Association between Early Cognitive Impairment and Short-Term Functional Outcome in Acute Ischemic Stroke

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Research Article

Association between early cognitive impairment and short-term functional outcome in acute ischemic stroke

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Short Title: Cognitive impairment in acute stroke and outcome

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Abstract

Background: Little is known about the association between poststroke cognitive impairment (PSCI) and functional outcome in acute care phase of ischemic stroke and the influence of the clinical condition of acute stroke on this association. We examined this issue, taking into account stroke-related factors, in a hospital-based prospective study of patients with acute ischemic stroke. The same analysis was also performed after subsequent rehabilitation to investigate whether the association observed in the acute care phase persisted after that. For comparison, the same analysis was performed for pre-stroke dementia (PreSD).

Methods: We included in the study a total of 923 patients with acute ischemic stroke who were admitted to a hospital from 2012 to 2020 in Japan. Cognitive function was assessed using the Mini-Mental State Examination and Raven's Colored Progressive Matrices test at an average of 6.3 days after stroke onset. The subjects were divided into three groups with normal cognition, PSCI, and PreSD. Study outcome was poor functional outcome defined as a modified Rankin Scale score of ≥3 at the end of acute care (median 21 days after admission). Among total subjects, 460 were also assessed for poor functional outcome after rehabilitation (median 77 days after admission). A logistic regression model was applied in this study.

Results: Patients with PSCI and PreSD had higher median National Institute of Health Stroke Scale scores than those with normal cognition (median [IQR]: 3 [2 – 6], 4 [2 – 12], and 2 [1 – 4], respectively). The age- and sex-adjusted cumulative incidence of poor functional outcome was significantly higher in patients with PSCI and PreSD than those with normal cognition in the acute care and rehabilitation phases. In the acute care phase, these associations remained significant after adjustment for stroke-related factors and other confounders (multivariable-adjusted odds ratio [OR] [95%CI] for PSCI vs. normal cognition: 3.28 [2.07–5.20]; for PreSD: 2.39 [1.40–4.08]). Similar results were observed in the rehabilitation phase (for PSCI: 2.48 [1.31–4.70]; for PreSD: 3.92 [1.94–7.92]).

Conclusions: Our findings suggest that PSCI, as well as PreSD, is possibly associated with the development of poor functional outcome in the acute care phase of ischemic stroke, and this association continues thereafter.

Introduction

Stroke and dementia, both of which are major causes of functional disability, are expected to become more frequent along with the growth of the elderly population worldwide [1, 2]. It is necessary to understand the association between the two diseases and create appropriate treatment strategies, because either disease confers a risk of developing the other and worsening the clinical outcome in older persons [3, 4]. Recently, dementia and cognitive impairment have come to the fore as risk factors for poor clinical outcome after stroke [5]. Several clinical studies have revealed an association between pre-stroke dementia (PreSD) and poor functional outcome [6, 7] and mortality [8, 9] in stroke patients. In other clinical studies, poststroke cognitive impairment (PSCI) assessed in the subacute stage of ischemic stroke (i.e. 3 months after stroke onset) was linked to a higher risk of long-term (5-12 years) mortality [10, 11]. Moreover, several clinical studies showed an association between PSCI determined in the acute stage of stroke (within 7 days) and short-term (within 3 months) to long-term (over a year) poor functional outcome [12–15]. However, there is scarce evidence regarding the association between PSCI and subsequent functional outcome in the acute care phase of ischemic stroke and the influence of the clinical condition of acute stroke on this association [16]. If PSCI is associated with the development of poor functional outcome in the early phase of ischemic stroke, and if this association persists thereafter, new treatment strategies aimed at preventing or reducing PSCI in this phase may have important implications for improving long-term clinical prognosis of stroke patients.

The purpose of the present investigation was to examine whether PSCI in the acute stage of ischemic stroke was associated with poor clinical outcome at the end of the acute care phase (approximately 3 weeks after stroke onset), taking into account stroke-related factors, by means of a hospital-based prospective study of stroke patients in Japan. The same analysis was also performed after subsequent rehabilitation (approximately 3 months after stroke onset) to investigate whether the association observed in the acute care phase persisted after that. For comparison, we performed the same analysis for PreSD.

