



# Plasma parameters and risk factors of patients with post-stroke cognitive impairment

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**Background:** It is high of the incidence of stroke and dementia with the advent of an aging society. Post-stroke cognitive impairment is one of the common complications of stroke, which not only seriously affects the life quality of patients, but also significantly reduces the survival time of stroke patients. Moreover, it also brings in heavy burden to the family and society. The development of vascular dementia could be reduced by early intervention after stroke. Management of vascular risk factors could be an effective way to prevent dementia. This study aimed to investigate the plasma biochemical parameters of post-stroke cognitive impairment (PSCI) and its potential risk factors.

**Methods:** Four hundred eighty-seven consecutive patients with ischaemic stroke were included and followed up for 3 years. Among these patients, 132 cases were diagnosed as PSCI. The cognitive impairment of patients with PSCI was assessed by the Mini Mental State Examination and Montreal cognitive assessment scale. The plasma biochemical parameters and blood coagulation, as well as computed tomography and magnetic resonance imaging of all the patients after admission, were measured.

**Results:** Multivariate analyses revealed that increased age, carotid plaque, cerebral atrophy, white matter lesions (WML), alcohol use, smoking and history of systolic blood pressure  $\geq 170$  mmHg was highly associated with PSCI ( $P < 0.05$ ). Elevated homocysteine, low-density lipoprotein (LDL), and uric acid were also highly associated with PSCI. Logistic regression analysis identified five risk factors correlated with PSCI including alcohol use [odds ratio (OR): 5.138, 95% confidence interval (CI): 1.014–26.04,  $P = 0.048$ ], history of high systolic blood pressure (OR: 12.171, 95% CI: 3.339–44.363,  $P = 0.001$ ), carotid plaque (OR: 1.692, 95% CI: 1.032–2.796,  $P = 0.040$ ), cerebral atrophy (OR: 2.280, 95% CI: 1.294–4.001,  $P = 0.004$ ), and WML (OR: 3.155, 95% CI: 1.868–5.324,  $P = 0.001$ ). Three plasma biochemical parameters were also associated with PSCI including homocysteine (OR: 1.018, 95% CI: 0.944–1.042,  $P = 0.010$ ), and LDL (OR: 0.83, 95% CI: 0.6–1.148,  $P = 0.051$ ), and uric acid (OR: 1.00, 95% CI: 0.998–1.002,  $P = 0.007$ ). The area under the receiver operating curve for the risk factors of PSCI was 0.821 with the sensitivity of 76.3% and specificity of 71.9%.

**Conclusions:** Elevated homocysteine, LDL, and uric acid were highly related to PSCI, which may help predict PSCI. These plasma biochemical parameters together with vascular risk factors, may improve the sensitivity for early detection of PSCI.

**Keywords:** Biochemical indexes; risk factor; post-stroke cognitive impairment (PSCI); ischemic stroke

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## Introduction

With a population that has an increased amount of aged individuals, there have been great improvements to the survival rate of individuals with cardiovascular disease and cerebrovascular disorders, as well as the prolongation of human life; however, the number of people suffering from dementia has increased dramatically. Due to a stroke being a major cause of dementia, the prevalence of dementia will rise in the future due to the increase of stroke incidences and a decrease in mortality among elderly people. Post-stroke dementia (PSD) leads to physical disability, and it decreases the patients' quality of life. Therefore, PSD has become one of the most serious public health problems worldwide.

Given the substantial health and economic burden of PSD, the early or timely identification of dementia has become a priority in many countries. More recently (1), cognitive decline has been identified even prior to the stage of dementia, while mild cognitive impairment related to vascular lesions has been identified as the preferred target of therapeutic strategies in order to slow or stop the decline, thus avoiding progression towards dementia and related loss of autonomy in daily living.

