

Post-Stroke Depression and Estimated Glomerular Filtration Rate: A Prospective Stroke Cohort

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Purpose: Post-stroke depression (PSD) is a frequent comorbidity in patients presenting with acute ischemic stroke. Impaired kidney function has been associated with depression in non-stroke subjects. We would like to evaluate whether the estimated glomerular filtration rate (eGFR) on admission is associated with the development of PSD.

Patients and methods: Total of 268 patients with acute ischemic stroke were recruited and completed 1-month follow-up visit. eGFR was calculated from the serum creatinine value, race, age, and sex by using the chronic kidney disease epidemiology collaboration equation (CKD-EPI creatinine equation). The 17-item Hamilton Depression Scale was used to evaluate depression symptoms. Patients with a depression score of ≥ 7 were evaluated using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th edition, for diagnosing post-stroke depression at 1 month. Meanwhile, 114 normal control subjects were also recruited.

Results: Ninety-three (34.7%) patients were diagnosed as having PSD at 1 month. There was a significant intergroup difference in eGFR levels within 24 hrs after admission ($F=13.608$, $p<0.001$). The levels of eGFR within 24 hrs after admission were significantly lower in both non-PSD patients and PSD patients than in normal controls. In logistic regression, the level of eGFR ($<82\text{mL/min/1.73m}^2$) was independently associated with increased risk of PSD even after adjusting for confounders ($\text{OR}=2.328$, 95% CI: 1.092–4.965, $p=0.029$).

Conclusion: Reduced eGFR was found to be correlated with the development of PSD and it suggests the need for greater attentions and potential interventions for depression in patients with stroke and with reduced eGFR.

Keywords: estimated glomerular filtration rate, eGFR, post-stroke depression, stroke, Depression

Introduction

Post-stroke depression (PSD), a serious and undertreated mood disorder, is regarded as important complication following stroke, with prevalence ranging from 29% to 39%.^{1–3} Study had shown that factors including history of depression before stroke, history of a previous stroke, stroke severity, and disability after stroke would contribute to the development of PSD.^{3–5} It is urgent for neurologists to early recognize and diagnose PSD because the presence of PSD not only affects the quality of life but also reduces functional ability, worsens rehabilitation outcomes, and increases mortality.^{3,6–8} However, being unable to understand the pathophysiological mechanisms completely makes it difficult to prevent and manage PSD.

Estimated glomerular filtration rate is an index reflecting the function of kidney. The lower the eGFR is, the worse the kidney function will be. Kidney disease, common

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among stroke patients,⁹ increases the risk of stroke^{10,11} and carotid atherosclerosis.¹² In a large, community-based population, an independent, graded association was observed between renal dysfunction as was estimated with glomerular filtration rate (GFR) and the risk of death, cardiovascular events, and hospitalization.¹³ Study shows that when the glomerular filtration rate was <81.0 mL/min/1.73 m², with each 10-unit drop, death and nonfatal cardiovascular events would increase by 1.1-fold.¹⁴ Furthermore, reduced eGFR was found to negatively correlate with stroke outcome,¹⁵ and the risk of recurrent stroke was significantly increased with the decline of eGFR.¹⁶ In addition, studies had observed that reduced kidney function is independently associated with cognitive decline.¹⁷ The elderly with impaired kidney function have a more rapid rate of cognitive decline.¹⁸ Also, anxiety symptoms are common in patients with CKD.¹⁹ As for depression, studies have indicated the association between reduced kidney function and depression,^{20,21} while others have different attitudes.²² The prevalence of depression in patients suffering from chronic kidney disease (CKD) is approximately 20–30%, which is higher than that of other chronic diseases,²³ such as 11% for diabetes mellitus,²⁴ 14% for congestive heart failure,²⁵ and 16% for coronary artery disease after acute myocardial infarction.²⁶ Interestingly, depression could also in turn accelerate the progression of CKD and lead to poor outcomes or earlier death in patients with CKD.²¹

However, to date, no previous study has explored the association between the estimated glomerular filtration rate (eGFR) on admission and the development of PSD. Considering the involvement of eGFR level in stroke as well as depression, we conducted this study to examine the extent to which the estimated glomerular filtration rate (eGFR) might be associated with PSD.

