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ORIGINAL REPORT

FACTORS ASSOCIATED WITH COGNITIVE IMPROVEMENT IN SUBACUTE STROKE SURVIVORS

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Objective: **To elucidate the characteristics of subacute stroke survivors with post-stroke cognitive impairment, and examine the factors associated with cognitive improvement.**

Design: **Retrospective cohort study.**

Participants: **A total of 218 consecutive stroke survivors, who were admitted to a rehabilitation hospital between April 2014 and March 2015, were included.**

Methods: **The prevalence of post-stroke cognitive impairment, defined as having a Mini-Mental State Examination (MMSE) score <24 was investigated. Among those with post-stroke cognitive impairment, the characteristics of patients with clinically significant improvement in MMSE scores (change ≥4) were explored. Univariable and multivariable regression analyses were performed to examine the relationship between Functional Independence Measure (FIM) items and improvement in post-stroke cognitive impairment.**

Results: **Post-stroke cognitive impairment occurred in 47.7% of participants. The mean improvement in their MMSE scores was 3.43. Participants who showed improvement had significantly higher FIM scores at discharge than those who did not show improvement. Regarding FIM items, eating (odds ratio 1.3; 95% confidence interval 1.0–1.7; $p=0.041$) and social interaction (odds ratio 1.5, 95% CI 1.1–2.1, $p=0.010$) were associated with cognitive improvement.**

Conclusion: **Approximately half of subacute stroke survivors have post-stroke cognitive impairment. Eating and social interaction are significantly associated with cognitive improvement.**

Key words: cerebrovascular disorders; vascular dementia; rehabilitation; recovery of function; cognition; subacute stroke.

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LAY ABSTRACT

Cognitive impairments after stroke inhibit the effectiveness of rehabilitation and limit the activities of daily living. Therefore, it is very important to take measures against cognitive impairments early on. Previous studies have shown that cognitive function improves to some extent after a stroke. However, there is a lack of knowledge on the improvement of cognitive function during subacute phase and its associate factors. We investigated the cognitive function of 218 patients with subacute stroke admitted to a rehabilitation hospital. As a result, we found that approximately half of the patients showed cognitive impairments on admission and approximately half of those eventually improved during hospitalisation. Furthermore, we found that the ability of eating and social interaction in daily life on admission were associated with cognitive improvement.

Post-stroke cognitive impairment (PSCI) occurs frequently and persists in many patients, not only in the acute phase, but also in the subacute phase, i.e. within 7 days to 6 months (1). It has been reported that 20–60% of stroke survivors show PSCI during the subacute phase during hospitalization (2–6). PSCI in the subacute phase in stroke patients inhibits subsequent recovery of motor functions, improvement in activities of daily living, and outcomes of rehabilitation (2, 7–11). In addition, cognitive impairment may lengthen the hospital stay, inhibiting discharge home from hospital (9, 11).

Cognitive impairment that manifests in the acute phase of stroke often improves over the months to years following stroke (12, 13). It has been reported that approximately 30% of stroke survivors with cognitive impairment, but not dementia, recover by 18 months after the stroke onset (10). Another study conducted cognitive assessments 3 and 15 months after stroke in 115 stoke survivors who showed no overt post-stroke dementia, and found that 50% of them demonstrated cognitive improvements after 15 months (14).

Although many studies have been conducted on cognitive impairment after stroke (15), a majority of the studies have focused on the incidence of cognitive impairment and its associated factors. Knowledge about factors related to the improvement in cognitive function in patients with stroke is limited.

The aim of this retrospective study was to elucidate the prevalence of PSCI in subacute stroke survivors, to explore the characteristics of stroke survivors with PSCI, and to examine the factors associated with cognitive improvement among stroke survivors who were admitted to subacute stroke rehabilitation wards.

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METHODS

Participants

A total of 375 consecutive stroke survivors who were admitted to the subacute stroke rehabilitation wards between April 2014 and March 2015 were enrolled in this retrospective cohort study. After excluding patients with aphasia and/or disturbed consciousness who could not be assessed on admission using the Mini-Mental State Examination (MMSE) (16), 218 patients who could be assessed using the MMSE on admission into the rehabilitation wards were included in the analysis. The study protocol was approved by the ethics committee of Tokyo Bay Rehabilitation Hospital (number No147-2). As this was a retrospective study, the requirement for informed consent was waived; if there was no opt-out, the participants were enrolled.

