Plasma Phosphorylated-tau181 is a Predictor of Post-Stroke Cognitive Impairment: A Longitudinal Study

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Research

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Abstract

Introduction

Post-stroke cognitive impairment (PSCI) cannot be neglected because it drastically influences the daily life of patients and their families. However, there are no studies exploring the association between preclinical blood biomarkers of neurodegeneration including plasma amyloid- β (A β), tau and brain-derived neurotrophic factor (BDNF) together with the risk of PSCI. The present longitudinal study was to investigate whether these blood biomarkers with imaging markers of cerebral small vessel disease can improve the prediction for PSCI. In addition, we also explored the association between blood biomarkers with the trajectories of PSCI.

Methods

Adult patients with first ever acute ischemic stroke were recruited, and the cognitive and functional abilities of these patients were evaluated. Furthermore, blood biomarkers of neurodegeneration including plasma A β -40, A β -42, total tau, phosphorylated tau 181 (p-tau181), and BDNF levels and image markers of cerebral small vessel disease were measured. Each patient was followed up at 3 and 12 months at the outpatient department.

Results

Of 136 patients, 40 and 50 patients developed PSCI at 3 and 12 months after stroke, respectively. In functional trajectories, 27 patients did not have PSCI at 3 months but did at 12 months. By contrast, the PSCI status of 17 patients at 3 months was reversed at 12 months. Patients with high acute plasma p-tau181 had a significantly lower PSCI risk at 3 months (odds ratio [OR] = 0.62, 95% confidence interval [CI] = 0.40–0.94, p = 0.0243) and 12 months (OR = 0.69, 95% CI = 0.47–0.99, p = 0.0443) after adjustment for covariates and image biomarkers. Discrimination and reclassification statistics indicated that the p-tau181 level can improve discrimination ability for PSCI at 3 and 12 months, respectively. Additionally, the plasma p-tau181 level was the highest in subjects without PSCI followed by those with delayed-onset PSCI and early-onset PSCI with reversal, whereas the lowest plasma p-tau181 level was found among those with persistent PSCI, showing a significant trend test (p = 0.0081).

Conclusions

Plasma p-tau181 is a potential biomarker for predicting early- and delayed-onset PSCI. Future studies should incorporate plasma p-tau181 as indicator for timely cognitive intervention in the follow-up of patients with stroke.

Introduction

Cognition decline after stroke is not rare. Clinical course of post-stroke cognitive impairment (PSCI) is not a unitary syndrome, but varies from individual to individual (1). Cognitive impairment assessment is often performed at 3–6 months after acute stroke to provide sufficient time for delirium resolution and neurological stability. Notably, stroke patients free of early-onset PSCI (3–6 months after stroke) are still at risk of delayed-onset PSCI (>6 months after stroke), which suggests an underlying pathological process beyond 3 months after stroke (2). Many risk factors for PSCI have been proposed based on observational studies, including age, sex, educational attainment, stroke severity, stroke histories, and cardiovascular risk factors—particularly diabetes mellitus and hypertension (3). Brain image risk factors include white matter hyperintensities and gray matter and hippocampal volumes loss (4-6). However, there is still a lack of precise blood biomarkers for predicting PSCI.

Accumulation of amyloid beta (A β) peptides and phosphorylated tau (p-tau) in brain are both key pathological feature of Alzheimer's disease (7, 8). Several previous studies implicated plasma A β 40 and A β 42 level was associated with cognitive decline among older adults and stroke patients (9, 10). Some cohorts found that plasma tau phosphorylated at threonine 181 (p-tau181) was associated with cognitive decline (11). In addition, brain-derived neurotrophic factor (BDNF) is an important neurotrophin in the adult brain, which can help the brain to repair (12). Previous study further found that serum BDNF levels are decreased in the acute phase of stroke, and lower circulating concentrations of BDNF protein are associated with poor long-term functional outcomes (13).

Since these key peptides and proteins play important roles in cognitive performance, and there are few studies to examine the plasma levels of A β 42, tau, BDNF, and p-tau181 in patients after stroke through longitudinal follow-up, the purpose of this study was to investigate whether these blood with imaging markers-can improve the prediction for PSCI. In addition, the association between blood biomarkers with the trajectories of PSCI was also examined.

