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Higher homocysteine and fibrinogen are associated with early-onset post-stroke depression in patients with acute ischemic stroke

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Background: Post-stroke depression (PSD) is a well-established psychiatric complication following stroke. Nevertheless, the relationship between early-onset PSD and homocysteine (Hcy) or fibrinogen remains uncertain.

Methods: Acute ischemic stroke (AIS) patients who met the established criteria were enrolled in this study. Early-onset PSD was diagnosed two weeks after the stroke. The severity of depressive symptoms was assessed by the Hamilton Depression Scale-17 items (HAMD-17), with patients scored ≥7 assigned to the early-onset PSD group. Spearman rank correlation analysis was employed to evaluate the associations between Hcy, fibrinogen, and HAMD scores across all patients. Logistic regression analysis was conducted to investigate the relationship between Hcy, fibrinogen, and early-onset PSD. Receiver operating characteristic curve (ROC) analysis was ASSDalso performed to detect the predictive ability of Hcy and fibrinogen for early-onset PSD.

Results: Among the 380 recruited patients, a total of 106 (27.89%) patients were diagnosed with early-onset PSD. The univariate analysis suggested that patients in the PSD group had a higher admission National Institutes of Health Stroke Scale (NIHSS) score, modified Rankin Scale score (mRS), Hcy, and fibrinogen levels than patients in the non-PSD group (P<0.05). The logistic regression model indicated that Hcy (odds ratio [OR], 1.344; 95% confidence interval [CI] 1.209–1.494, P<0.001) and fibrinogen (OR, 1.57 6; 95% CI 1.302–1.985, P<0.001) were independently related to early-onset PSD. Area under curve (AUC) of Hcy, fibrinogen, and Hcy combined fibrinogen to predict early-onset PSD was 0.754, 0.698, and 0.803, respectively.

Conclusion: This study indicates that Hcy and fibrinogen may be independent risk factors for early-onset PSD and can be used as predictive indicators for early-onset PSD.

KEYWORDS

post-stroke depression, acute ischemic stroke, homocysteine, fibrinogen, inflammation

Introduction

Post-stroke depression (PSD) is a severe and frequent complication of mental disorders followed by stroke, with an estimated prevalence range from 18% to 33% (1, 2). The clinical manifestations of PSD are characterized by low mood, loss of interest, and even suicidal tendencies (3). PSD is associated with increased death rates and places additional burdens on both the affected individuals' families and society as a whole (4). PSD can occur in different stages after stroke, early-onset PSD refers to patients exhibiting depression within two weeks after acute stroke onset (5, 6). Compared to late-onset PSD, early-onset PSD is characterized by a greater prevalence of depressive symptoms and is substantially associated with a greater chance of poor outcomes (7). Thus, it is of great value to detect predictive factor for early-onset PSD.

Inflammation plays a crucial role in the pathophysiology of PSD (8). Several studies have reported a strong correlation between Hcy levels and inflammation (9, 10). Fibrinogen is a common biomarker of inflammation (11, 12). Studies have shown that serum Hcy levels are elevated in patients with depression and correlate with the severity of depressive symptoms (13). Reducing Hcy might help alleviate anxiety and depression (14). In addition, previous studies have shown that elevated Hcy at admission is associated with PSD at 3 months after stroke (15). High-sensitivity C-reactive protein combined with Hcy can more accurately predict PSD at three months and one year after stroke (16, 17). Genetic factors may affect the serum levels of Hcy (18). The C677T is a non-synonymous variant, leading to a reduction in the activity of methylenetetrahydrofolate reductase (MTHFR) and folate levels and elevating serum Hcy levels (19, 20). MTHFR C677T mutations and folate deficiency could increase the risk of coronary heart disease and ischemic stroke in later life (21). A previous study found that the MTHFR C677T AG genotype and A allele increased the risk of PSD (22). Furthermore, a recent study showed that MTHFR C677T may exert an effect on PSD via mediating Hcy level (18). So far, the relationship between Hcy and early-onset PSD is still unclear. Based on the above research, we speculate that Hcy may be closely related to the occurrence and development of early-onset PSD.