Study setting

The study was performed in convalescent rehabilitation wards (Kaifukuki Rehabilitation Wards; KRWs) in Tokyo Bay Rehabilitation Hospital, located in the urban area of Chiba Prefecture, Japan. The KRW is the system for intensive inpatient rehabilitation for patients during the subacute period, covered by a governmental medical insurance, and was introduced in Japan in 2000 (17). In case of stroke, patients were eligible for admission to the KRW within 2 months (early subacute) (1) and could stay for up to 180 days for patients with stroke accompanying severe disabilities and cognitive disorders. In KRW, physical, occupational, and speech-language-hearing therapies, lasting for a maximum of 3 h/day, 7 times a week were provided. Rehabilitation consisted mainly of repetitive, task-specific training, aimed at reacquiring activities of daily living. Speech-language-hearing therapy training includes feeding and swallowing training and cognitive training for cognitive impairment. Cognitive training is aimed at improving each isolated cognitive domain and is intended to be generalized to non-training tasks. Task-oriented cognitive training was also provided for cognitive problems in daily living situations. The transdisciplinary team provided patients and their families with a comprehensive monthly rehabilitation plan, including information about achieved goals, planned goals, and rehabilitative approaches to the planned goals, discharge planning, and social resources necessary for discharge.

Data collection

Age, sex, type of stroke, history of stroke and dementia, duration from onset of stroke to admission to the rehabilitation ward, and length of stay were collected as background information. The MMSE and Functional Independence Measure (FIM) scores (18, 19) were recorded at admission and discharge. The MMSE is a cognitive screening tool with high inter-rater reliability (20), which has been widely used for the assessment of stroke survivors (21, 22). It is designed as a 30-item questionnaire with a score range of 0–30. The FIM is a validated and reliable tool used to assess cognitive status and motor recovery in stroke survivors (23). The FIM consists of 18 items grouped into 2 domains: the motor and cognitive domains. The motor domain includes 13 items with scores ranging from 13 to 91, whereas the cognitive domain includes 5 items with scores ranging from 5 to 35. The total score (sum of the motor and cognitive scores) ranges from 18 to 126, with higher scores indicating higher degrees of independence. The MMSE was assessed by a trained occupational therapist within 5 days of admission and within 5 days before discharge. The FIM was assessed by a trained nurse within 1 week of admission and 1 week prior to discharge, in order to evaluate daily life situations in the ward.

Analysis

In the current study, participants with PSCI were defined as those who had an MMSE score <24, which is a well-known cut-off MMSE score (20, 24–25). Background information, MMSE score, FIM score, and FIM efficiency were compared between those who had PSCI on admission and those who did not. A scatter diagram of the MMSE scores, with scores recorded on admission on the x-axis and those recorded at discharge on the y-axis was created to examine the overall trend of the changes in scores. Furthermore, participants with PSCI were divided into 2 groups, based on an improvement ≥4 in the MMSE score, which is known as the minimal clinically important difference (MCID) (26). Those who showed an improvement in MMSE score ≥4 points from admission to discharge were classified into the improvement group, and those who showed an improvement <4 points were classified into the non-improvement group. The characteristics and functional outcomes (measured using FIM) of the groups were compared. For group comparisons, the χ^2 test and the Mann–Whitney *U* test were used for categorical and continuous variables, respectively.

Univariable and multivariable regression analyses were conducted to determine which patients' characteristics on the disability aspects (measured with FIM items) on admission were associated with subsequent improvement in cognition (defined as MCID of MMSE) at discharge. First, to examine the relationships between cognitive improvement and each item of FIM on admission, univariable regression analyses (crude analyses) were performed; where the dependent variable was cognitive improvement (MCID of MMSE) and the independent variable was each item of FIM on admission. Since there was a marginally significant difference in age and a significant difference in MMSE on admission between the MCID improvement and non-improvement group, multivariable regression analyses were performed with these adjusted factors. Furthermore, the goodness of fit of the model was examined using the Hosmer–Lemeshow test. All statistical analyses were performed using SPSS version 26 (IBM Japan, Tokyo, Japan). A p-value <0.05 was considered statistically significant.