Post-stroke cognitive impairment (PSCI) was a major complication of a stroke, which has numerous risk factors associated with it. A scale designed to classify the risk of cognitive impairment 6 months after a mild stroke will be useful for clinicians as a guideline. Therefore, it will be useful to develop a risk score based on clinical and plasma biochemical parameters to identify mild ischemic stroke patients at high risk for PSCI. PSCI encompasses the whole spectrum of cognitive disorder after stroke, including post-stroke mild cognitive impairment and PSD. As the prevalence of stroke is high, it is necessary to evaluate the risk of PSCI among stroke patients so that preventive measures and rehabilitation therapy can be used to target those most at risk. Prevention and treatment of PSCI are critical priorities for both clinical care and scientific research. The growing health, social, and economic burden of PSCI is driving the demand for clinical studies that evaluate the benefits and risks of both pharmacological and non-pharmacological interventions (2).

Although many studies explored the incidence and correlated factors of cognitive impairment after stroke (3-6), the mechanism for PSCI is unclear, and the relationship with plasma biochemical indicators of PSCI remains uncertain.

In this study, we investigated the plasma biochemical parameters of PSCI and its potential risk factors.

## Methods

### Patients

From 1 January 2014 to 12 October 2016, we recruited 487 inpatients and outpatients with a stroke in the First People's Hospital of Bengbu Medical University. Among these patients, 241 of them were male. The mean age of these patients was  $71.51 \pm 10.15$  years (range: 55–80 years).

### Inclusion criteria of patients with PSCI

- (I) Available medical and neurological history.
- (II) Presence of acute or subacute nervous system symptoms and signs of PSCI.
- (III) Dementia diagnosed using the criteria of the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) and the International Classification of Diseases-10 (ICD-10).
- (IV) History of coronary heart disease, arterial hypertension, hyperlipidemia, or diabetes.
- (V) Fluctuating course or progressive development.
- (VI) Hachinski ischemia scale score  $>7$ .
- (VII) Computed tomography (CT) and magnetic resonance imaging (MRI) revealing multiple cortical or subcortical ischemic brain lesions.

All the patients were followed up with for 3 years after a stroke. We used the Mini Mental State Examination (MMSE) score, Montreal Cognitive Assessment Scale (MoCA) score, clinical dementia rating (CDR), activities of daily living of these patients. Patients with mild dementia can often still make judgments about society and social interactions. They could communicate with people and make decisions for themselves, such as whether to participate in a research study. For patients with moderate or severe dementia, as well as those with severely damaged social, social communication skills, and judgment ability, the patient's legal representative decided whether to provide consent for the patient's participation in the study.

After patients were selected, we explained to them (or their representatives) the purpose and significance of our study and the possible benefits and risks. All eligible patients (or their representatives) were informed that participation in the study was voluntary and that they could withdraw from the study at any time. Thus, all included participants,

or their representative, provided written informed consent.

All included participants underwent brain CT in the acute phase. Additionally, 397 patients (81.7%) underwent MRI 3 months later. White matter lesion (WML) was defined as none to mild, moderate, or severe, in accordance with the Leukoaraiosis and Disability in the Elderly Study (7).

All patients underwent a detailed systemic and neurological examination, routine laboratory examinations (e.g., blood biochemistry test including electrolyte and lipid panels, blood sugar, complete blood count), electrocardiography (EKG), chest radiography, color ultrasound diagnostic imaging of atherosclerotic plaques in the carotid and vertebral arteries, and echocardiography to identify cardiac sources of emboli and other cardiac disorders.

### *Clinical evaluation*

Medical and neurological histories were recorded, as described previously. In the basic cohort of 487 patients, there were 339 (69.6%) patients with first-ever stroke and 151 patients (31%) with recurrent stroke. Stroke severity was assessed using the modified Rankin score at 3 months (8). Patients' educational level was divided into two categories: low (0–6 years of formal education) and high (>6 years of formal education). Smoking habits were dichotomized as follows: nonsmoking and smoking (current or former). Alcohol use was categorized on admission as non-alcohol user and alcohol user (past or current alcohol use).

All available hospital records were reviewed to determine whether patients had a history of hyperlipidemia, atrial fibrillation, arterial hypertension, or diabetes. History of hypertension was defined as systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg. Diabetes was considered if the patient had a previously documented diagnosis with fasting blood sugar  $\geq 110$  mg/dL or if the patient was currently under antidiabetic or insulin treatment.