Methods

Study participants

Patients aged ≥ 20 years who were admitted to Shuang-Ho Hospital, Taipei Medical University within 7 days of acute ischemic stroke were screened for enrollment between 2015 and 2018. Patients with known premorbid cognitive impairment or neurodegenerative diseases that have impaired daily activities were excluded. In order to focus on the cognitive trajectory after stroke, we excluded the major cognitive impairment of stroke: large-scale infarcts that cause immediate consciousness impairment; strategic infarcts involving the thalamus, hippocampus, or medial frontal cortex; and severe language or physical disabilities that hinder neuropsychological testing. Each patient was evaluated in the hospital within 7 days of stroke and followed up in the outpatient clinic at 3 and 12 months. The Institutional Review Board of Taipei Medical University approved the study. Written informed consent was obtained from all patients or their legal guardians.

Data collection

Brain magnetic resonance images were obtained once at admission, including T1- and T2-weighted images, T2 fluid-attenuated inversion recovery (T2 FLAIR) images, diffusion-weighted images (DWI), apparent diffusion coefficient (ADC) maps, T2 star-weighted angiography (SWAN) and time-of-flight magnetic resonance angiograms. Acute ischemic brain infarction was confirmed with hyperintensity on DWI with corresponding ADC maps. Visual ratings of white matter hyperintensities (WMH) were performed by an investigator who was blinded to the clinical details by applying Fazekas rating scale (14). Microbleeds were rated as round or oval-shaped dark blooming signals (2–10 mm in diameter) using the Microbleeds Anatomical Rating Scale (MARS) on the SWAN image and were classified into deep, lobar, and infratentorial categories (15). Stroke severity was assessed using the National Institute of Health Stroke Scale (NIHSS) at admission. The stroke etiological subtype was classified according to The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification by an experienced neurologist who was unaware of outcomes of patients. Two neuropsychologists conducted cognitive function assessments using the Taiwanese version of the Montreal Cognitive Assessment (MoCA) screening instrument (16) and the Clinical Dementia Rating (CDR) global score, Sum of Boxes (CDR-SB; range: 0–18). MoCA showed a low ceiling effect with high sensitivity and specificity when used for assessing cognitive impairment after stroke (17). The CDR-SB comprises six cognitive and functional domains (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care), which yield additional information, particularly regarding mild impairment (18). In this study, we defined PSCI as a CDR-SB > 0 when the patient presented with functional impairment after stroke in either one or more of the six domains. In addition, we further classified patients based on the 3-month and 12-month CDR-SB assessments to understand the trajectory of PSCI after stroke. Persistent non-PSCI is defined as 3-month and 12-month CDR-SB = 0 ($n = 69$), delayed-onset PSCI is CDR-SB = 0 at 3 months while CDR-SB ≥ 0.5 at 12 months ($n = 27$), early PSCI with reversal is 3-month CDR-SB ≥ 0.5 and 12-month CDR-SB = 0 ($n = 17$), and persistent PSCI is CDR-SB ≥ 0.5 at 3 months and 12 months ($n = 23$).

Measurement of plasma biomarkers

Two 10-mL non-fasting venous blood were collected within 7 days of stroke onset. The blood samples were centrifuged at $1,500 \times g$ for 15 min and stored at -80°C . Plasma A β 40, A β 42, total tau, and p-tau181 were analyzed using immunomagnetic reduction (IMR) assays manufactured by MagQu Co. Ltd. (New Protein Analysis Taipei City, Taiwan). Technical details of IMR assays have been described in previous studies (10, 19). BDNF was quantified through enzyme-linked immunosorbent assay by using cytokine detection kits (DY248; R&D Systems, Minneapolis, MN, USA) according to the manufacturer's protocol. Absorbance at 450 nm was measured with a SpectraMax microplate reader (Molecular Devices, San Jose, CA, USA). All samples were analyzed in duplicate.

Statistical analysis

Continuous variables are presented as mean and standard deviation, and data with non-normal distribution are expressed as medians with interquartile ranges. Categorical variables are presented in terms of frequency with percentage. Univariate logistic regression was used to estimate the odds ratios (ORs) of PSCI at 3 and 12 months based on clinical characteristics and laboratory data. The identified important covariates with borderline significant in the univariate analysis were then verified in the multivariate logistic model by using automatic forward selection methods. Receiver operating characteristic (ROC) analysis was conducted to estimate the performance of plasma biomarkers combined important covariates for differentiating PSCI risk at 3 and 12 months. In addition, the net reclassification index (NRI) and integrated discrimination improvement (IDI) were computed to evaluate the incremental prognostic value of plasma

biomarkers beyond conventional risk factors as well as image biomarkers. All statistical analyses were performed using SAS (version 9.4, Cary, North Carolina). A two-tailed p value < 0.05 was considered statistically significant.