Methods

Study Subjects

Our Hakujyuji Hospital is a mixed care-type hospital that includes both acute care units and recovery rehabilitation units. It provides medical care to the western area of Fukuoka, the metropolitan area of Kyushu, in Japan. From August 2012 to October 2020, a total of 1,617 patients with acute ischemic stroke who were admitted to the acute care units of the hospital's stroke center within 7 days after onset were consecutively registered in the hospital database (online suppl. Figure 1). From this group, we excluded 439 patients with pre-stroke dependency (modified Rankin Scale score of 3–5), 217 who had not received cognitive function tests during the acute stage due to impairment of consciousness and/or delirium (n=161), too-short hospitalization for minor symptoms (54), or refusal of cognitive function tests (2), and 38 who were transferred to other hospitals in the middle of treatment for other diseases. The remaining 923 patients were included in the present study and in the initial analysis of the association between baseline cognitive impairment and functional outcome at the end of the acute care phase (median 21 [interquartile range: 15–29] days after admission: analysis of the acute care phase). Among these 923 patients, 463 patients were discharged from the hospital after acute treatment, and the remaining 460 patients were transferred to the rehabilitation units in the hospital. In the latter patients, we also examined the association between baseline cognitive impairment and functional outcome at the end of rehabilitation (median 77 [45–150] days after admission: analysis of the rehabilitation phase). In Japan, recovery rehabilitation facilities or units for patients in the convalescent stage who still need assistance in activities of daily living are operated under the Japanese National Insurance System. Here, stroke patients receive physical, occupational, and speech therapy, including cognitive rehabilitation, for up to 180 days, depending on their condition.

Assessment of Cognitive Impairment

Cognitive function was assessed using the Mini-Mental State Examination (MMSE) [17] by professional speech therapists and occupational therapists at an average of 6.3 ± 6.5 days after stroke

onset. The MMSE, along with the Montreal Cognitive Assessment (MoCA), has been widely used as a screening tool for PSCI in clinical studies of stroke patients [18], and its utility in the assessment of cognitive function has been reported to be comparable to that of the MoCA, especially in Asian stroke patients [19]. The Raven's Colored Progressive Matrices (RCPM) test was also conducted in patients with aphasia [20], because aphasia affects test performance of MMSE. This test is a non-verbal, visual test used to assess cognitive function in patients with aphasia [21]. Cognitive function tests were performed on all subjects except 33 patients with PreSD. In patients who did not have PreSD, PSCI was defined as MMSE ≤23 [17] or MMSE ≤23 and RCPM ≤24 (the cut-off score in Japanese) if there was aphasia [22]. PreSD was defined as any type of dementia that was present prior to the index stroke. Assessment of cognitive and functional status before stroke onset was based on clinical interview on a knowledgeable informant. PreSD was diagnosed by attending physicians according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition Text Revision criteria [23].

Assessment of Stroke-related Factors and Vascular Risk Factors

At admission, we evaluated stroke-related factors and vascular risk factors which could affect cognitive function and thereby the subsequent association between cognitive impairment and functional outcome. The definitions of these factors were described in Supplementary Material (see online suppl. methods).

Study Outcome

The modified Rankin Scale score was evaluated by stroke neurologists in person on admission, at the end of acute care phase, and at the end of rehabilitation phase. Poor functional outcome, namely functional disability and death, was defined as its score of 3–6, at the end of acute care phase and at the end of rehabilitation phase.