Clinical cognitive assessment was performed using the MMSE and MoCA to measure the level of cognitive dysfunction. The neurological assessment included attention, orientation, language tests, and structuring subtests.

The severity of stroke was determined according to the National Institute of Health Stroke Scale. Furthermore, social functioning after stroke was assessed using the Index of Activities of Daily Living (ADL).

The study was approved by the Ethics Committee of

the First People's Hospital of Bengbu Medical College (approved date: 2013-11-10).

### *Data analysis and statistics*

All data were analyzed using IBM SPSS 21.0 statistical software (IBM Corp., Armonk, NY, USA). The Crosstabs was used to assess categorical variables between patients with and without PSCI. Demographic was reported as number and percentage. An independent student *t*-test was used to calculate numerical variables and compare patients with and without PSCI. An independent samples test was performed to test the significance of plasma biochemical parameters. The level of statistical significance for all statistical analyses was set at  $P < 0.05$ . Furthermore, forward stepwise logistic regression analysis was used to estimate the relative risk [odds ratio (OR) with a 95% confidence interval (CI)]. A receiver operating characteristic (ROC) curve was used to assess the sensitivity and specificity of independent risk factors in predicting PSCI.

### **Results**

In total, 487 consecutive patients were included in the study. Among these patients, 132 (27.1%) patients were diagnosed as PSCI based on the criteria of DSM-IV. Age was related to PSCI (*Table 1*). In the statistical analysis, age  $\geq 70$  years was statistically significant ( $P = 0.001$ ). There was no significant difference in age between patients with 60 and 69 years. Another notable factor was systolic blood pressure history (SBP). Although there was no significant difference when the threshold of SBP was set to  $\geq 140$  and  $< 170$  mmHg, there were significant differences between the PSCI and non-PSCI groups when  $\geq 170$  mmHg was used as the threshold.

In addition, smoking ( $P = 0.024$ ) and alcohol consumption ( $P = 0.02$ ), above moderate cerebral atrophy ( $P = 0.001$ ), above moderate WML ( $P = 0.001$ ), and above moderate carotid plaque ( $P = 0.032$ ) were significantly more prevalent in PSCI patients than those without PSCI (*Table 1*). However, there was no difference between the two groups for other factors such as education, gender, hyperlipidemia, diabetes, or atrial fibrillation ( $P > 0.05$ ).

We then performed plasma biochemical parameters analysis to compare patients with PSCI and without PSCI with respect to creatinine, blood urea nitrogen (BUN), retinol-binding protein, uric acid (UA), cystatin C, sialic acid, triglyceride, cholesterol, high density lipoprotein,

**Table 1** Comparison of demographics and risk factors of patients with and without post-stroke cognitive impairment

Variable	Total (N=487)	PSCI (N=132)	NPSCI (N=355)	$\chi^2$ value	P value
Age, years	71.5±10.2	67.5±15.8	64.5±13.6	22.064	0.001
Gender, n (%)					
Male	241 (49.5)	63 (26.1)	178 (73.9)	0.126	0.723
Female	246 (50.5)	69 (28.0)	177 (72.0)		
Education level, n (%)				0.475	0.491
<6 years	324 (66.5)	82 (25.3)	242 (74.7)		
≥6 years	163 (33.5)	50 (30.7)	113 (69.3)		
Smoking, n (%)				37.7	0.024
No smoking	410 (84.2)	86 (21.0)	324 (79.0)		
Smoking	77 (15.8)	46 (59.7)	31 (40.3)		
Alcohol use, n (%)				5.407	0.02
None use	385 (79.1)	92 (23.9)	293 (76.1)		
Use	102 (20.9)	40 (39.2)	62 (60.8)		
Hyperlipemia, n (%)				0.1	0.92
None	185 (38.0)	49 (26.5)	136 (73.5)		
Have	302 (62.0)	83 (27.5)	219 (72.5)		
Diabetes, n (%)				0.712	0.399
None	235 (48.3)	70 (29.8)	165 (70.2)		
Have	252 (51.7)	62 (24.6)	190 (75.4)		
Artrial fibrillation, n (%)				1.532	0.216
None	293 (60.1)	87 (29.7)	206 (70.3)		
Have	194 (39.8)	45 (23.2)	149 (76.8)		
Hypertension history (SBP ≥170 mmHg), n (%)					
SBP ≤170 mmHg	62 (12.7)	7 (11.3)	55 (88.7)	17.299	0.001
SBP ≥170 mmHg	425 (87.3)	125 (29.4)	300 (70.6)		
Carotid plaque, n (%)				4.617	0.037
None to mild	210 (43.1)	49 (23.3)	161 (76.7)		
Above moderate	277 (56.9)	83 (30.0)	194 (70.0)		
Brain atrophy, n (%)				37.726	0.001
None to mild	213 (43.7)	30 (14.1)	183 (85.9)		
Above moderate	274 (56.3)	102 (37.2)	172 (62.8)		
WML, n (%)				59.89	0.001
None to mild	358 (73.5)	65 (18.2)	293 (81.8)		
Above moderate	129 (26.5)	67 (51.9)	62 (48.1)		