Materials and Methods

Subjects

The study was a prospective cohort study, which was approved by the Medical Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University. Participants were consecutively recruited from all patients with recent ischemic stroke hospitalized in the Stroke Unit of our hospital from October 2013 to June 2015, with written informed consents signed. And this study was conducted in accordance with the Declaration of Helsinki.

The inclusion criteria were: (1) Chinese ethnicity; (2) between 18 and 80 years old; (3) onset of acute stroke

events was less than 7 days at admission; (4) diagnosed by cranial-computed tomography (CT) or magnetic resonance imaging (MRI) at admission. The exclusion criteria included: (1) transient ischemic attack (TIA) or primary haemorrhagic stroke; (2) pre-stroke diagnosis of significant cognitive impairment or dementia; (3) patients with a history of depression (clinical diagnosis or previous treatment) or other psychiatric disorders; (4) history of severe central nervous system diseases such as craniocerebral trauma, Parkinson's disease or hydrocephalus; (5) a history of nootropic or antipsychotic drug use; (6) any situation that make them failed to the neuropsychological assessments such as visual or auditory impairment, chaotic conscious state, severe aphasia or dysarthria; (7) history of chronic kidney disease (clinical diagnosis or previous treatment); (8) comorbid malignancy or clinically thyroid disease, or undergoing glucocorticoid therapy at admission. Meanwhile, 114 healthy control subjects were recruited from a health survey. The subjects with any personal or familial history of psychiatric illness were excluded. All subjects were free of severe physical diseases including acute ischemic stroke.

Clinical Measurements

A standard questionnaire was administered by trained staff to obtain information on demographic characteristics. Patient's age, sex, income, years of education and marital status, personal history (smoking or drinking) and medical history (hypertension, diabetes, coronary artery disease or previous stroke) were recorded. Cranial computerized and magnetic resonance imaging were performed within 24 to 72 hrs after admission in order to assess the site of the brain infarct.

Assessment

The 17-item Hamilton depression Rating Scale (HAMD) was adopted to assess the depressive symptoms in this population at 1 month after stroke.²⁷ And there are already many studies using 1 month as evaluation point for PSD.^{28–30} A score of 0 to 7 is considered to be normal, while a score of ≥ 7 is indicative of depression. Patients with a HAMD score of ≥ 7 were evaluated using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) for the diagnosis of post-stroke depression by a neurologist/psychiatrist who was blind to the laboratory results of stroke patients.³¹

Stroke severity was assessed by trained neurologists using the National Institutes of Health Stroke Scale

(NIHSS) within 24 hrs of admission. Functional outcome was evaluated by the modified Rankin Scale (mRS) and the Barthel Index (BI) at discharge. Cognition function was assessed by the Mini-Mental State Examination (MMSE) at 1 month.

Laboratory Tests

Peripheral blood was drawn from fasting patients on the second day after admission. Blood urea nitrogen (BUN), serum creatinine (Scr), hemoglobin, uric acid and high-sensitivity C-reactive protein (hs-CRP) were determined with a Beckman Coulter AU5800 automatic analyzer at our hospital's laboratory. The eGFR was calculated on the basis of Scr concentration, race, age and sex using the chronic kidney disease epidemiology collaboration equation (CKD-EPI creatinine equation). According to the number of patients and the distribution of the eGFR level with the highest differences in this study, eGFR levels were further divided into tertiles ($<82\text{mL/min/1.73m}^2$, $82\text{--}97\text{mL/min/1.73m}^2$, and $>97\text{mL/min/1.73m}^2$).

Statistical Analyses

The results were represented as percentages for categorical variables, while continuous variables depending on their normal distribution were expressed as mean $\pm$ standard deviation (SD) or median (interquartile range, IQR). The Chi-squared test was employed for proportions and the normally distributed variables were compared using Student's *t*-test and analysis of variance (ANOVA), while the Mann-Whitney *U*-test was employed for the asymmetrically distributed variables. Pearson correlation coefficient was performed for bivariate correlation. Binary logistic regression analysis was used to analyze association of PSD and reduced eGFR. The odds ratio (OR) value of PSD were recorded after adjusting for potential confounding variables. Data were managed and analyzed using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). A *p*-value of <0.05 (two-tailed) was considered to be statistically significant.