Results

Study participants

All 173 participants completed initial clinical and neuropsychological examinations as well as plasma biomarker assays and a brain MRI scan within 7 days after stroke. No patient died during the follow-up time of 1 year. Attrition was due to loss to follow-up in 37 patients at 3 months. Data from 136 patients was processed in the final analysis. At 3 months after stroke, 40 patients met criteria for PSCI according to CDR-SB > 0, whereas at 12 months after stroke, 50 patients had PSCI (Figure 1).

Characteristics of study subjects

Demographic data, brain MRI visual rating scores and plasma biomarkers are summarized in Table 1. Dividing into two groups according to whether positive of PSCI at 3 months after stroke, the mean ages of patients with and without PSCI were 61.43 ± 12.57 and 57.73 ± 12.66 years, respectively. A total of 40% PSCI patients have an education level of >9 years, which is significantly lower than that of non-PSCI patients. A remarkably high frequency of hypertension was observed among patients with PSCI compared with those without PSCI. Most patients had mild stroke severity, and median NIHSS scores within 7 days for patients with and without PSCI were 4 and 3, respectively. Periventricular white matter Fazeka scale was significantly different between two groups. MoCA scores at 3 and 12 months were significantly lower in patients with PSCI than in those without PSCI. Furthermore, the plasma p-tau181 level in patients with PSCI (3.19 ± 1.77 pg/mL) was significantly lower than in those without PSCI (4.16 ± 2.18 pg/mL).

Univariate and multivariate regression analyses of PSCI risk

Table 2 presents the results of univariate and multivariate logistic regression analyses for patients with and without PSCI at both 3 and 12 months, respectively. For PSCI at 3 months, education level, plasma p-tau181 level, periventricular white matter Fazeka scale, and MARS lobar score were significant factors in the univariate model. These identified important covariates together with hypertension were then verified in then multivariate analysis. After forward selection, education level, hypertension and plasma p-tau181 level were significantly independent factors of PSCI, showing the patients having an increased p-tau181 level had a significantly lower risk of PSCI at 3 months (OR = 0.62, 95% confidence interval [CI] = 0.40–0.94, p = 0.0243). Similar findings were found when the patients followed up to 12 months. For patients with increment of p-tau181 level had a 0.69-fold risk of PSCI at 12 months (95% CI = 0.47–0.99, p = 0.0443). However, plasma tau, A β 42, A β 40, and BDNF were not predictors of PSCI at 3 or 12 months.

Predictive accuracy of p-tau181 for assessing PSCI

To examine the effect of p-tau181 on PSCI at 3 and 12 months in addition to conventional risk factors, discrimination and reclassification statistics were calculated. Figure 2 illustrates the area under the curve (AUC) of the model based only on conventional risk factors was 0.7632 (95% CI = 0.6520–0.8744), but it slightly increased to 0.7655 (95 %CI = 0.6549–0.8761) when image biomarkers were added. After integrating plasma p-tau181 level, the performance has been greatly improved, which achieved to good discrimination ability (AUC = 0.8067; 95 % CI = 0.7066–0.9067). According to the NRI and IDI indexes, adding the p-tau181 level to the model containing conventional risk factors and image biomarkers significantly improves the measure of reclassification and discrimination for PSCI at 3 and 12 months (Table 3).

Association between plasma biomarkers and different persistent cognitive impairment status

Plasma biomarkers were analyzed according to the trajectory of cognitive impairment status defined by the CDR-SB at 3 and 12 months. Table 4 presents the levels of plasma tau, A β 42, A β 40, A β 42/40 ratio, p-tau181, and BDNF among the four subgroups. The results indicated that only plasma p-tau181 level differed among the four groups, with the highest level in the persistent non-PSCI group (4.40 ± 1.77 pg/mL) followed by the delayed-onset PSCI (3.65 ± 1.41 pg/mL), early PSCI with reversal (3.36 ± 1.38 pg/mL) groups, and the lowest level was in the persistent PSCI group (3.12 ± 0.78 pg/mL), showing a significant trend test (p = 0.0081).