Previous studies have found that patients with acute coronary syndrome revealed high levels of fibrinogen, and they were significantly higher among patients with anxiety and depressive disorders (23). In healthy individuals, psychological distress is also correlated with hypercoagulability (24). Both coagulation and fibrinolysis increase from baseline in response to acute stress, but coagulation increases more than fibrinolysis (25). Meanwhile, a high level of fibrinogen has been associated with depression 1- or 3-months post-stroke onset (26, 27). The underlying mechanism of how fibrinogen causes PSD remains unclear. Some researchers have proposed that fibrinogen might be a mediator between stroke severity and inflammatory response, the latter leading to depressive symptoms (26, 28). To date, there have been few studies concerning the relationship between fibrinogen and early-onset PSD.

At present, numerous risk factors, including gender, age, inflammatory cytokines, lesion localization, stroke severity, a history of depression, and symptomatic plaque enhancement, have been identified by researchers as being associated with PSD (2, 29). However, the relationship between Hcy and early-onset PSD remains unknown, and there have been few studies concerning the relationship between fibrinogen and early-onset PSD. In this study, we aimed to investigate the association of Hcy and fibrinogen with early-onset PSD and to explore whether Hcy and fibrinogen can serve as predictive indicators for early-onset PSD.

Materials and methods

Study design and participants

Acute ischemic stroke (AIS) patients were prospectively recruited from the Affiliated Changsha Central Hospital, Hengyang Medical School, University of South China, between January and August 2023. This study was approved by the Ethics Committee of the Affiliated Changsha Central Hospital, Hengyang Medical School, University of South China. Eligible participants were enrolled in the final analysis if they met the following criteria. Inclusion criteria: (1) patients who fulfilled the diagnostic criteria for ischemic stroke as outlined in the Chinese guidelines for diagnosis and treatment of acute ischemic stroke 2018 (30), with AIS confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) within 24 hours after admission; and (2) patients aged between 18 and 85 years; and (3) patients who were admitted to the hospital within 72 hours after the onset of stroke. Exclusion criteria: (1) patients with severe aphasia or dysarthria and a consciousness disorder that prevents

them from completing evaluations and questionnaires; (2) patients with a pre-existing diagnosis of dementia or significant cognitive impairment prior to the stroke; (3) patients with severe heart, liver, or renal insufficiency; (4) patients who self-report having any psychiatric illness, including depression, or who were using psychotropic drugs prior to the stroke onset; (5) patients with medical histories of other central nervous system diseases such as Parkinson's disease and epilepsy;(6) patients with malignant tumors that may potentially cause metabolic abnormalities; and (7) patients with nutritional disorders. There were 380 AIS patients recruited between January and August 2023 (Figure 1).

Clinical characterization

All participants underwent standard evaluations of their age, sex, body mass index, vascular risk factors (hypertension, diabetes mellitus, atrial fibrillation, coronary artery disease, current drinking and smoking, and laboratory data) on the day of admission. Smoking was defined as a patient who had smoked continuously for 5 years with at least 10 cigarettes per day. Alcohol consumption was defined as a patient who had drunk continuously for 5 years with at least 20g ethanol per day. The National Institutes of Health Stroke Scale (NIHSS) was used to evaluate stroke severity at admission by trained neurologists. NIHSS scores were assessed within 24 h after admission. The Barthel Index (BI) scores were assessed at discharge. In addition, the functional outcome was also assessed according to the modified Rankin Scale (mRS) score at follow-up after 1 month. The lesion site and stroke subtype were determined by computed tomography, magnetic resonance, electrocardiogram, echocardiography, carotid ultrasonography, and transcranial doppler.