Results

Characteristics of Patients in the PSD Group, Non-PSD Group, and Normal Group

Among 512 subjects with acute stroke screened, 347 met the study entry criteria and were included in the study and 268 completed 1-month follow-up (Figure 1). Overall, 93

(34.7%, 49 men, 44 women) were into the group with post-stroke depression and 175 (65.3%, 122 men, 53 women) had no depressive symptoms after stroke. The clinical characteristics of patients in the PSD group, non-PSD group, and normal group are presented in Table 1.

The mean ($\pm$ SD) eGFR level for all stroke patients was $89.58\pm 19.42\text{ mL/min/1.73m}^2$; the mean ($\pm$ SD) eGFR levels in normal subjects, non-PSD patients and PSD patients were $98.31\pm 16.44\text{ mL/min/1.73m}^2$, $92.69\pm 19.02\text{ mL/min/1.73m}^2$ and $83.71\pm 18.91\text{ mL/min/1.73m}^2$, respectively. A significant intergroup difference in eGFRs within 24 hrs after admission was revealed ($F=13.608$, $p<0.001$). Indeed, the eGFR was significantly lower in non-PSD patients and PSD patients than in normal controls; the eGFR was significantly decreased in PSD patients than in non-PSD patients.

Patients with post-stroke depression also had more severe strokes ($z=-5.10$, $p<0.001$) and poorer functional outcomes ($z=-5.92$, $p<0.001$) and cognitive function ($z=-2.60$, $p<0.05$). In addition, post-stroke depression group was more likely to be female, older and more current drinking and have higher blood urea nitrogen levels (all $p<0.05$). There were no significant differences in the distribution of stroke lesion between the two groups. Also, no associations were found in serum creatinine and hemoglobin and uric acid between PSD and non-PSD groups, as well as hs-CRP ($p>0.05$) (Table 1).

eGFR Level Tertiles of Patients

Significant differences were found between the PSD and non-PSD groups in eGFR level tertiles of patients ($P=0.011$). Indeed, the proportion of patients in the lowest tertile ($<82\text{mL/min/1.73m}^2$) was significantly higher in the PSD group ($P=0.032$), while the proportion of patients in the highest quartile ($>97\text{mL/min/1.73m}^2$) was significantly lower in the PSD group ($P=0.003$) (Table 2).

Predictors of PSD After Stroke

The Logistic regression analysis showed that the risk of post-stroke depression significantly increased with the decline of eGFR ($<82\text{mL/min/1.73m}^2$), which was still significant after adjusting for age, sex, current drinking, NIHSS score, mRS score, BI score, MMSE score, Hs-CRP and Diabetes mellitus (OR=2.328, 95% CI: 1.029–4.965, $p=0.029$). In addition, the NIHSS scores at admission (OR=1.189, 95% CI: 1.028–1.376, $p=0.020$) were independently associated with depression, after adjusting for the above variables (Table 3).