Statistical Analysis

The differences in the mean values and frequencies of baseline stroke-related factors and vascular risk factors between groups of cognitive state were tested using a linear or logistic regression model, as appropriate. The age- and sex-adjusted cumulative incidence of poor functional outcome in the acute care and rehabilitation phases of ischemic stroke was calculated using a direct method with the age and sex distributions of the overall study group. The age- and sex-adjusted and multivariate-adjusted odds ratios (ORs) and their 95% CIs were estimated using the logistic regression model. We used a 3-step approach to adjust for other baseline variables: model 1 was adjusted for age and sex; model 2 was adjusted for the variables included in model 1 and stroke-related factors, namely previous stroke, National Institute of Health Stroke Scale (NIHSS) score, stroke subtype (cardioembolic infarction vs. other subtypes of ischemic stroke), laterality of infarction (left hemisphere No vs. Yes, right hemisphere No vs. Yes), location of infarction (cortex No vs. Yes, basal ganglia No vs. Yes, brainstem/cerebellum No vs. Yes), and reperfusion therapy; and model 3 was further adjusted for the variables included in model 2 and vascular risk factors, namely, hypertension, diabetes, dyslipidemia, coronary heart disease, current smoking, and current alcohol intake. The heterogeneity in the association between PSCI or PreSD and poor functional outcome by categories of stroke-related factors and vascular risk factors was also tested by adding a multiplicative interaction term in the logistic model. The quality of logistic model was evaluated by calculating the Cox & Snell R^2, Nagelkerke R^2, and area under curve (AUC) values. To assess the issue of multi-collinearity between the independent variables, we calculated the variance inflation factor (VIF) between all variables used in the multivariable analysis. We performed a complete case analysis because there were no missing data except information about smoking habits and alcohol intake in 17 (1.8%) patients. The SAS

software package (University Edition; SAS Institute, Cary, NC) was used to perform all statistical analyses. Two-sided values of P <0.05 were considered statistically significant in all analyses.

Results

The average age of the 923 patients was 72±11 years, and 60.3% were men. Among total subjects, 635 (68.8%) had normal cognition, 157 (17.0%) had PSCI, and 131 (14.2%) had PreSD. The baseline characteristics of the study subjects are summarized in Table 1. Patients with PSCI and PreSD were older and less likely to be men than those with normal cognition. In regard to stroke-related factors, the frequency of previous stroke was higher in patients with PreSD than those with normal cognition. Compared with those having normal cognition, patients having PSCI and PreSD had higher median NIHSS scores and higher frequencies of cardioembolic stroke, left hemisphere infarction, and cortical infarction. In regard to vascular risk factors, the patients with PSCI were more likely to have atrial fibrillation and coronary heart disease, and less likely to have current alcohol intake. In patients with PreSD, the frequencies of dyslipidemia, current smoking, and current alcohol intake were lower than those in patients with normal cognition, whereas the frequency of atrial fibrillation was higher in patients with PreSD.

A total of 260 (28.2%) and 116 (25.2%) subjects developed poor functional outcome in the acute care and rehabilitation phases, respectively. Figure 1 demonstrates the age- and sex-adjusted cumulative incidence of poor functional outcome according to cognitive state in the acute care and rehabilitation phases of ischemic stroke. Compared with those having normal cognition, the cumulative incidence of poor functional outcome was significantly increased in both subjects having PSCI and those having PreSD in each phase. Table 2 shows the ORs and 95% CIs of PSCI and PreSD for the development of poor functional outcome. In the acute care phase, the age- and sex-adjusted ORs for poor functional outcome were significantly higher in patients with PSCI and PreSD relative to those with normal cognition (model 1). To exclude the influence of the clinical condition of acute ischemic stroke on these associations, we further adjusted for stroke-related factors in model 2. As a consequence, PSCI and PreSD were significantly associated with the development of poor functional

outcome. These associations were unchanged even after adjustment for vascular risk factors (in the acute care phase, OR [95%CI] for PSCI vs. normal cognition: 3.28 [2.07–5.20]; for PreSD: 2.39 [1.40–4.08], in the rehabilitation phase, for PSCI: 2.48 [1.31–4.70]; for PreSD: 3.92 [1.94–7.92]).