PSCI, post-stroke cognitive impairment; NPSCI, non-PSCI; SBP, systolic blood pressure; WML, white matter lesion.

**Table 2** Comparison of biochemical indicators in patients with and without post-stroke cognitive impairment

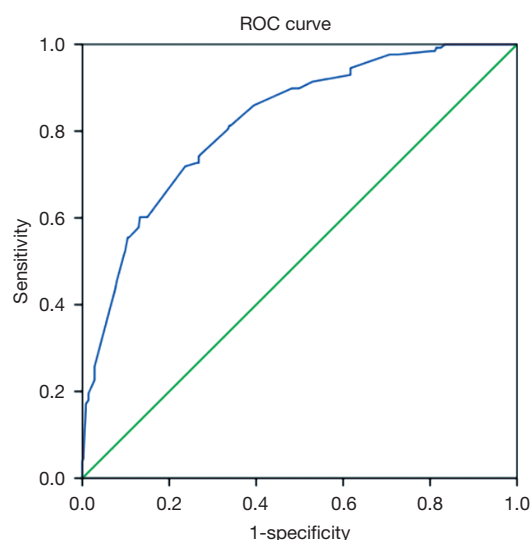
Variable <sup>†</sup>	PSCI (N=132)	NPSCI (N=355)	P value
BUN	6.42±3.57	7.20±17.06	0.596
Creatinine	80.45±40.40	80.26±65.99	0.975
Cystatin C	1.44±0.59	1.98±7.83	0.450
Retinol-binding Protein	51.32±14.34	53.65±14.72	0.110
UA	344.14±102.61	332.78±98.42	0.012
Homocysteine	25.30±37.76	20.58±10.04	0.020
Sialic acid	53.57±11.61	51.77±9.61	0.070
Triglyceride	2.01±6.61	1.61±1.27	0.243
Cholesterol	6.38±24.28	4.42±1.08	0.101
High-density Lipoprotein	1.20±0.39	1.47±4.80	0.507
Low-density Lipoprotein	2.62±0.83	2.83±0.84	0.013
Apolipoprotein A1	1.21±0.43	1.22±0.61	0.781
Apolipoprotein B	0.96±0.44	1.20±4.67	0.547

<sup>†</sup>, values are given as mean ± standard deviation. PSCI, post-stroke cognitive impairment; NPSCI, non-PSCI; BUN, blood urea nitrogen; UA: uric acid.

**Table 3** Logistic regression analysis of independent risk factors as predictors of PSCI

Variable	OR value	95% CI	P value
Smoker	0.265	0.10–0.256	0.001
Alcohol use	5.138	1.014–26.04	0.048
Carotid plaque	1.692	1.032–2.796	0.040
Age ≥70 years	0.466	0.27–0.8	0.006
History SBP ≥170 mmHg	12.171	3.339–44.363	0.001
Cerebral atrophy	2.280	1.294–4.001	0.004
WML	3.155	1.868–5.324	0.001
LDL	0.83	0.6–1.148	0.051
CHY	1.018	0.944–1.042	0.010
UA	1.00	0.998–1.002	0.007

PSCI, post-stroke cognitive impairment; OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; WML, white matter lesion; LDL, low-density lipoprotein; CHY, homocysteine; UA, uric acid.

