phenomenon and poorly understood [16].

The relationship between PSF and functional recovery, including motor function, cognitive function, and activities of daily living (ADL), remains unclear. Previous studies have reported associations between PSF and ADL in patients with stroke [6,15,17,18]. However, Park et al. [19] found that the fatigue score after stroke was not significantly correlated with motor function, cognitive function, and ADL. Another study reported that acute-phase PSF limited ADL recovery 18 months after stroke [20]. Although previous studies have explored the effects of PSF on functional recovery, few have reported its impact within Korean rehabilitation settings. We believe that fatigue after stroke may lead patients to avoid physical activity or experience emotional exhaustion. This may reduce participation in rehabilitation programs and adversely affect the functional recovery. Therefore, this study aimed to investigate the relationship between acute phase PSF and functional recovery from admission to discharge in acute and sub-acute rehabilitation wards. We hypothesized that higher levels of PSF would be associated with poorer functional recovery over time.

MATERIALS AND METHODS

Participants

We retrospectively analyzed the medical records of 260 patients with acute and subacute strokes admitted to the Department of Rehabilitation Medicine of Kangwon National University Hospital between March 2019 and December 2021. Patients were excluded from the study based on predefined criteria. Forty-four patients were excluded due to communication difficulties preventing accurate Fatigue Severity Scale (FSS) assessment, while 39 were excluded due to missed FSS assessments at critical time points. To maintain study validity and account for the potential influence between fatigue and rehabilitation, patients who initiated rehabilitation before completing the initial FSS assessment post-admission or transfer were excluded. Furthermore, patients with earlier than anticipated or unplanned discharges, resulting in incomplete final FSS assessments, were also excluded. In total, 177 patients were included in this study (**Fig. 1**). All patients participated in intensive rehabilitation programs.

Demographic and clinical characteristics of the recruited post-stroke patients, including age, sex, presence or absence of depression, stroke type, hemiplegic side, and length of

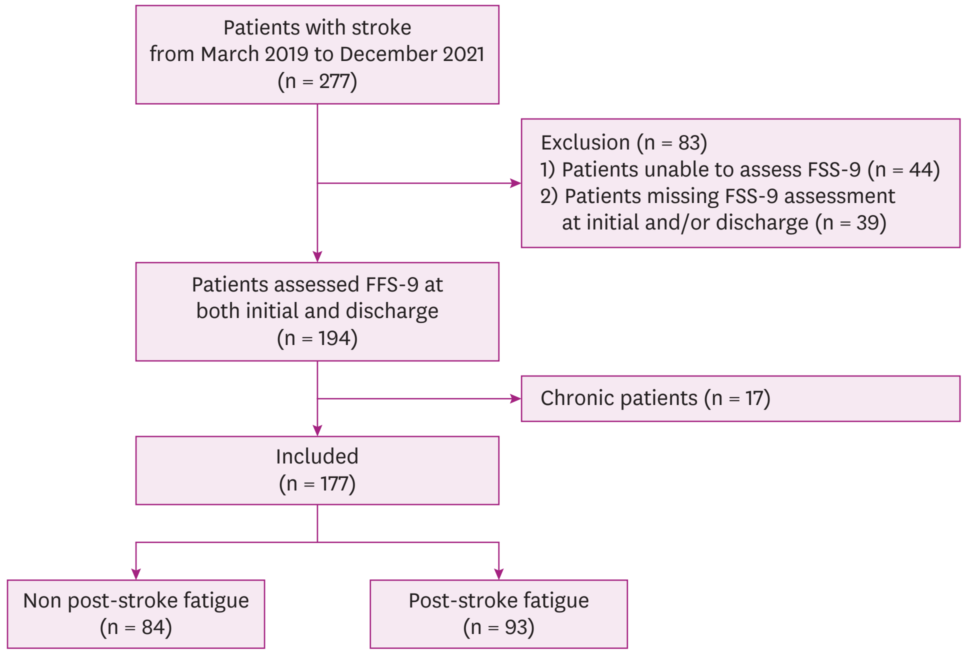

Fig. 1. Inclusion flow chart of the study.
FSS-9, Fatigue Severity Scale-9.

hospital stay, were collected from the medical records. Depression was assessed using Beck's Depression Inventory (BDI), which is a self-report questionnaire, and a total BDI score of ≥ 16 was considered indicative of depression [21]. The stroke type was classified as ischemic or hemorrhagic, and the hemiplegic side was classified as right, left, or both. This study was approved by the Institutional Review Board of Kangwon National University Hospital (KNUHIRB 2024-02-010).