There was no evidence of heterogeneity between the two categories of each stroke-related factor in the OR of PSCI for poor functional outcome in the acute care phase, except NIHSS score (*P* for heterogeneity = 0.04) (online suppl. Table 1). In regard to PreSD, significant heterogeneity was observed between the two categories of stroke subtype in the acute care phase (*P* for heterogeneity = 0.04) (online suppl. Table 1). However, these heterogeneities were not found in the rehabilitation phase (online suppl. Table 2). There was also no heterogeneity between the two categories of each vascular risk factor in the OR of PSCI and PreSD in either phase, except hypertension in the acute care phase (*P* for heterogeneity = 0.02) (online suppl. Tables 3 and 4).

In this study, we found no problem with the quality of multivariable logistic model and the results of the multi-collinearity assessment between independent variables (online suppl. Tables 5 and 6).

Discussion

In this study, cognitive impairment caused by acute ischemic stroke was possibly associated with worsening functional outcome in the acute care phase of stroke, independently of stroke-related factors and vascular risk factors. This association was remained significant after rehabilitation. Similar results were observed for PreSD in the acute care and rehabilitation phases.

Some clinical studies have reported an association of PSCI or PreSD assessed in the acute or subacute stage of stroke with subsequent clinical outcome [6–16]. Among them, several studies examined the association between PSCI in the acute stage of stroke and functional outcome [12–16]. In four of these studies, cognitive impairment as determined by a lower level of MoCA score in the acute stage of ischemic stroke was associated with short-term to long-term poor functional outcome [12, 13, 15, 16]. Another study also showed that domain-specific cognitive impairment determined within the first 3 weeks after stroke was a risk factor for long-term poor functional outcome [14].

These findings agree with our present results that PSCI is linked to poor functional outcome in the acute care and rehabilitation phases of ischemic stroke. It has been reported that stroke-related factors, such as history of stroke, stroke severity, stroke subtype, and location, affect cognitive function of stroke patients [4]. This suggests that the clinical condition in the acute stage of stroke influences the performance of cognitive function tests, and thereby the association between PSCI and functional outcome. However, no reports have fully examined this issue with respect to the association between PSCI and functional outcome after stroke. In our study, PSCI was associated with the development of poor functional outcome even after adjusting for these stroke-related factors in addition to vascular risk factors in the acute care phase of ischemic stroke, and this association continued at least through the rehabilitation phase. These findings, together with those of the aforementioned clinical studies [12–16], suggest that PSCI is possibly independently associated with poor functional outcome even in the acute care phase of ischemic stroke, and this association lasts for a long time after that.

Although the potential mechanisms underlying the association between PSCI and poor functional outcome in the acute care and rehabilitation phases of ischemic stroke are still unclear, several possible explanations can be considered. It has been reported that stroke patients with cognitive impairment, including dementia, have a pronounced disturbance in cerebrovascular hemodynamics, an attenuated vasodilatation in cerebral blood vessels, and alterations in the blood–brain barrier [24, 25]. In our patients with PSCI, these pathophysiological conditions might have been caused by index ischemic stroke. Alternatively, these patients might have had these conditions before stroke onset, even in the absence of cognitive impairment or dementia. In any case, such conditions in combination with acute ischemic stroke might have increased the risk of poor functional outcome in patients with PSCI. In addition, it has been shown that patients with cognitive impairment or dementia are likely to have a higher risk of adverse events such as falls, pressure sores, and fractures, particularly in acute care hospitals [26]. In patients with PSCI, these adverse events may interfere with the effectiveness of acute treatment. Moreover, cognitive impairment has been shown to reduce the effectiveness of rehabilitation by decreasing participation in rehabilitation therapy and preventing the acquisition of protocols for independence after stroke [27]. This might be one of the reasons for the

association between patients with PSCI and poor functional outcome after rehabilitation in our study. Further studies will be needed to elucidate other possible pathogenetic mechanisms underlying the association between PSCI and functional outcome after ischemic stroke.

The present study has several strengths. The number of subjects was large, and almost all of them underwent tests of cognitive function by experts. In addition, possible confounding factors, including stroke-related factors, were adjusted for in multivariable analysis.