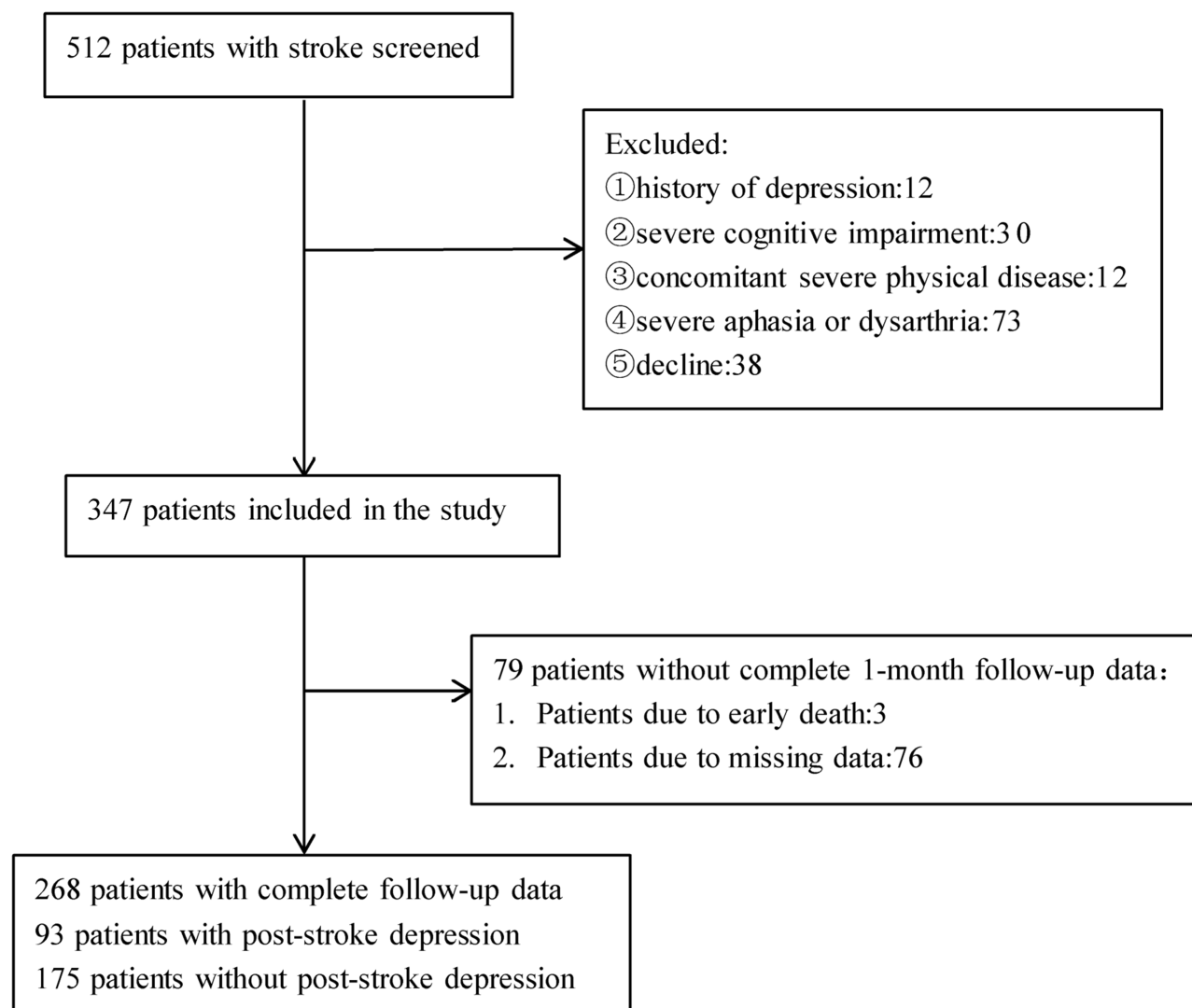


Figure 1 Study recruitment profile. PSD indicates post-stroke depression.

Discussion

To the best of our knowledge, this is the first study evaluating the relationship between the estimated glomerular filtration rate (eGFR) and the development of depression in stroke survivors. Our results point out that the eGFR is an important indicator of risk of the development of PSD.

We estimated the prevalence of post-stroke depression at 1 month. About 34.7% of stroke patients met the diagnosis of PSD, which was in line with the result of previous studies.^{1,32} Importantly, our results also demonstrated that patients with more severe stroke and more serious physical disability were susceptible to develop depression, which broadly agreed with the findings of earlier studies.^{3,33} Some studies had suggested that the location of stroke lesion might play a role in the etiology of post-stroke depression.³⁴ However, in the present study, there is no association between the location of lesion

and the presence of depression, consistent with other studies.³⁵ Additionally, we did not find any significant association between the development of PSD and other controversial variables, such as MMSE scores,^{3,33,36} although previous studies had provided inconclusive results in these aspects. These relationships need to be further explored with more advanced imaging techniques and accurate analysis in future studies.