Assessment of fatigue

PSF was assessed in all patients using the FSS immediately after transfer or admission (initial) and immediately before discharge. All patients self-assessed the FSS, and if they had difficulty reading it due to illiteracy or poor vision, doctors read the questions face-to-face and evaluated them. The FSS consists of nine items, each scored on a Likert-type scale ranging from one (strongly disagree) to seven (strongly agree). The Korean version of the FSS has a sensitivity of 84.1% and specificity of 85.7% [22]. The total score is the sum of the nine items divided by the number of responses. Higher scores indicate more severe fatigue. A mean score ≥ 4 indicates fatigue [12]. We also set a cut-off score of 4 points, classifying patients with scores below 4 points into the non-PSF group and those with scores of 4 points or higher in the PSF group.

Functional evaluation

National Institutes of Health Stroke Scale (NIHSS) was used to assess the severity of neurologic damage [23]. Gait function was evaluated using the Functional Ambulation Category (FAC) [24]. To assess balance and functional mobility, we used the Berg Balance Test (BBT), which measures a patient's ability to execute a task or action [25]. The Korean version of the Modified Barthel Index (K-MBI) was used to assess ADL [26]. Cognitive function was evaluated using the Korean version of the Mini-Mental State Examination (MMSE-K) [27].

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Statistical analysis

Statistical analyses were performed using SPSS for Windows ver. 25.0 (IBM, Armonk, NY, USA). The associations of age, sex, presence or absence of depression, type of stroke, and hemiplegic side between the groups were compared using the χ^2 test. The mean age and length of hospital stay in each group were analyzed using t-tests. The comparisons of the initial and discharge NIHSS, FAC, BBT, K-MBI, and MMSE-K scores between the groups were based on a t-test. The differences between the initial and discharge times of the FAC, BBT, K-MBI, and MMSE-K scores were analyzed using one-way analysis of variance (ANOVA) and multivariable logistic regression analysis with adjustment by each age, initial BDI score, and initial NIHSS score as these factors are known to be closely related to PSF based on previous research [11,13,17,28,29]. Additionally, duration of inpatient rehabilitation was also adjusted. We used repeated measures of ANOVA with "group" (PSF and non-PSF group) and "time" (initial and discharge) as the repeated measure to compare the effects of "group" and "time" on functional outcomes. Changes in the initial and discharge scores ([discharge score − initial score]) were calculated, and multivariable logistic regression analysis was performed. Statistical significance was set at $p < 0.05$.

RESULTS

Characteristics of recruited post-stroke patients

Patients were classified into two groups according to the FSS score: the PSF group (93 patients, 52.5%) and the non-PSF group (84 patients, 47.5%). The median score of FSS in the PSF group was 4.84 (interquartile range, 4.17–5.44) points, compared to 2.71 (interquartile range, 2.03–3.44) points in the non-PSF group.

Table 1 shows the demographic and clinical characteristics of subjects. The mean age of the participants was 73.29 years, with no significant difference between the two groups ($p > 0.05$). Depression was significantly more prevalent in the PSF group compared to the non-PSF group ($p < 0.001$). The proportion of hemorrhagic stroke was significantly higher in the PSF group than in the non-PSF group ($p = 0.032$). No significant differences were observed between the two groups in terms of hemiplegic side or length of hospital stay.