Discussion

The present study investigated 136 patients with acute ischemic stroke and followed them up for consequential cognitive function trajectory for 1 year. The results demonstrated that a high plasma p-tau181 level in the acute post-stroke stage is related to a low PSCI risk at 3 (OR = 0.62, 95% CI = 0.40–0.94, $p = 0.0243$) and 12 (OR = 0.69, 95% CI = 0.47–0.99, $p = 0.0443$) months. Integrating p-tau181 to the model containing conventional risk factors (age, education, hypertension, diabetes mellitus, and NIHSS score at ≤ 7 days) and image biomarker significantly improves prediction.

Cognitive improvement after stroke often occurs within 6 months, and early recognition of PSCI is necessary for assessing the need for rehabilitation (20). In the case of cerebral ischemia, hyperphosphorylated tau protein may play a protective role by promoting β -catenin and other proteins to inhibit cell apoptosis, suggesting that neurons survive apoptotic attacks and achieve self-repair (21). Phosphorylation of tau results in reduced binding to microtubules and potentially enhances plasticity, as observed during brain development, which is also important in neural repair after stroke (22). In Alzheimer disease (AD), plasma p-tau181 is a prognostic and confirmatory biomarker (23). Hyperphosphorylated tau protein forms paired helical filaments and progressively aggregates to form the main component of neurofibrillary tangles in AD pathology (24). However, unlike in AD pathology, neurofibrillary tangles are rarely seen in the brain after stroke. Studies of cerebrospinal fluid (CSF) samples from patients with acute stroke showed that CSF p-tau did not increase persistently, whereas CSF total tau increased and returned to normal levels at 3–5 months after stroke, suggesting different pathogenic processes from AD (25–27). Therefore, the diagnostic criteria for vascular cognitive disorders from the International Society of Vascular Behavioral and Cognitive Disorders statement suggest excluding CSF p-tau when diagnosing vascular cognitive impairment in research (28), whereas a persistent increase in CSF p-tau is considered a defining biomarker of AD in the National Institute on Aging–Alzheimer’s Association Research Framework (29). In addition, plasma p-tau181 predicted PSCI in a dose-dependent manner in our longitudinal cohort study, and the p-tau181 level was the highest in the persistent non-PSCI group and the lowest in the persistent PSCI group. A protective role for tau phosphorylation at threonine 181 could facilitate its binding to exosomes and the release of excess tau (30). Further studies are warranted to understand the mechanism underlying this finding.

Previous studies have revealed that plasma A β 42/40 ratios are surrogate biomarkers of cortical A β deposition (31). High plasma concentrations of A β 40, especially when combined with low concentrations of A β 42, indicate an increased dementia risk (32). In our study, A β 42, A β 40, and A β 42/40 ratio were not different between patients with and without PSCI, which suggests the involvement of additional processes other than amyloid pathology. In addition, BDNF was found to be an indicator of long-term functional outcomes after ischemic stroke, although the additional predictive value of BDNF was modest according to clinical data (13). Our data showed that there was no significant difference in circulating BDNF levels regardless of whether the patient had PSCI or not, which may be due to its limited impact on cognitive outcomes.

CDR-SB was adopted to define PSCI in our study. Given the diverse clinical presentation of PSCI, not only memory but also other cognitive domains should be evaluated (33). The global CDR is weighted more on memory dysfunction, whereas CDR-SB is weighted equally for all domains (34). In addition, CDR-SB has been considered as an effective and reliable assessment method, which combines two sets of questions, one set is for the insider and the other is for the subject. This implies the use of CDR-SB to define the PSCI has a clinically significant impact in the follow-up after stroke. In our study, none of the patients had dementia before stroke. However, the prevalence of PSCI at 3 and 12 months after stroke was 29.4% and 36.8%, respectively, during the longitudinal follow-up. The reported prevalence varied among previous studies depending on divergent estimates of PSCI according to the population under study and the methods of defining PSCI, suggesting a need for diagnosis criteria consensus (35, 36).

Notably, in our cohort, 27 patients without PSCI at 3 months developed PSCI at 12 months after stroke (late PSCI: 19.9%), and 17 patients reversed from PSCI at 3 months to Non-PSCI at 12 months (reversal: 42.5%). Our findings further revealed that a dose-dependent trend of plasma p-tau181 level existed among patients with various persistent cognitive impairment statuses, with the highest level in the non-PSCI group followed by the early PSCI with reversal and delayed-onset PSCI groups; the lowest level was in the persistent PSCI group, which implicated the protective effect on longitudinal cognitive function after a minor ischemic stroke.