RESULTS

A flow diagram of participants is shown in Fig. 1. The characteristics of the participants and the com-

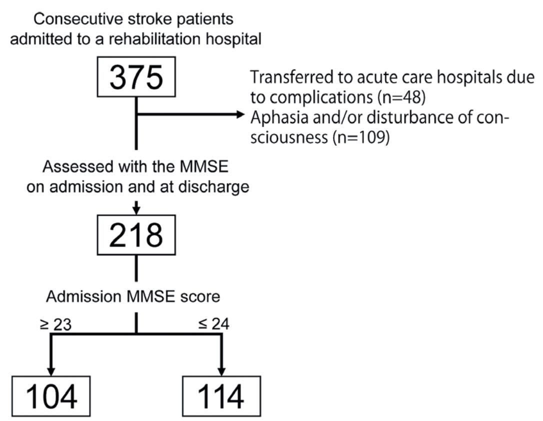

Fig. 1. Flow chart of the participants in the study. MMSE: Mini-Mental State Examination.

Table I. Participants' characteristics and comparison between those with post-stroke cognitive impairment (PSCI), defined as having Mini-Mental State Examination (MMSE) score ≤ 23 and those without

	With PSCI (*n* = 104)	Without PSCI (*n* = 114)	Total (*n* = 218)	*p*-values
Age, years, mean (SD)	74.9 (11.6)	65.6 (12.5)	70.1 (12.9)	< 0.001
Sex, male/female, *n*	47/57	72/42	119/99	0.007
Type of stroke, infarction/haemorrhage/subarachnoid haemorrhage, *n*	70/23/11	71/37/6	141/60/17	0.201
Past history of stroke, *n* (%)	29 (27.9)	14 (12.3)	43 (19.7)	< 0.001
Past history of dementia, *n* (%)	15 (14.4)	1 (0.9)	16 (7.3)	< 0.001
Duration from stroke onset to admission, days, median (min–max)	37.5 (14–58)	29.0 (9–58)	33 (9–58)	< 0.001
Length of stay in the rehabilitation hospital, days, median (min–max)	96.0 (10–179)	70.0 (15–179)	85.0 (10–179)	< 0.001
MMSE, median (IQR)				
Admission	19 (15–22)	28 (26–29)	24 (19–28)	< 0.001
Discharge	22 (18–25)	29 (26–30)	26 (22–29)	< 0.001
Difference	3 (1–5)	1 (–0.75–2)	1.0 (0–4)	< 0.001
FIM, median (IQR)				
Motor domain				
Admission	34.5 (24–54)	58 (45.75–72.25)	49.5 (32–66)	< 0.001
Discharge	67.5 (49–81)	85 (77–88)	79 (63.75–87)	< 0.001
Efficiency	0.28 (0.15–0.37)	0.32 (0.23–0.42)	0.30 (0.20–0.40)	0.004
Cognitive domain				
Admission	19 (15–24)	30 (25–33)	25 (18–30)	< 0.001
Discharge	24 (18–28.75)	33 (30–35)	30 (24–34)	< 0.001
Efficiency	0.03 (0.00–0.07)	0.03 (0.00–0.07)	0.03 (0.00–0.07)	0.990
Total				
Admission	53 (40–76)	88.5 (74–102)	75 (51–92)	< 0.001
Discharge	67 (48.5–81)	115 (110.25–121)	110 (88.25–117.75)	< 0.001
Efficiency	0.31 (0.19–0.43)	0.34 (0.26–0.49)	0.33 (0.22–0.47)	0.010

SD: standard deviation; FIM: Functional Independence Measure; IQR: interquartile range.

parisons between those with and without PSCI are shown in Table I. The mean (standard deviation; SD) age of participants was 70.1 years (SD 12.9), with 119 participants being males, and mean (SD) time from onset was 33.8 days (SD 12.6). At admission to the rehabilitation wards, 47.7% (104/218) of participants had PSCI. Those who had PSCI were significantly older, more likely to be female, more likely to have a history of stroke and dementia, had longer duration from stroke onset to admission to rehabilitation wards, longer length of hospital stay, lower MMSE scores at admission and discharge, and lower FIM motor and cognitive scores at admission and discharge than those who did not have PSCI. In addition, those who had PSCI showed lower FIM motor efficiency, that is, FIM score gain divided by the length of hospital stay, than those who did not have PSCI.

A scatter plot was created to analyse the distribution of MMSE and the overall trend of the changes in scores from admission to discharge (Fig. 2). The MMSE scores demonstrated an overall tendency to improve; however, the higher scores showed a ceiling effect. The median (interquartile range; IQR) improvement in MMSE scores from admission to discharge was 1.0 (0–4) (mean 1.96 (SD 3.33)). For the participants with PSCI (MMSE < 24), the median (interquartile range) improvement in MMSE scores was 3.0 (1–5) (mean 3.43 (SD 3.61)) (Table I).