Several limitations of the present study should be addressed. First, in our study, the estimation of pre-stroke cognitive status was performed without quantitative neuropsychological assessments, and thus patients with mild dementia may not have been appropriately identified. This may have caused a misclassification from PreSD to PSCI, resulting in an overestimation of the likelihood for poor functional outcome in PSCI patients. However, there is no material difference in the proportion of PreSD among all subjects in this study (14.2%) and those in the previous hospital-based studies (14–16%) [6, 7, 28]. In addition, in our study, the likelihood of poor functional outcome was not different between patients with PSCI and those with PreSD (P=0.29 and 0.21 in the acute care and rehabilitation phases, respectively). Therefore, this limitation might not have exerted a meaningful influence on the results of our study. Second, cognitive function was assessed using only MMSE (or +RCPM), a brief screening tool of global cognitive impairment, rather than by using domain-specific neuropsychological tests [29]. We selected this measure because it is difficult to examine all domains of cognition including attention, memory, language, perceptual motor, and executive function using combined neuropsychological batteries in a large number of acute stroke patients. Therefore, the present study may have missed mild domain-specific cognitive impairment, and our findings are likely to be conservative. Third, in the rehabilitation phase of our study, the number of subjects decreased to about half of that in the acute care phase, which may have resulted in a selection bias. At the end of the acute care phase, however, we found an association of PSCI or PreSD with poor functional outcome in patients discharged from acute care units as well as those transferred to rehabilitation units (online suppl. Table 7), suggesting that the selection bias was not large in our study. Fourth, in our study, no clinical information was available on neurological or psychiatric conditions other than stroke and

dementia, nor on medication. These factors may have some influence on the association between cognitive impairment and poor functional outcome in stroke patients. In addition to this issue, there may be other residual confounding in the present findings. Fifth, our study was performed only in a Japanese cohort, and thus, the generalizability of the present findings should be interpreted with caution.

Conclusions

This large sample-size hospital-based prospective study demonstrated that PSCI, as well as PreSD, was associated with the development of poor functional outcome in the acute care phase of ischemic stroke, and this association remained in the rehabilitation phase. Screening of cognitive function in the acute stage of ischemic stroke may be useful for predicting high-risk populations with poor functional outcome. Further studies will be required to provide specific therapies and rehabilitation plans that can prevent the development and deterioration of PSCI in the acute stage of ischemic stroke to improve its prognosis.

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Statement of Ethics

The ethics committee of the Hakujyuji hospital approved this study (Reference No. 155). Written informed consent was obtained from all study subjects. This study was performed in accordance with the Declaration of Helsinki and its subsequent amendments.

Conflict of Interest Statement

The authors declare no conflict of interest relevant to this study

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Author Contribution

Takuya Kiyohara– data collection, design, data analysis, data interpretation, and draft.

Yasuhiro Kumai– data collection, design, data interpretation, and draft.

Tomohiro Yubi– data collection, data interpretation, and draft.

Eiichi Ishikawa– data collection, data interpretation, and draft.

Yoshinobu Wakiska– design, data interpretation, supervising, and draft.

Tetsuro Ago– supervising, data interpretation, and draft.

Takanari Kitazono– supervising, data interpretation, and draft.

All authors had final approval of the version to be published.

Data Availability Statement

Anonymized data will be shared by request from any qualified investigator for purposes of replicating procedures and results.

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Figure Legends

Fig. 1. Age- and sex-adjusted cumulative incidence of poor functional outcome according to cognitive state in the acute care and rehabilitation phases

(a) Cumulative incidence of poor functional outcome in the acute care phase (n=923).

(b) Cumulative incidence of poor functional outcome in the rehabilitation phase (n=460).

PreSD, pre-stroke dementia; and PSCI, poststroke cognitive impairment.