Clinical assessment and subject grouping

According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) (31), trained neurologists and psychiatrists diagnosed patients with PSD 2 weeks after stroke onset. The severity of depressive symptoms was evaluated with the Hamilton Depression Scale 17 items (HAMD-17) (32). According to the recommendation, HAMD-17 scores <7 mean normal condition (33), and patients with these scores were enrolled in the non-PSD group. Patients with HAMD-17 scores greater than or equal to 7 were included in the PSD group. A score of 7–17, 18–23, and more than 24 indicates mild depression, moderate depression, and severe depression, respectively (33–35). According to the scores obtained, patients were classified into the mild, moderate, or severe PSD groups.

Blood Biomarker Examination.

Blood samples of all patients who within 72 hours after the onset of stroke were collected at 6–7 a.m. the day after fasting for at least 8 h. Two milliliters of EDTA-anticoagulated whole blood were used for routine blood tests (automated hematology analyzer, BZ6800, CHINA) that included white blood cell (WBC), neutrophils, and lymphocyte counts. Five milliliters of blood containing coagulant were used for a common biochemical examination (automatic analyzer, HITACHI 7600, JAPAN) that included creatinine (Cr), uric acid (UA), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), homocysteine (Hcy), and fibrinogen. All the indicators were tested using commercial kits, which were operated by qualified professionals in accordance with the specifications.

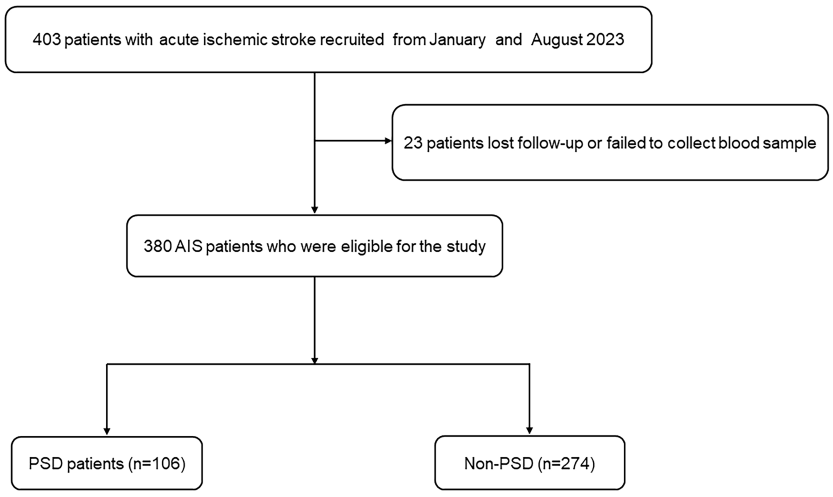

FIGURE 1
The study flow diagram. AIS, acute ischemic stroke; PSD, post-stroke depression.

Statistical analysis

Data analysis was performed using SPSS 25.0 (IBM SPSS Statistics software, Version 25.0). Categorical variables were expressed as n (%), and normally distributed continuous variables were expressed as means (standard deviation, SD), otherwise, the data are presented as the median (interquartile range). Differences in baseline characteristics between groups were analyzed using the one-way ANOVA test or Mann-Whitney U test for continuous variables as well as the chi-squared test or Fisher's exact test for categorical variables, as appropriate. We used the scatter plot to show the distribution of serum Hcy and fibrinogen levels among PSD of different severity. Analyses using the Spearman rank correlation were carried out to investigate the correlation that exists between the Hcy, fibrinogen, and HAMD scores in all patients. Binary logistic regression analysis for risk factors with PSD. A MedCalc 15.6.0 (MedCalc Software Acacialaan 22, B-8400 Ostend, Belgium) packet program was used to obtain a receiver operating characteristic (ROC) curve to test the overall discriminative ability of Hcy and fibrinogen for PSD. A two-tailed value of $P<0.05$ was considered significant.