**Figure 1** ROC curve evaluating the sensitivity and specificity of independent risk factors for PSCI. ROC, receiver operating characteristic; PSCI, post-stroke cognitive impairment.

apolipoprotein A1, apolipoprotein B, homocysteine and low-density lipoprotein (LDL). We included a total of 13 factors in the evaluation (*Table 2*). The level of homocysteine (HCY), LDL, and UA between PSCI and non-PSCI patients were significantly different ( $P<0.05$ ). However, no differences were identified for the other biochemical indicators ( $P>0.05$ ).

Logistic regression analysis found that multiple variables including alcohol use (OR: 5.138, 95% CI: 1.014–26.04,  $P=0.048$ ), history of high systolic blood pressure (OR: 12.171, 95% CI: 3.339–44.363,  $P=0.001$ ), carotid plaque (OR: 1.692, 95% CI: 1.032–2.796,  $P=0.040$ ), cerebral atrophy (OR: 2.280, 95% CI: 1.294–4.001,  $P=0.004$ ), and WML (OR: 3.155, 95% CI: 1.868–5.324,  $P=0.001$ ) were all independently and significantly associated with PSCI (*Table 3*). Logistic regression also showed that homocysteine (OR: 1.018, 95% CI: 0.944–1.042,  $P=0.010$ ) and UA (OR: 1.00, 95% CI: 0.998–1.002,  $P=0.007$ ) and LDL (OR: 0.83, 95% CI: 0.6–1.148,  $P=0.051$ ) significantly predicted PSCI development.

ROC curve analysis of the sensitivity and specificity of PSCI prediction found that the area under the curve (AUC) was 0.821 (95% CI: 0.78–0.862) (*Figure 1*). AUC had a certain accuracy at 0.7–0.9 and higher accuracy at 0.9 or above.



## Discussion

This study revealed that older age and the presence of carotid plaque, cerebral atrophy, above moderate WML, alcohol use, and smoking were all highly associated with the development of PSCI.

A number of studies have shown that having a stroke is highly correlated with cognitive impairment, which all share common risk factors (9). A report by Sibolt *et al.* (10) highlighted that an ischemic stroke is a risk factor for cognitive impairment and dementia; while, there are many other studies that have confirmed that PSD is associated with the recurrence of an ischemic stroke (11,12). One study found that the risk of incidents of dementia increased 4 folds among ischemic stroke patients relative to clinically stroke-free elderly control participants (13).

During the research, our data showed that age is related to PSCI occurrence. Age is one of the independent risk factors for PSCI. These results indicate that older patients are more prone to vascular cognitive impairment. In addition, our results revealed a relationship between alcohol consumption and cognitive impairment. Chronic alcohol consumption induces damage to the brain that can cause various forms of dementia. An abundance of acetaldehyde is produced by excessive alcohol consumption and accumulates in the body to induce oxidative stress, apoptosis, and inflammation in neuronal cells, which results in learning and cognitive decline (14). The presence of WML may be another predictor that is closely related to PSCI. In support of these findings, a review by Ihara (15) indicated that the presence and severity of WMLs measured by MRI might predict PSD. The authors also suggested that microstructural changes of normal-appearing white matter (WM), as evident in diffusion tensor imaging, maybe a good predictor of cognitive decline in patients with WM hyperintensities. A follow-up study of SMART-MR (16) found that cerebral atrophy, in combination with vascular brain lesions (WML and infarcts), was associated with an accelerated decline of executive functioning and memory. Our logistic regression analysis revealed that moderate and above brain atrophy is highly correlated with PSCI, which is consistent with the results of the above previous studies.