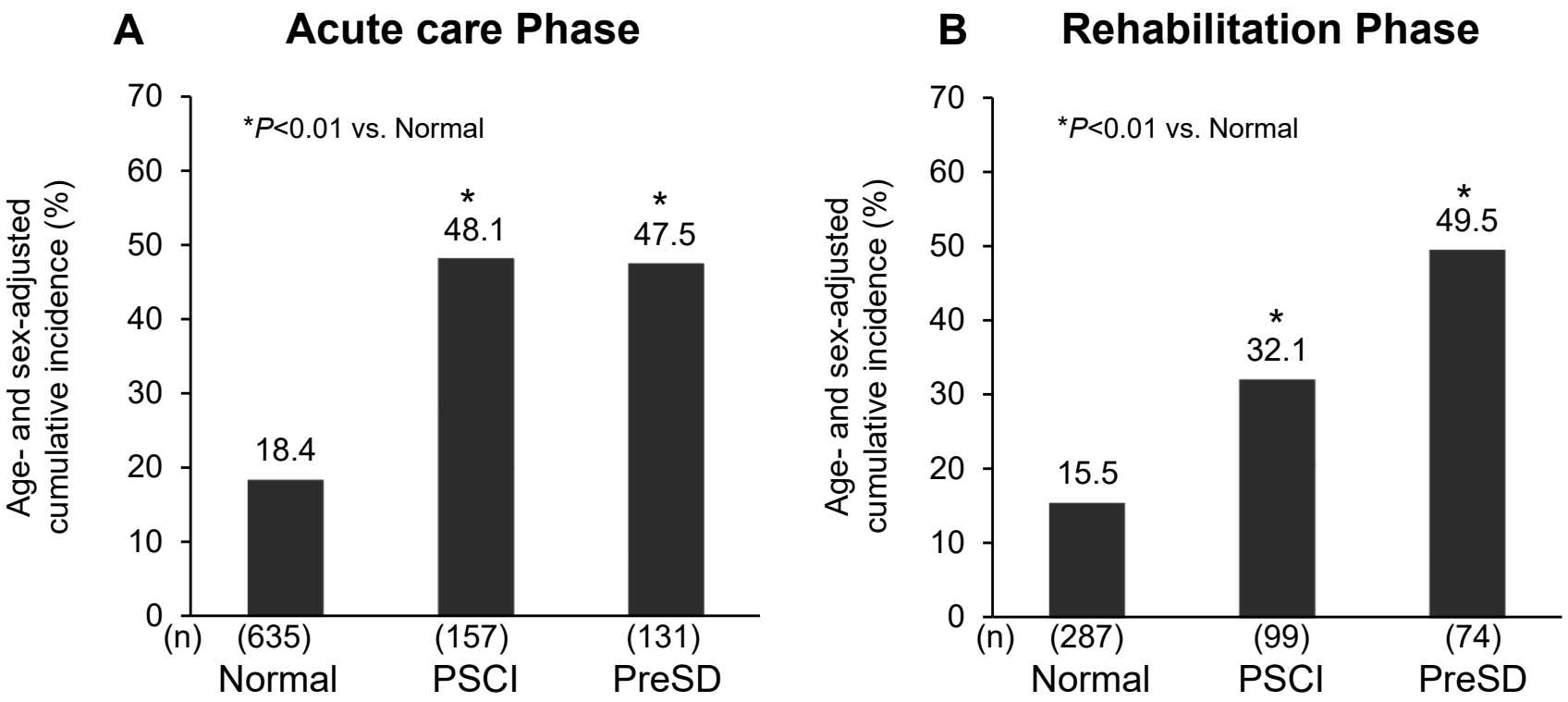
A
Acute care Phase
*P<0.01 vs. Normal
Age- and sex-adjusted cumulative incidence (%)
70
60
50
40
30
20
10
0
18.4
*
48.1
*
47.5
(n)
(635)
(157)
(131)
Normal
PSCI
PreSD
B
Rehabilitation Phase
*P<0.01 vs. Normal
Age- and sex-adjusted cumulative incidence (%)
15.5
*
32.1
*
49.5
(n)
(287)
(99)
(74)
Normal
PSCI
PreSD