Fifty of the 104 (48%) participants who had an MMSE with PSCI achieved MCID (≥4 points) at discharge. The comparison between the improvement and non-improvement groups is shown in Table II. Those in the improvement group had significantly lower MMSE scores on admission and significantly higher MMSE scores at discharge than those in the non-improvement group. In addition, participants in the improvement group had significantly higher motor and total FIM scores at discharge and higher FIM cognitive efficiency scores than those in the non-

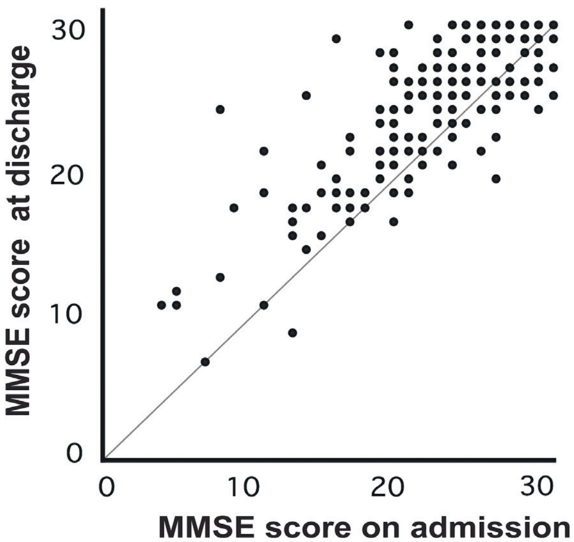

Fig. 2. Scatter diagram of Mini-Mental State Examination scores (*n* = 218). Scores recorded on admission are on the x-axis and those recorded on discharge are on the y-axis. Improvement was obvious at discharge. The higher scores recorded at admission showed a ceiling effect.

Table II. Comparison between participants with improved Mini-Mental State Examination (MMSE) score changed by ≥ 4 and those without

	MMSE change ≤ 3 (*n* = 54)	MMSE change ≥ 4 (*n* = 50)	Total (*n* = 104)	*p*-values
Age, mean (SD)	77.2 (10.0)	72.6 (12.8)	74.9 (11.6)	0.054
Sex, male/female, *n*	25/29	22/28	47/57	0.814
Type of stroke, infarction/haemorrhage/subarachnoid haemorrhage, *n*	37/13/4	33/10/7	70/23/11	0.558
Past history of stroke,nn (%)	16 (29.6)	13 (26.0)	29 (27.9)	0.680
Past history of dementia, *n* (%)	9 (16.7)	6 (12)	15 (14.4)	0.499
Duration from stroke onset to admission, days, median (min–max)	39 (14–58)	36.0 (15–60)	37.5 (14–60)	0.344
Length of stay in the rehabilitation hospital, days, median (min–max)	91.5 (10–179)	98.0 (11–177)	96.0 (10–179)	0.290
MMSE, median (IQR)				
Admission	20 (16.75–22)	19 (13.75–21)	19 (15–22)	< 0.019
Discharge	20.5 (18–23)	24 (19–27)	22 (18–25)	< 0.001
Difference	1 (0–2)	5.5 (4–7)	3 (1–5)	< 0.001
Patients with MMSE ≥24 at discharge, *n* (%)	10 (19)	30 (60)	40 (38.5)	< 0.001
FIM, median (IQR)				
Motor domain				
Admission	33.5 (21.75–48.25)	37 (24–57)	34.5 (24–54)	0.369
Discharge	58 (40.25–77)	74 (56–84.25)	67 (47.5–81)	0.008
Efficiency	0.26 (0.11–0.39)	0.28 (0.20–0.37)	0.28 (0.15–0.37)	0.216
Cognitive domain				
Admission	19 (14.75–24)	18 (15–24)	19 (15–24)	0.797
Discharge	22 (17.75–28.25)	25 (19–29.25)	24 (18–28.75)	0.207
Efficiency	0.02 (0.00–0.06)	0.05 (0.02–0.09)	0.03 (0.00–0.07)	0.026
Total				
Admission	52.5 (37.5–74.3)	54 (42–79)	53 (40–76)	0.464
Discharge	81 (59.3–100)	98 (74.75–109.25)	67 (48.5–81)	0.014
Efficiency	0.27 (0.12–0.43)	0.34 (0.22–0.43)	0.31 (0.19–0.43)	0.068