The present study has several limitations. First, there was no formal test conducted for measuring baseline cognitive function before stroke in our participants. However, patients with known cognitive impairment or neurodegeneration that impaired daily activities before stroke were excluded based on their medical histories at the screening phase. Additionally, this study adopted the CDR-SB to define PSCI in order to distinguish functional changes after stroke since we relied on informant-based evidence rather than performance-based tests. Second, the severity of stroke in the patients in this study is relatively small and mainly involves small vessel diseases which might influence the generalizability of the findings to large brain infarction or intracranial hemorrhage. Future studies will be needed to elucidate the natural course of other types of brain insults. Third, in our study, no further AD diagnosis was performed; however,

previous findings indicated that after ischemia with reperfusion in the brain, secondary neurodegeneration of AD type may occur (37). Further longitudinal studies regarding biomarkers are needed to distinguish PSCI and AD processes.

In conclusion, PSCI is not uncommon in the population with minor stroke. Using plasma p-tau181 as a surrogate biomarker for predicting early- and delayed-onset PSCI is helpful in interventional studies and clinical follow-up.

List Of Abbreviations

PSCI: post-stroke cognitive impairment; A β : amyloid- β ; BDNF: brain-derived neurotrophic factor; p-tau181: phosphorylated tau 181; OR: odds ratio; CI: confidence interval; T2 FLAIR : T2 fluid-attenuated inversion recovery ; DWI: diffusion-weighted images; ADC: apparent diffusion coefficient; WMH: white matter hyperintensities; MARS: Microbleeds Anatomical Rating Scale; NIHSS: National Institute of Health Stroke Scale; TOAST: The Trial of ORG 10172 in Acute Stroke Treatment; MoCA: Montreal Cognitive Assessment; CDR: Clinical Dementia Rating; CDR-SB: Clinical Dementia Rating global score, Sum of Boxes; IMR: immunomagnetic reduction; ROC: Receiver operating characteristic; NRI: net reclassification index; IDI: integrated discrimination improvement; AUC: area under the curve; AD: Alzheimer disease; CSF: cerebrospinal fluid.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Taipei Medical University. Written informed consent was obtained from all patients or their legal guardians.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no conflict of interest.

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Authors' Contributions

LKH wrote the manuscript with support from YCH. YCH verified the analytical methods. CJH conceived the study and were in charge of overall direction and planning. YCL aided in interpreting the results and worked on the manuscript. All authors discussed the results and contributed to the final manuscript.

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Tables

Table 1. Basic characteristics of study subjects with and without PSCI defined at 3 months after stroke

Variables	With PSCI		Without PSCI		P-value	
Demographics	N=40		N=96			
AGE, y, mean(SD)	61.43	(12.57)	57.73	(12.66)	0.1225	
Male, n(%)	30	(75.00)	67	(69.79)	0.5406	
BMI, kg/m ² , median(IQR)	25.71	(3.95)	25.68	(4.14)	0.2448	
Education>9 years, n(%)	16	(40.00)	58	(60.42)	0.0294	
Cigarette smoking, n(%)	25	(62.50)	46	(48.42)	0.1347	
Alcohol drinking, n(%)	4	(10.00)	11	(11.58)	0.7898	
Medical history						
Hypertension, n(%)	36	(90.00)	72	(75.00)	0.0487	
Diabetes mellitus, n(%)	16	(40.00)	32	(33.33)	0.4585	
Dyslipidemia, n(%)	31	(77.50)	72	(75.00)	0.7566	
Clinical features						
Fasting glucose, mg/dL, median(IQR)	111.00	(30.00)	110.00	(29.00)	0.7986	
Total cholesterol, mg/dL, median(IQR)	203.00	(66.50)	198.00	(62.00)	0.6652	
NIHSS ≤7 days, score, median(IQR)	4.00	(3.50)	3.00	(3.00)	0.5064	
MoCA at 3 months, score, median(IQR)	22.50	(6.50)	26.00	(5.00)	<0.0001	
MoCA at 12 months, score, median(IQR)	23.00	(7.00)	27.00	(5.00)	0.0007	
Plasma biomarkers						
Aβ 42, pg/mL, median(IQR)	15.54	(2.48)	15.66	(3.18)	0.5763	
Aβ 40, pg/mL, median(IQR)	49.45	(7.76)	49.75	(7.22)	0.6824	
Aβ 42/40 ratio, %, median(IQR)	32.60	(10.47)	34.56	(11.32)	0.3166	
Tau, pg/mL, median(IQR)	18.87	(9.43)	18.64	(13.71)	0.4920	
p-tau181, pg/mL, mean(SD)	3.19	(1.77)	4.16	(2.18)	0.0053	
BDNF, pg/mL, median(IQR)	732.43	(317.00)	724.97	(387.01)	0.7755	
TOAST						
Large artery atherosclerosis, n(%)	8	(20.00)	17	(17.71)	0.3289	
Small vessel occlusion, n(%)	24	(60.00)	61	(63.54)		
Cardioembolism, n(%)	3	(7.50)	10	(10.42)		
Specific etiology, n(%)	3	(7.50)	1	(1.04)		
Undetermined etiology, n(%)	2	(5.00)	7	(7.29)		
Fazekas scale						
Periventricular white matter	0	4	(10.26)	33	(34.38)	0.0036
	1	12	(30.77)	34	(35.42)	
	2	6	(15.38)	4	(4.17)	
	3	17	(43.59)	25	(26.04)	
Deep white matter lesion	0	5	(12.82)	27	(28.13)	0.1803