Our results, however, are not in agreement with the other reports on the relationship between hypertension and PSCI. A recent review (17) confirmed the close association of hypertension with having a stroke and reported there to be a relationship with cognitive impairment and dementia. From the findings of the previous reports,

it can be concluded that arterial hypertension is likely the strongest risk factor for the different forms of VaD (18-20). On the contrary, Tamam *et al.* (21) argued that PSD did not significantly correlate with hypertension. Our study showed there was a significant difference between patients with and without PSCI in terms of a history of systolic blood pressure  $\geq 170$  mmHg. We found that 60% of patients with PSCI had a history of hypertension, and about 75% had a history of systolic blood pressure  $\geq 170$  mmHg. Yet there was no statistically significant difference between the two patient groups for a history of systolic blood pressure between 140 and 170 mmHg. Hypertension is one of the most important risk factors for atherosclerosis, which causes a stroke. Cerebral ischemia and hypoxia caused by stroke lead to neuronal damage and vascular cognitive impairment.

We extended our exploration to 13 plasma biochemical indicators for early prediction of PSCI and found significant differences in plasma HCY, LDL, and UA levels between patients with and without PSCI. HCY is a thiol-containing non-essential amino acid produced in all cells, as a product of normal folate and methionine metabolism. Elevated plasma homocysteine leads to hyperhomocysteinemia (HHcy). HHcy is a robust and independent risk factor for stroke and cognitive impairment (22-24). In the early stage of PSCI, cognitive function may be impaired by HHcy through: (I) pathway of vascular damage dependent on HCY; (II) disorder of lipid metabolism and promoting atherosclerosis; (III) promoting neuronal apoptosis; (IV) promoting neuronal development toxic effects of fenvalerate; (V) effects on nerve conduction and other mechanisms of cognitive function (25).

LDL transports all lipid molecules to the cells via the blood. LDL can be involved in the progression of atherosclerosis if these lipoproteins become oxidized within the artery walls. The formation of superoxide and free radicals causes oxidative damage to blood vessel walls, leading to thrombosis and the occurrence of ischemic cerebral infarction. Li *et al.* (26) demonstrated 87% sensitivity of LDL oxidation in the detection of VaD, which may serve as a novel biomarker to distinguish VaD and AD. A recent study in an elderly Brazilian population demonstrated that VLDL was associated with dementia as well as cognitive impairment without dementia (27).

Uric acid (UA) is the product of purine metabolism, which is a powerful antioxidant that may have neuroprotective properties, yet it is also a risk factor of vascular disease that predisposes individuals to cognitive

impairment. In this study, we have shown that there is a positive association between serum UA concentrations and cognitive impairment. UA could stimulate vascular smooth muscle cell proliferation and induce endothelial dysfunction by inhibiting nitric oxide production. Elevated serum UA levels are also associated with systemic inflammation. These pathological changes also cause brain damage (28). Therefore, elevated plasma UA level is a potent risk factor for the development of cognitive impairment, which is consistent with many studies (28-30). Suzuki *et al.* reported (28) that elevated serum UA levels and cognitive deterioration remained statistically significant even after adjusting for confounding factors such as age, sex, BMI, education, SBP, fasting blood sugar, triglyceride, HDL-cholesterol, LDL-cholesterol, and serum creatinine levels. Therefore, the results of our study are of great significance.

Recently, the BMJ sub-journal (31) published a study on the dementia risk prediction model, which included factors such as age, sex, education level, cholesterol, alcohol consumption, and MMSE. Most of our research factors were included in this model. As the sample size and follow-up time were different between our study and the BMJ study, the prediction accuracy also varied. The AUC ranged from 0.63 to 0.92 in the BMJ study, while our ROC curve was 0.821. Our results show that the careful consideration of these factors will have better accuracy in predicting PSCI. And these indicators are routine diagnostic and therapeutic indicators not harmful to patients.

In conclusion, the variables such as drinking, cerebral atrophy, systolic blood pressure history, WML, carotid plaque between patients with PSCI, and without PSCI were significantly different while HCY, LDL, and UA may be risk factors of PSCI, which may be useful in the prediction of early dementia. Early identification of these factors will undoubtedly contribute to the prevention of PSCI. Therefore, further exploration of additional biomarkers warrants to understand the significance of these factors in PSCI better.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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