Table 1. Baseline characteristics of patients with acute ischemic stroke according to cognitive state

	Normal cognition (n=635)	PSCI (n=157)	PreSD (n=131)
Age, mean (SD), y	69 ± 11	76 ± 9*	81 ± 10*
Men, n (%)	411 (64.7)	84 (53.5)*	62 (47.3)*
MMSE score, mean (SD)	27.5 ± 2.2	19.5 ± 5.2*	18.3 ± 5.9*
Stroke-related clinical factors			
Previous stroke, n (%)	94 (14.8)	26 (16.6)	39 (29.8)*
NIHSS score, median (IQR)	2 [1 – 4]	3 [2 – 6]*	4 [2 – 12]*
Cardioembolic stroke, n (%)	88 (13.9)	46 (29.3)*	31 (23.7)*
Laterality of infarction			
Left hemisphere, n (%)	296 (46.6)	102 (65.0)*	70 (53.4)†
Right hemisphere, n (%)	241 (38.0)	64 (40.8)	56 (42.8)
Location of infarction			
Cortex, n (%)	205 (32.3)	80 (51.0)*	80 (61.1)*
Basal ganglia, n (%)	342 (53.9)	88 (56.1)	64 (48.9)
Brainstem/cerebellum, n (%)	164 (25.8)	28 (17.8)	25 (19.1)
Reperfusion therapy, n (%)	54 (8.5)	7 (4.5)	15 (11.5)
Vascular risk factors			
Hypertension, n (%)	526 (82.8)	129 (82.2)	105 (80.2)
Diabetes mellitus, n (%)	211 (33.2)	48 (30.6)	40 (30.5)
Dyslipidemia, n (%)	367 (57.8)	85 (54.1)	57 (43.5)*
Atrial fibrillation, n (%)	80 (12.6)	40 (25.5)*	34 (26.0)*
Coronary heart disease, n (%)	57 (9.0)	24 (15.3)†	23 (9.2)
Current smoking, n (%)	188 (30.0)	43 (27.7)	23 (18.3)*
Current alcohol intake, n (%)	321 (51.4)	61 (39.1)*	32 (25.4)*

IQR, interquartile range; MMSE, Mini-Mental State Examination; NIHSS, National Institutes of Health Stroke Scale; PreSD, pre-stroke dementia; and PSCI, poststroke cognitive impairment.
*$P < 0.01$, † $P < 0.05$ compared with normal cognition.

Table 2. Association of cognitive state with poor functional outcome (mRS 3–6) in the acute care and rehabilitation phases

	No. of events	Model 1		Model 2		Model 3	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Acute care phase (n=923)							
Normal cognition (n=635)	108	1.00 (reference)		1.00 (reference)		1.00 (reference)	
PSCI (n=157)	80	4.14 (2.81-6.10)	<0.001	3.30 (2.09-5.19)	<0.001	3.28 (2.07-5.20)	<0.001
PreSD (n=131)	72	4.19 (2.72-6.45)	<0.001	2.37 (1.41-3.99)	<0.01	2.39 (1.40-4.08)	<0.01
Rehabilitation phase (n=460)							
Normal cognition (n=287)	39	1.00 (reference)		1.00 (reference)		1.00 (reference)	
PSCI (n=99)	36	2.76 (1.59-4.77)	<0.001	2.36 (1.27-4.38)	<0.01	2.48 (1.31-4.70)	<0.01
PreSD (n=74)	41	5.37 (2.94-9.82)	<0.001	4.05 (2.04-8.04)	<0.001	3.92 (1.94-7.92)	<0.001

mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PreSD, pre-stroke dementia; and PSCI, poststroke cognitive impairment.
Model 1 was adjusted for age and sex.
Model 2 was adjusted for the variables included in model 1 and previous stroke, NIHSS score, stroke subtype, laterality of infarction, location of infarction, and reperfusion therapy.
Model 3 was adjusted for the variables included in model 2 and hypertension, diabetes, dyslipidemia, coronary heart disease, current smoking, and current alcohol intake.