	1	17	(43.59)	42	(43.75)	
	2	9	(23.08)	13	(13.54)	
	3	8	(20.51)	14	(14.58)	
Mirobleed anatomical rating scale						
Infratentorial score	0	29	(76.32)	81	(84.38)	0.2812
	1	7	(18.42)	8	(8.33)	
	2-4	2	(5.26)	7	(7.29)	
	>4	0	(0)	0	(0)	
Deep score	0	27	(71.05)	76	(79.17)	0.5389
	1	6	(15.79)	10	(10.42)	
	2-4	4	(10.53)	9	(9.38)	
	>4	1	(2.63)	1	(1.04)	
Lobar score	0	25	(65.79)	74	(77.08)	0.0617
	1	3	(7.89)	13	(13.54)	
	2-4	9	(23.68)	7	(7.29)	
	>4	1	(2.63)	2	(2.08)	

Abbreviation: PSCI, post-stroke cognitive impairment; BMI, body mass index; NIHSS, National Institute of Health Stroke Scale; MoCA, Montreal Cognitive Assessment; A β , amyloid beta; p-tau181, phosphorylated tau 181; BDNF, Brain-derived neurotrophic factor; IQR, interquartile range; SD, standard deviation.

Table 2. Univariate and multivariate logistic regression analyses for patients with PSCI and without PSCI at 3 months and 12 months, respectively

Variables	3 months		12 months					
	OR(95%CI)	P-value	OR ^a (95%CI)	P-value	OR(95%CI)	P-value	OR ^a (95%CI)	P-value
AGE	1.02(0.99-1.06)	0.1240			1.03(1.00-1.06)	0.0261		
Male	1.30(0.56-3.00)	0.5412			0.90(0.42-1.94)	0.7947		
Education>9	0.44(0.21-0.93)	0.0312	0.27(0.09-0.81)	0.0191	0.51(0.25-1.04)	0.0645		
Hypertension	3.00(0.97-9.30)	0.0571	8.39(1.44-48.90)	0.0181	0.87(0.37-2.05)	0.7563		
Diabetes mellitus	1.33(0.62-2.86)	0.4592			1.58(0.76-3.26)	0.2135		
Dyslipidemia	1.15(0.48-2.75)	0.7568			1.02(0.45-2.31)	0.9563		
Smoking	1.78(0.83-3.78)	0.1368			1.52(0.74-3.09)	0.2481		
Drinking	0.85(0.25-2.84)	0.7900			0.40(0.11-1.50)	0.1754		
NIHSS $\leq$ 7 days	1.01(0.91-1.11)	0.9176			1.01(0.92-1.10)	0.9206		
Plasma biomarkers at baseline								
Tau, pg/mL	0.97(0.92-1.01)	0.1737			1.00(0.96-1.04)	0.9822		
A β 42, pg/mL	0.98(0.83-1.16)	0.7846			1.05(0.90-1.23)	0.5597		
A β 40, pg/mL	1.01(0.93-1.10)	0.7445			1.07(0.98-1.17)	0.1458		
p-tau181, pg/mL	0.63(0.43-0.91)	0.0151	0.62(0.40-0.94)	0.0243	0.72(0.51-1.02)	0.0640	0.69(0.47-0.99)	0.0443
BDNF, pg/mL	1.00(1.00-1.00)	0.6768			1.00(1.00-1.00)	0.1198		
Fazekas scale								
Periventricular white matter	1.66(1.20-2.31)	0.0024			1.45(1.07-1.97)	0.0154		
Deep white matter lesion	1.44(0.99-2.10)	0.0547			1.09(0.77-1.55)	0.6323		
Mirobleed anatomical rating scale								
Intratentorial score	1.43(0.95-2.15)	0.0832			1.49(0.94-2.36)	0.0916		
Deep score	1.42(0.99-2.03)	0.0549			1.31(0.94-1.82)	0.1109		
Lobar score	1.60(1.08-2.37)	0.0190			1.34(0.97-1.86)	0.0791		