Results

Clinical and demographic characteristics of non-PSD and early-onset PSD

The demographic and clinical characteristics are comprehensively elaborated in Table 1. Early-onset PSD was observed in 106 patients (27.89%), and non-PSD was observed in 274 patients (72.11%), respectively. In the early-onset PSD group, current smoking ($P=0.022$), NIHSS score ($P=0.004$), mRS ($P<0.001$), HAMD-17score ($P<0.001$), Hcy ($P<0.001$) and fibrinogen ($P<0.001$) were significantly higher than those in the non-PSD group, while the BI score ($P<0.001$) was significantly lower than those in the non-PSD group. In addition, serum Hcy and fibrinogen levels were compared among early-onset PSD of different severity (Figure 2). Plasma Hcy ($r=0.441$, $p<0.001$) and fibrinogen ($r=0.407$, $P<0.001$) were positively correlated with HAMD scores (Figure 3).

Logistic regression analysis for risk factors with early-onset PSD

Logistic regression models were used to examine the risk factors associated with early-onset PSD. Table 2 illustrates the results of crude models for early-onset PSD. Crude models showed that gender, current smoking, NIHSS score, mRS score, BI score, Hcy, and fibrinogen were associated with early-onset PSD ($P<0.05$). In addition, increased Hcy level depends on age. We classified age as a binary categorical variable. After adjustment for all potential confounders, fibrinogen (OR, 1.576; 95% CI 1.302–1.985, $P<0.001$) and Hcy (OR, 1.344; 95% CI 1.209–1.494, $P<0.001$) were identified as independent factors for early-onset PSD (Figure 4).

ROC curves for the Hcy and fibrinogen were used to test the overall discriminative ability for early-onset PSD

We employed ROC curves to test the overall discriminatory ability of Hcy and fibrinogen for early-onset PSD (Figure 5). We observed that the area under the curve (AUC) of the Hcy level to discriminate early-onset PSD was 0.754 (95% CI, 0.708–0.797, $P<0.001$), the optimal cutoff was 10.55, and the sensitivity and specificity were 67.7% and 73.5%, respectively. The AUC of the fibrinogen was 0.698 (95% CI, 0.649–0.744, $P<0.001$), the cutoff was 2.95, and the sensitivity and specificity were 47.2% and 86.7%, respectively. In addition, we also conducted an ROC analysis for the combination of Hcy and fibrinogen levels in discriminating between non-PSD and early-onset PSD. The AUC for Hcy and fibrinogen was 0.803 (95% CI: 0.759–0.842, $P<0.001$), the optimal cutoff was 0.69, and the sensitivity and specificity were 77.3% and 71.4%, respectively.

Discussion

Our findings provide several novel observations. First, patients in the early-onset PSD group had higher Hcy, fibrinogen, NIHSS scores and mRS scores and a lower BI score than patients in the non-PSD group. Second, the logistic regression model indicated that Hcy and fibrinogen were independent factors for early-onset PSD. Finally, based on ROC analysis, the Hcy combined fibrinogen exhibited respectable early-onset PSD discriminating power. Together, these data support the hypothesis that Hcy and fibrinogen were associated with early-onset PSD.

In our study, 27.89% of the patients were diagnosed with early-onset PSD at 2 weeks after stroke onset. Similar to our results, a meta-analysis reported that approximately 31% of stroke survivors were found to have depression at any time-point up to 5 years after stroke (36). We discovered that the early-onset PSD group showed a higher NIHSS and mRS score and a lower BI score compared to the non-PSD group, which indicated the higher severity of disability and stroke in the early-onset PSD group. Adverse physical conditions may be stressors for developing psychological problems like depression (37). Previous studies have shown that Hcy level increased with age (38). We classified age as a binary categorical variable, and after adjustment for all potential confounders, we discovered that serum levels of Hcy were independently related to early-onset PSD. The result indicated that high serum levels of Hcy in the acute phase of ischemic stroke may be a risk factor for early-onset PSD. Elevated serum Hcy levels at admission were associated with depression at 2 weeks and 6 months after stroke onset (18, 39), which is consistent with our findings. In addition, Hcy has been associated with depressive symptoms 1 year after stroke in older Swedish adults (40). Previous studies have shown that stroke patients with higher Hcy and lower folate levels may be more susceptible to PSD (41). A meta-analysis reports that serum Hcy level can be used as a biomarker to predict the risk of early-onset PSD (42). In our study, the Hcy exhibited

TABLE 1 Characteristics of patients in the non-PSD and PSD groups.