There were no statistically significant differences between the PSF and non-PSF groups in the initial NIHSS scores, initial and discharge FAC, BBT, and initial K-MBI scores (all $p > 0.05$). However, significant differences were observed in other measures. The discharge K-MBI score of the PSF group (52.86 ± 29.35) was significantly lower than that of the non-PSF group (65.97 ± 24.77, $p = 0.019$). Similarly, the PSF group showed significantly lower MMSE-K scores both at initial assessment (17.03 ± 8.46 vs. 21.65 ± 6.37, $p < 0.001$) and at discharge (20.68 ± 7.10 vs. 23.36 ± 5.17, $p = 0.005$).

Comparison of FAC, BBT, MBI and MMSE scores at the initial and discharge

Repeated-measures ANOVA revealed a significant group effect on the MMSE-K ($F = 4.571$, $p = 0.035$). Additionally, we observed significant "time" effects on FAC ($F = 29.726$, $p < 0.001$) and K-MBI ($F = 15.348$, $p < 0.001$). Notably, a significant "time x group" interaction was found exclusively for K-MBI ($F = 4.284$, $p = 0.041$). There were no significant "group" effects on FAC, BBT and K-MBI, nor were there any "time" effects on BBT and MMSE-K, and no "time x group" effects on FAC, BBT and MMSE-K (**Fig. 2**).

Table 1. Demographic characteristics of recruited post-stroke patients (n = 177)

Variables	Post-stroke fatigue (n = 93)	Non post-stroke fatigue (n = 84)	p value
Age (yr)	73.78 ± 11.20	72.74 ± 12.01	0.549
< 65	20 (21.5)	25 (29.8)	0.456
≥ 65	73 (78.5)	59 (70.2)	0.223
Sex			
Male	44 (47.3)	43 (51.2)	0.915
Female	49 (52.7)	41 (48.8)	0.399
Depression			
BDI ≥ 16	45 (48.4)	13 (15.5)	< 0.001†
BDI < 16	48 (51.6)	71 (84.5)	0.035*
Type of stroke			
Infarction	61 (65.6)	67 (79.8)	0.596
Hemorrhage	32 (34.4)	17 (20.2)	0.032*
Hemiplegic side			
Right	23 (24.7)	30 (35.7)	0.336
Left	37 (39.8)	26 (31.0)	0.166
Both	5 (5.4)	2 (2.4)	0.257
None	28 (30.1)	26 (31.0)	0.785
Length of stay (day)	24.34 ± 11.66	23.27 ± 10.61	0.759
NIHSS			
Initial	6.17 ± 4.26	5.65 ± 5.31	0.379
FAC			
Initial	1.41 ± 1.46	1.79 ± 1.64	0.055
Discharge	2.52 ± 1.83	2.94 ± 1.71	0.198
BBT			
Initial	18.18 ± 19.22	23.56 ± 20.39	0.251
Discharge	29.41 ± 20.56	33.92 ± 20.09	0.441
K-MBI			
Initial	38.54 ± 27.19	47.46 ± 27.16	0.965
Discharge	52.86 ± 29.35	65.97 ± 24.77	0.019*
MMSE-K			
Initial	17.03 ± 8.46	21.65 ± 6.37	< 0.001†
Discharge	20.68 ± 7.10	23.36 ± 5.17	0.005*

Values are presented as mean ± standard deviation or number (%).
BDI, Beck's Depression Inventory; NIHSS, National Institutes of Health Stroke Scale; FAC, Functional Ambulation Category; BBT, Berg Balance Test; K-MBI, Korean version of Modified Barthel Index; MMSE-K, Korean version of Mini-Mental State Examination.
*$p < 0.05$, †$p < 0.01$, statistically significant differences between non post-stroke fatigue group and post-stroke fatigue group by Pearson's χ^2 test or independent samples t-test.