a: multiple logistic regression model using the automatic forward selection

Abbreviation: PSCI, post-stroke cognitive impairment; NIHSS, National Institute of Health Stroke Scale; Aβ, amyloid beta; p-tau181, phosphorylated tau 181; BDNF, Brain-derived neurotrophic factor

Table 3. Discrimination and reclassification statistics of p-tau181 level for patients with PSCI at 3 months and 12 months, respectively

Clinical outcomes	Model	NRI index			IDI index		
		Estimate	95%CI	p-value	Estimate	95%CI	p-value
PSCI at 3 month	Conventional model						
	Conventional model + image biomarker	0.369	(0.002-0.735)	0.0522	0.035	(0.004-0.067)	0.0289
	Conventional model + image biomarker +p-tau181 level	0.786	(0.417-1.155)	0.0010	0.144	(0.074-0.214)	<0.0001
PSCI at 12 months	Conventional model						
	Conventional model + image biomarker	0.235	(-0.111-0.582)	0.1884	0.016	(-0.002-0.034)	0.0890
	Conventional model + image biomarker +p-tau181 level	0.730	(0.326-1.134)	0.0023	0.086	(0.028-0.145)	0.0040

Conventional risk factors included age, gender, education, hypertension, diabetes mellitus, and NIHSS ≤7 days

Abbreviation: PSCI, post-stroke cognitive impairment; NRI, net reclassification index; IDI, integrated discrimination improvement; p-tau181, phosphorylated tau 181

Table 4. Association between plasma biomarkers and different persistent cognitive impairment status according to CDR-SB at 3 months and 12 months

Plasma biomarkers	Persistent Non-PSCI (n=69)		Delayed-onset PSCI (n=27)		Early PSCI with reversal (n=17)		Persistent PSCI (n=23)		p-value
Aβ 42, pg/mL, median(IQR)	15.65	(3.26)	16.04	(3.86)	15.84	(2.86)	15.40	(2.29)	0.7145
Aβ 40, pg/mL, median(IQR)	49.58	(7.03)	49.99	(8.68)	48.22	(5.01)	51.49	(8.75)	0.1796
Aβ 42/40 ratio, %, median(IQR)	0.35	(0.10)	0.33	(0.11)	0.33	(0.17)	0.32	(0.12)	0.2213
Tau, pg/mL, median(IQR)	18.43	(11.62)	19.69	(16.03)	19.63	(9.33)	18.54	(7.38)	0.6076
p-tau181, pg/mL, mean(SD)	4.40	(1.77)	3.65	(1.41)	3.36	(1.38)	3.12	(0.78)	0.0081
BDNF, pg/mL, median(IQR)	776.52	(359.35)	639.77	(378.88)	750.62	(261.49)	729.74	(402.71)	0.9267

Abbreviation: PSCI, post-stroke cognitive impairment; CDR-SB, Clinical Dementia Rating global score, Sum of Boxes; Aβ, amyloid beta; p-tau181, phosphorylated tau 181; BDNF, Brain-derived neurotrophic factor; IQR, interquartile range; SD, standard deviation.

Figure 1

Flowchart of patient enrollment and cognitive function changes during the 12 months' follow-up.

Figure 2

The area under the receiver operating characteristic of the ptau-181 predicting PSCI at 3 (A) and 12 months (B), respectively, when compared to conventional risk factors with image markers