As mentioned earlier, a large number of studies have already reported the relationship between the reduced eGFR and the poor outcome, and greater mortality of ischemic stroke. However, limited studies have explored the relationship between the reduced eGFR and depression, especially in patients with acute ischemic stroke. We found that the levels of eGFR were significantly lower in stroke patients groups than in normal controls, which was consistent with

Table I Clinical and Demographic Characteristics of the Samples Under Study

Variables	PSD (n = 93)	Non-PSD (n = 175)	Normal Control (n=114)
Demographic characteristics			
Age (years), mean $\pm$ SD	65.46 $\pm$ 8.68 ^b	61.88 $\pm$ 10.28	62.70 $\pm$ 10.45
Male/Female	49/44 ^b	122/53	65/49
Married status, n (%)	82 (88.2)	162 (92.6)	
Income, n (%)			
Low	56 (60.2)	97 (55.4)	
Medium	33 (35.5)	70 (40.0)	
High	4 (4.3)	8 (4.6)	
Years of education	4 (0–6)	4 (0–7)	
Lesion location, n (%)			
Left hemisphere	57 (61.3)	112 (64.0)	
Right hemisphere	22 (23.7)	42 (24.0)	
Other	14 (15.1)	21 (12.0)	
History of stroke	12 (12.9)	16 (9.1)	
Vascular risk factors, n (%)			
Hypertension	70 (75.3)	129 (73.7)	
Diabetes mellitus	22 (23.7)	34 (19.4)	
Coronary artery disease	4 (4.3)	14 (8.0)	
Smoking			
No smoking	55 (59.1)	82 (46.9)	
Quit smoking	16 (17.2)	29 (16.6)	
Current smoking	22 (23.7)	64 (36.6)	
Current drinking	27 (29.0) ^b	76 (43.4)	
Neuropsychological function			
NIHSS score, median (IQR)	4 (2–7) ^a	2 (1–3)	
mRS score, median (IQR)	2 (1–4) ^a	1 (1–2)	
BI score, median (IQR)	90 (55–100) ^a	100 (90–100)	
MMSE score, median (IQR)	24 (20–28) ^b	26 (22–28)	
HAMD score, median (IQR)	9(8–12) ^a	3 (1–5)	
Laboratory data			
Scr(umol/L), median (IQR)	73 (56–87.5)	72 (60–85)	
BUN(mmol/L), median (IQR)	5.2 (4.35–6.1) ^b	4.9 (3.9–5.8)	
Hemoglobin(g/L), mean $\pm$ SD	133.3 $\pm$ 17.88	137.84 $\pm$ 18.29	
Uric acid(umol/L), mean $\pm$ SD	293.88 $\pm$ 90.43	290.93 $\pm$ 91.75	
Hs-CRP(mg/L), median (IQR)	2.89 (1.05–7.79)	2.25 (0.74–6.46)	
eGFR(mL/min/1.73m ²), mean $\pm$ SD	83.71 $\pm$ 18.91 ^{a,c}	92.69 $\pm$ 19.02 ^d	98.31 $\pm$ 16.44

Notes: ^aP < 0.001 compared to Non-PSD. ^bP < 0.05 compared to Non-PSD. ^cP < 0.001 compared to Normal Controls. ^dP < 0.05 compared to Normal Controls.

Abbreviations: BI, modified Barthel Index; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; HAMD, Hamilton Depression Rating Scale 17-item; Hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; MMSE, Mini-Mental State Examination; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PSD, post-stroke depression; SD, standard deviation; Scr, serum creatinine.

previous studies.^{10,37,38} In this stroke patients-based prospective cohort study, our results indicated that the eGFR was decreased enormously in patients with PSD than non-PSD, which was in agreement with previous studies.³⁹ Likewise, individuals with reduced eGFR were increasingly likely to experience lower Health-related quality of life.⁴⁰

Depression and suicidal ideation were related closely with reduced kidney function. The risk of having depression and suicidal ideation increased even in patients with mild-reduced kidney function.⁴¹ Campbell et al found, whether proteinuria exists or not, lower eGFR was associated with a markedly increased risk of depressive symptoms after

Table 2 eGFR Level Tertiles of Patients

Variables	PSD (n = 93)	Non-PSD (n = 175)	χ^2	P Value
eGFR			9.094	0.011
Tertile 1	38(40.9)	49(28)	4.581	0.032
Tertile 2	32(34.4)	52(29.7)	0.788	0.375
Tertile 3	23(24.7)	74(42.3)	8.602	0.003