Multivariable logistic regression analysis of functional and cognitive changes in relation to PSF

A multivariable logistic regression analysis was conducted to examine the relationship between PSF and functional and cognitive recovery. The dependent variables were the changes (Δ) in functional and cognitive measures from admission to discharge: ΔFAC, ΔBBT, ΔK-MBI, and ΔMMSE-K. These delta values were utilized to quantify the improvement in each measure. The analysis was adjusted for age, BDI score, duration of inpatient rehabilitation, and initial NIHSS score to control for potential confounding factors. ΔK-MBI showed a statistically significant association with PSF (odds ratio [OR], 0.957; 95% confidence interval [CI], 0.918–0.997, p = 0.036). The results suggest an inverse association between K-MBI score improvements and PSF likelihood. Changes in other measures, ΔFAC, ΔBBT, and ΔMMSE-K did not show statistically significant associations with PSF. The ΔFAC showed an OR of 0.789 (95% CI, 0.418–1.490; p = 0.465), while the ΔBBT had an OR of 1.031 (95% CI, 0.984–1.079; p = 0.198). The ΔMMSE-K demonstrated an OR of 1.127 (95% CI, 0.973–1.305; p = 0.111) (**Table 2**).

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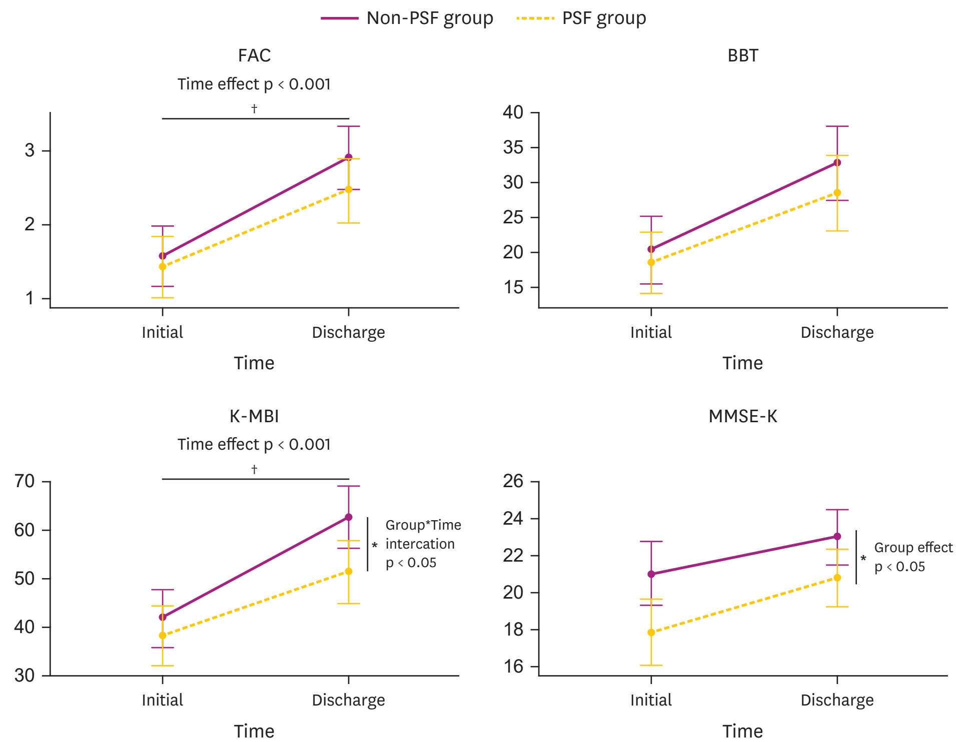

Fig. 2. Visual representation of repeated measures ANOVA results dots: mean values; bars: 95% confidence intervals. FAC, Functional Ambulation Category; PSF, post-stroke fatigue; BBT, Berg Balance Test, K-MBI, Korean version of Modified Barthel Index; MMSE-K, Korean version of Mini-Mental State Examination; ANOVA, analysis of variance.
*$p < 0.05$, †$p < 0.001$, statistically significant differences by repeated measures of ANOVA with adjustment by each age, presence or absence of depression and initial National Institutes of Health Stroke Scale score.