Variable	Non-PSD (n=274)	PSD (n=106)	T/Z	*P*
Demographic characteristics				
Age, years	64.42 ± 11.22	66.15 ± 12.04	-1.249	0.212
Male, n (%)	211(77.01)	70(66.04)	4.774	0.029
BMI, kg/m^2	23.69 ± 3.32	23.29 ± 3.56	1.283	0.202
Vascular risk factors, n (%)				
Hypertension	230(83.94)	82(77.36)	2.254	0.133
Diabetes mellitus	101(36.86)	35(33.02)	0.491	0.483
Coronary artery disease	49(17.88)	15(14.15)	0.760	0.383
Current smoking	148(54.01)	43(40.57)	5.530	0.019
Current drinking	66(24.09)	28(26.42)	0.222	0.637
Lesion location, n (%)			**4.667**	**0.097**
Anterior circulation	164(59.85)	74(69.81)		
Posterior circulation	96(35.04)	25(23.58)		
Both	14(5.11)	7(6.60)		
Medication use history, n (%)				
Previous antiplatelet	36(13.14)	12(11.32)	0.229	0.632
Previous statin	25(9.12)	9(8.49)	0.038	0.846
Previous antihypertension	158(57.67)	58(54.72)	0.271	0.603
Previous hypoglycemic agents	43(15.69)	15(14.15)	0.297	0.586
Neuropsychological evaluation				
NIHSS score, median (IQR)	1(1–3)	2(1–4)	-2.860	0.004
mRS score, median (IQR)	1(1–2)	2(1–3)	-3.663	<0.001
BI score, median (IQR)	95(75–100)	75(45–100)	-4.443	<0.001
HAMD-17score, median (IQR)	5(3–5)	11(8–15)	-14.787	<0.001
laboratory data				
WBC ($\times10^9$/L)	6.87 ± 1.88	6.68 ± 1.86	0.883	0.378
Neutrophils ($\times10^9$/L)	4.49 ± 1.64	5.57 ± 1.83	-0.584	0.559
Lymphocytes ($\times10^9$/L)	1.76 ± 0.68	1.61 ± 0.66	1.899	0.058
Cr (μmol/L)	71.76 ± 21.64	75.95 ± 38.81	-1.320	0.188
UA (μmol/L)	341.27 ± 81.87	328.27 ± 98.12	1.177	0.691
TG (mmol/L)	2.14 ± 2.09	2.51 ± 9.04	-0.398	0.496
TC (mmol/L)	4.55 ± 1.44	4.28 ± 1.08	1.923	0.055
HDL-C(mmol/L)	1.02 ± 0.30	1.02 ± 0.26	-0.071	0.944
LDL-C(mmol/L)	2.69 ± 0.96	2.51 ± 0.85	1.743	0.082
Fibrinogen (g/L)	2.4(2.2–2.8)	2.9(2.4–3.5)	-5.858	<0.001
Hcy (μmol/L)	9.55(6.88–10.78)	11.8(10–14)	-7.498	<0.001

NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; BI, Barthel Index; HAMD-17, Hamilton depression scale 17 items; WBC, white blood cell; Hcy, homocysteine; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; Cr, creatinine; UA, Uric acid. Values are shown as number (percentage) or as medians (IQR) and mean (SD). Differences in characteristics between groups were analyzed using one-way ANOVA test or Mann-Whitney U test for continuous variables as well as the chi-squared test or Fisher's exact test for categorical variables. A two-tailed value of P<0.05 was considered significant.