SD: standard deviation; FIM: Functional Independence Measure; IQR: interquartile range.

improvement group. Table III shows the results of the logistic regression analyses. The FIM "eating" item (odds ratio (OR) 1.33; 95% confidence interval (CI) 1.01–1.74; $p=0.041$) and "social interaction" item (OR 1.52; 95% CI 1.11–2.08; $p=0.010$) were significantly associated with improvement in MMSE score when adjusted for age and MMSE score on admission. The Hosmer–Lemeshow test revealed good model fit for these items (eating, $p=0.452$; and social interaction, $p=0.782$).

DISCUSSION

The prevalence and characteristics of PSCI among stroke survivors who were admitted to subacute stroke rehabilitation wards were investigated. Furthermore, the current study clearly revealed the characteristics of stroke survivors with PSCI who achieved MCID of MMSE in the subacute phase, and the factors associated with cognitive improvement. It was found that approximately half (47.7%) of the participants in this study had PSCI on admission. Among FIM items on

Table III. Logistic regression analyses of Functional Independence Measure items for the improvement in Mini-Mental State Examination (MMSE) score in participants with MMSE ≤ 23 at admission (*n*=104)

	Univariable regression			Multivariable regression adjusting with age and MMSE		
Items	OR	95% confidence interval	*p*-value	OR	95% confidence interval	*p*-value
Eating	1.22	0.97–1.52	0.092	1.33	1.01–1.74	0.041
Grooming	1.00	0.81–1.24	0.974	1.03	0.81–1.31	0.815
Bathing	0.95	0.76–1.18	0.643	1.02	0.80–1.29	0.892
Dressing upper body	1.07	0.86–1.33	0.533	1.07	0.84–1.36	0.585
Dressing lower body	1.06	0.85–1.31	0.598	1.05	0.82–1.33	0.704
Toileting	1.08	0.88–1.32	0.472	1.08	0.86–1.35	0.495
Bladder management	1.15	0.96–1.38	0.123*	1.22	0.99–1.50	0.060
Bowel management	1.08	0.91–1.29	0.390	1.15	0.93–1.41	0.198
Transfers bed, chair, wheelchair	1.21	0.98–1.50	0.081	1.20	0.94–1.52	0.140
Transfers toilet	1.21	0.97–1.51	0.091	1.21	0.95–1.54	0.132
Transfers tub, shower	1.10	0.72–1.68	0.664*	1.04	0.67–1.60	0.871
Walk	1.06	0.86–1.31	0.578	1.04	0.83–1.30	0.716
Stairs	1.30	0.55–3.03	0.551*	1.25	0.51–3.02	0.682
Comprehension	0.91	0.68–1.21	0.507	1.15	0.80–1.65	0.499
Expression	0.94	0.71–1.24	0.671	1.16	0.83–1.61	0.390
Social interaction	1.17	0.92–1.50	0.198	1.52	1.11–2.08	0.010
Problem solving	0.96	0.74–1.24	0.742	1.15	0.84–1.57	0.397
Memory	0.83	0.64–1.08	0.170	0.94	0.69–1.27	0.670

**p*-values < 0.05 with Hosmer–Lemeshow goodness-of-fit test. OR: odds ratio.

admission, eating and social interaction item scores were associated with cognitive improvement in participants with PSCI.

Regarding the prevalence of PSCI as determined with MMSE, it has been reported that PSCI is observed in 20–65% of stroke survivors 3 months after the onset of stroke (4−6). Although the timing of the evaluation in those studies (4–6) differed from that in the current study, the current results are similar to those of previous studies. The participants with PSCI had significantly lower total and motor efficiency FIM scores than those without PSCI. These findings are consistent with those of previous studies that indicated that cognitive impairment predicts poor functional outcomes (8, 11).