Table 2. ORs for the association between change of functional and cognitive outcome and post-stroke fatigue

Changes	B (SE)	OR	95% CI	p value
ΔFAC	−0.237 (0.324)	0.789	0.418–1.490	0.465
ΔBBT	0.030 (0.023)	1.031	0.984–1.079	0.198
ΔK-MBI	−0.044 (0.021)	0.957	0.918–0.997	0.036*
ΔMMSE-K	0.119 (0.075)	1.127	0.973–1.305	0.111

OR, odds ratio; SE, standard error; CI, confidence interval; FAC, Functional Ambulation Category; BBT, Berg Balance Test; K-MBI, Korean version of Modified Barthel Index; MMSE-K, Korean version of Mini-Mental State Examination.
*$p < 0.05$, multivariable logistic regression analysis was performed with adjustment by each initial National Institutes of Health Stroke Scale score, age, duration of inpatient rehabilitation and Beck's Depression Inventory score.

DISCUSSION

This study investigated the impact of PSF on functional recovery in acute and subacute stroke patients. The 52.5% of participants experienced fatigue (FSS score ≥ 4). The PSF group showed significantly lower discharge K-MBI scores and both initial and discharge MMSE-K scores compared to the non-PSF group. PSF was associated with differences in ADL recovery, with the PSF group demonstrating a more modest improvement in K-MBI scores over time, as evidenced by repeated measures ANOVA. To account for potential confounding factors, a multivariable logistic regression was conducted, adjusting for age, depression, initial stroke severity, and duration of rehabilitation. The analysis showed that PSF was independently associated with lower improvements in K-MBI scores, indicating that fatigue significantly influences recovery in ADL.

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To assess fatigue, we used the FSS, which is a widely recognized tool for measuring fatigue in stroke patients [12]. Although various fatigue scales such as Fatigue Impact Scale, Visual Analog Scale for fatigue, Fatigue Assessment Scale, Multidimensional Fatigue Symptom Inventory, and Fatigue Subscale Profile of Mood States are also used in patients with stroke the FSS has emerged as the most frequently employed, valid, and reliable scale [12]. Originally developed for conditions like multiple sclerosis and systemic lupus erythematosus, the FSS has been extensively validated for use in stroke patients therefore, making it an appropriate instrument for our study [12].

The principal finding of this study was the association between PSF and diminished recovery of ADL, as assessed using K-MBI in patients with acute and subacute stroke undergoing rehabilitation in a ward setting. The deleterious effects of PSF on ADL functionality have been corroborated in several studies. Barker-Collo et al. [30] discussed the methodology of fatigue after stroke educational recovery and highlighted the importance of targeted interventions to mitigate the impact of PSF on ADL recovery, as assessed using the MBI. Similarly, Oyake et al. [17] demonstrated that PSF at admission was significantly linked to lower levels of independence in ADL, as measured using the Functional Independence Measure (FIM), in patients with subacute stroke, although the disparity in FIM scores between admission and discharge was not statistically significant between the PSF and control groups. In terms of QOL, Ali et al. [18] identified a moderate negative correlation between PSF and the Barthel Index in chronic patients with stroke, while Naess et al. [28] found that PSF severity was the most significant predictor for both ADL and QOL in patients with ischemic stroke. Askari et al. [31] explored the impact of cognitive fatigue on daily activities, emphasizing the complexity of post-stroke cognitive fatigue and its significant negative effect on daily life, thereby affecting QOL. Lerdal et al. [32] reported that acute-phase fatigue after stroke could be an independent risk factor for impaired ADL 18 months post-stroke. Although several of these studies provided cross-sectional analyses, our research uniquely evaluated the negative impact of acute PSF on ADL recovery from admission to discharge in a subacute rehabilitation ward. This longitudinal approach allowed us to capture changes over time and to provide a more dynamic understanding of the relationship between PSF and ADL recovery. Our findings highlight the critical need for comprehensive assessments and targeted interventions to address PSF in stroke rehabilitation, particularly considering its profound impact on ADL and QOL.