Abbreviation: eGFR, estimated glomerular filtration rate.

taking cardiovascular comorbidities into account among older adults with diabetes.³⁹ Similarly, Hedayati et al showed that a major depressive episode was common in patients with earlier stages of CKD, and participants with CKD who had diabetic were twice as likely to have a major depressive episode compared with those without diabetes.²³

The mechanisms of reduced eGFR and depressive symptoms remained not completely understood. Acute ischemic stroke triggered a series of inflammatory responses including central and peripheral, characterized by rapid infiltration of microglia and upregulation of proinflammatory cytokines.⁴² Inflammatory response plays an important role in the pathogenesis of depression,⁴³ which accorded well with one study conducted by Raison et al that pro-inflammatory cytokines participated in many of the pathophysiological mechanisms of depression, involving neuroendocrine function, neurotransmitter metabolism, synaptic plasticity, and behaviour.⁴⁴ Evidence shows that higher concentrations of pro-inflammatory cytokines have been identified among clinically depressed individuals and those with symptoms of

depression.^{45,46} Meanwhile, it has been suggested that systemic inflammation and oxidative stress are known to be aggravated with reductions of kidney function.⁴⁷ In addition, the orbitofrontal cortex (OFC) is recognised as a vital part of networks involving emotional processing.⁴⁸ It is proposed to make decisions in experiencing pleasure and reward which are likely to be impaired in depression.⁴⁹ At the same time, a study found that higher scores on the Hamilton Depression Rating Scale (HDRS) were associated with decreased cerebral glucose metabolism of the OFC in pre-dialysis CKD patients.⁵⁰ It is in line with studies showing that in CKD patients global gray matter clusters reduced in OFC.^{51,52} Furthermore, a study conducted by Schaefer et al revealed that the amino acid neurotransmitter milieu altered in uremic rats, suggesting that uremic toxins may influence mental health and behavior.⁵³ Besides, multiple comorbidities that are related to precede kidney function decline, such as hypertension, diabetes, stroke and chronic heart disease could also play roles in increasing the risk of depression.⁵⁴ Therefore, these factors may affect mental health even in asymptomatic subjects whose kidney function is only mildly decreased. Thus, considering the role of reduced kidney function in ischemic stroke as well as depression, it may involve in the development of PSD.

There are still some limitations in our study. Firstly, eGFR levels were measured only 1 time at admission, suggesting that further studies are needed to evaluate how eGFR levels changed across time following stroke and whether its levels increased at later points improving stroke outcomes. Secondly, patients with aphasia or a serious condition were excluded, which might underestimate the actual incidence of PSD, and in the future, these patients should be evaluated using other scales such as Stroke Aphasic Depression Questionnaire (SADQ).⁵⁵ Thirdly, further follow-up is necessary so that we could further explore the link between eGFR and PSD. Finally, the application of our conclusion may be limited in those minor stroke subjects, for most of the patients with higher NIHSS scores have been excluded, and patients with higher NIHSS scores should be included in future researches.

Conclusion

In summary, our study demonstrates an important relationship between declining eGFR levels and the development of PSD. Furthermore, the prevalence of these mental health problems after stroke increased obviously even when eGFR level is reduced mildly. Future studies on larger populations should be encouraged to confirm these findings.

Table 3 Multivariate Logistic Model of the Clinical Determinants of PSD

Variables	OR	95% CI	P Value
eGFR			0.003
Tertile 1	2.328	1.092–4.965	0.029
Tertile 2	1.468	0.678–3.179	0.330
Age	1.021	0.986–1.057	0.246
Sex	0.575	0.283–1.168	0.126
Current drinking	1.434	0.706–2.913	0.318
NIHSS score	1.189	1.028–1.376	0.020
mRS score	1.121	0.774–1.623	0.545
BI score	0.982	0.962–1.003	0.088
MMSE	0.980	0.921–1.043	0.528
Diabetes mellitus	0.951	0.472–1.917	0.888
Hs-CRP	0.994	0.975–1.013	0.522

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; BI, modified Barthel Index; MMSE, mini-mental state examination; eGFR, estimated glomerular filtration rate; PSD, Post-stroke depression; OR, odds ratio, 95% CI, 95% confidence interval.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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