Approximately half (48.1%, 50/104) of the participants with PSCI on admission eventually achieved the MCID of MMSE score (≥4 points). It is important to note that improvement in MCID of MMSE scores did not mean the recovery of cognitive impairment. However, it is worth noting that, in the group that achieved MCID, the median MMSE score at discharge reached 24 points and 60% (30/50) showed recovery; while in the group that did not achieve MCID, only 19% (10/54) showed recovery. There are 2 possible mechanisms of improvement in cognitive function. The first is the improvement in cognitive function due to spontaneous biological recovery, which is defined as improvements in the absence of a specific, targeted treatment (27). The duration of the window of this recovery varies across neural systems. For example, recovery of arm movement has been reported to be seen within weeks to months after a stroke (28), whereas that of language has been reported to take longer (29). Previous studies have reported that cognitive impairment that appears in the acute phase of stroke often improves within a few months to a few years after stroke onset (12, 13). Furthermore, the cognitive decline observed at the onset of stroke has been shown to improve in 30–50% of patients at 15–18 months after the onset of stroke (10, 14). Although it is difficult to know the extent of the contribution of spontaneous recovery while recovering from cognitive impairment, it is possible that a certain period of time after onset includes this spontaneous biological recovery process, which may have contributed to the improvement in cognitive function seen in the subacute patients in the current study. The second possible mechanism is intervention-related changes. Rehabilitation may have had a positive effect on cognitive function. Systematic reviews suggest that physical activity has a positive effect on improving global cognitive ability and a potential benefit on memory, attention, and the visuospatial domain of cognition in stroke survivors (31). Some mechanisms have been suggested to explain the effects of exercise on cognition after stroke: the increase in cerebral blood volume, increased expression of growth factors, such as brain-derived neurotrophic factor, and a positive effect on depressive symptoms (31). The reasons for the improvement in cognitive function was thought to be related to the aforementioned 2 mechanisms; however, it is not clear to what extent spontaneous biological recovery and rehabilitative interventions were involved in the improvement in cognitive function.

The comparison and logistic regression analyses showed that MMSE score on admission and FIM "eating" and "social interaction" scores on admission were significantly associated with clinically significant improvement in cognitive function (>MCID of MMSE score) among individuals who had an MMSE score <24 on admission. In addition, age had a marginally significant association with cognitive improvement. It is not surprising that MMSE score on admission and age were associated with cognitive improvement. Regarding the MMSE score on admission, a ceiling effect may have strongly contributed to the finding, as indicated in the scatter plot (Fig. 2). Age, which has a significant influence on all human functions, is also known to be associated with cognitive impairment in stroke survivors (12–15).

The association between FIM "eating" score on admission and cognitive improvement could be explained by the difficulty level of the FIM eating task. Eating is characterized by the lowest difficulty level compared with other items on the scale (32). Due to this characteristic, the floor effect is less likely to occur; thus, the item can identify the differences in the physical and cognitive conditions of individuals with poor conditions more sensitively than other items.

It was noteworthy that the FIM "social interaction" score on admission was found to be associated with cognitive improvement. There were 2 possible reasons for this finding. The first is that the item is reflected by symptoms related to cognitive decline, such as behavioural and psychological symptoms of dementia, which have been reported to correlate with cognitive function (33). The second possible explanation is that a higher training effect could be obtained in individuals with preserved social interaction than in those without. The FIM social interaction item is defined as "skills related to getting along and participating with others in therapeutic and social situations. It represents how one deals with one's own needs together with the needs of others" (18). Social interaction has been reported to be a useful predictor for activities of daily living in stroke survivors. It has been speculated that this may be due to a favourable training effect from good relationships with therapists (7). Good cognitive function is said to lead to better results in rehabilitation (8, 11). However, the results of this study suggest that, even if cognitive function is impaired, subsequent improvement in cognitive function and training effects may be expected if social interaction is maintained.

This study has some limitations. It was conducted in a single rehabilitation facility in Japan, and patients were in the subacute phase and undergoing rehabilitation. Furthermore, although the validity of the MMSE in screening for dementia after stroke has been proven, other tools, such as MOCA, have also been used to screen people with dementia (21, 22). A multi-centre prospective study including patients in various phases with different evaluation methods is required to confirm the findings of the current study. In addition, further studies including a wide range of factors on various aspects, such as stroke severity and site of brain lesions, could identify better prognostic factors for the improvement in PSCI.

In conclusion, approximately half of subacute stroke survivors who were admitted to rehabilitation wards had PSCI, and approximately half of those eventually improved cognitive function. In addition to MMSE score and age on admission, FIM "eating" and "social interaction" scores on admission were found to be factors associated with cognitive improvement. Even if stroke survivors have cognitive dysfunction on admission, good improvement in cognitive function is expected if FIM "eating" or "social interaction" scores are well maintained.

The authors have no conflicts of interest to declare.

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