Understanding the influence of PSF on functional recovery, specifically gait and balance, is critical in the field of post-stroke rehabilitation. Our results demonstrate that PSF does not significantly associate with poor recovery of gait and balance, as assessed by the FAC and BBT. However, studies examining the impact of PSF on gait and balance recovery in acute and subacute stroke patients are limited, with most existing research being cross-sectional in nature [33-35]. A recent prospective multicenter observational study by Zeng et al. [36] reported findings that contrast with our results. Their study on inpatient rehabilitation outcomes found that patients with lower fatigue levels showed higher motor function independence at discharge compared to those with higher fatigue levels. The discrepancy between our findings and those of Zeng et al. [36] may be attributed to several factors. The methodological differences between our study and Zeng et al.'s [36] include the choice of assessment tools and potentially different initial functional status of participants. We used the FAC and BBS for motor function assessment, while Zeng et al. [36] utilized the FIM. For fatigue evaluation, our study employed the FSS, whereas Zeng et al. [36] used the Visual Analog Fatigue Scale. These factors may explain the discrepancies in our findings. These differences highlight the complexity of PSF's impact on functional recovery and underscore the need for further longitudinal studies in acute and subacute stroke populations. Further research may benefit from considering various factors such as initial functional status, assessment timing, and specific functional domains when examining the relationship between PSF and recovery of gait and balance abilities.

Our investigation revealed that the PSF group exhibited significantly lower MMSE-K scores at both admission and discharge. However, a direct association between PSF and the trajectory of cognitive function recovery was not observed. These findings suggest a potentially complex and nuanced relationship between PSF and cognitive function in stroke patients. The extant literature presents heterogeneous findings regarding this relationship, with some studies reporting no significant correlation between PSF and cognitive measures, while others indicate significant associations [19,37]. This variability in results may potentially be attributed to the multifaceted nature of cognition, which encompasses various domains including attention, memory, and executive function. A recent study has reported an association between PSF and diminished performance in specific cognitive tasks, particularly those related to attention. However, these investigators also suggest that the impact of PSF may vary across different cognitive domains and stages of recovery [36]. Considering these complexities, further research appears necessary to elucidate the mechanisms underlying the PSF-cognition relationship. Such investigations could potentially contribute to the development of more effective, targeted rehabilitation strategies for stroke patients experiencing fatigue.

Our results were evaluated after adjusting for age, initial neurological severity by NIHSS score, and depression, all of which are highly related to PSF. In our study, there was a linear correlation between age, initial NIHSS score, and FSS score, and a significant relationship was observed between depression and fatigue after stroke. These findings are consistent with those of many previous studies that have reported a strong correlation between depression and fatigue [10,11,13,18,19,38-40].

This study has several limitations. First, it was designed as a retrospective chart review, which may introduce selection bias owing to the nature of the data collection. Second, patients' medical conditions or comorbidities during admission were not considered when evaluating the FSS. Because some medical conditions can affect fatigue, we controlled for the initial neurological severity using the NIHSS score. Additionally, our study included only patients admitted to the Rehabilitation Medicine Department who had received rehabilitation treatment and excluded those who were too medically unstable to participate. Third, although the FSS is primarily based on patient self-reports, which generally minimizes rater discrepancy, the use of multiple evaluators and the necessity for face-to-face assessments for participants with visual impairments or literacy challenges introduced potential methodological inconsistencies. To mitigate these inconsistencies, we ensured that all assessment items were presented verbatim, whether in written form for self-assessment or read aloud during direct assessments. Fourth, in our study, significant differences in initial and discharge MMSE-K scores between PSF and non-PSF groups were observed, highlighting a group effect. However, the causal relationship between PSF and cognitive decline remains unclear; PSF could be either a result or a cause of decreased cognition. Although we found no significant difference in MMSE-K score improvements between the groups after rehabilitation, caution is needed when interpreting these results due to the initial score differences. Future research should explore this relationship further to clarify the directionality and potential mediating factors. Further controlled cohort studies and long-term follow-up studies are necessary to address these limitations and determine the impact of fatigue on recovery outcomes.

Fatigue after stroke adversely affects the ability of patients with acute and subacute stroke to recover their independence in ADL compared with those without PSF. This study suggests that early regulation and management of fatigue could positively affect functional recovery, especially in ADL. However, this study only examined functional recovery during rehabilitation, and the long-term effects of PSF were not studied. Therefore, further prospective and controlled studies, as well as long-term follow-up investigations, are warranted to evaluate the impact of PSF on functional recovery. These findings highlight the need for clinical screening for early PSF in patients with stroke.

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