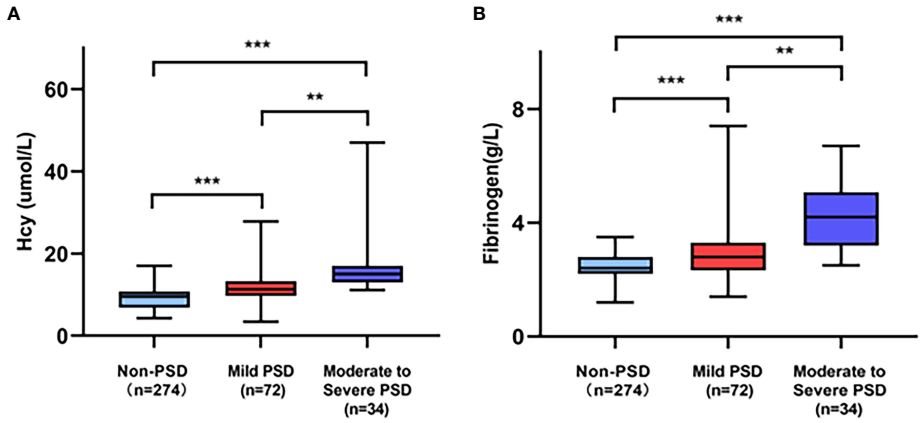

FIGURE 2
Comparison of serum Hcy **(A)** and fibrinogen **(B)** level among PSD of different severity. ***p<0.001, **p<0.01.

respectable early-onset PSD discriminating power with AUC values of 0.754, this is consistent with previous studies (43).

Previous studies have proposed that there are several factors influencing Hcy levels, such as age, sex, BMI, smoking, coffee drinking, poor nutrition, vitamin intake, folate, and ultraviolet radiation (44, 45). In our study, there was no significant correlation between age and Hcy. In addition, genetic variants in the folate and methionine cycles affect males and menopausal women differently (46). However, there was no significant relationship between Hcy concentrations and sex in our study. We believe that the variances in the ethnicity of the research populations, the small sample sizes, the medication status, and the severity of the condition may be the causes of the discrepancies between various studies.

The role of Hcy in early-onset PSD may involve multiple mechanisms. Firstly, an increase in Hcy levels can lead to a reduction in S-adenosylmethionine synthesis in the methionine cycle, which leads to depression (47). Secondly, hyperhomocysteinemia is toxic to nerve cells and endothelial cells. High serum Hcy levels cause mitochondrial dysfunction, leading to neuronal damage in the ischemic cerebral cortex and hippocampus of rats (48). Hcy can aggravate depression-like disorders in post-stroke rats (49). Meanwhile, Hcy exerts a neurotoxic effect on hippocampal neuronal cells by regulating ionic glutamate receptors and inducing apoptosis in hippocampal neurons (50), which promotes the occurrence and development of depression. Thirdly, elevated Hcy levels lead to vascular endothelial dysfunction (51) and an inflammatory response (52). Depression has been associated to the emergence and progression of proinflammatory cytokines, vascular endothelial cell injury and death, and disruption of the blood brain barrier (53, 54). Furthermore, a strong association between Hcy level and inflammation has been reported in various studies (9, 10), and inflammatory processes have been implicated in the pathophysiology of depression (55).

As a type of plasmatic coagulation factor and inflammatory marker, increased fibrinogen concentrations are common in ischemic stroke patients and associated with psychological distress (26). In our research, it was shown that fibrinogen levels were positively correlated with early-onset PSD severity. Furthermore, after adjustment for confounding factors, we found that serum fibrinogen levels were independently associated with early-onset PSD, consistent with previous findings (26, 28, 43). In this study, the AUC of the fibrinogen was 0.698 and may be used as a predictive indicator for early-onset PSD. Although the underlying mechanism

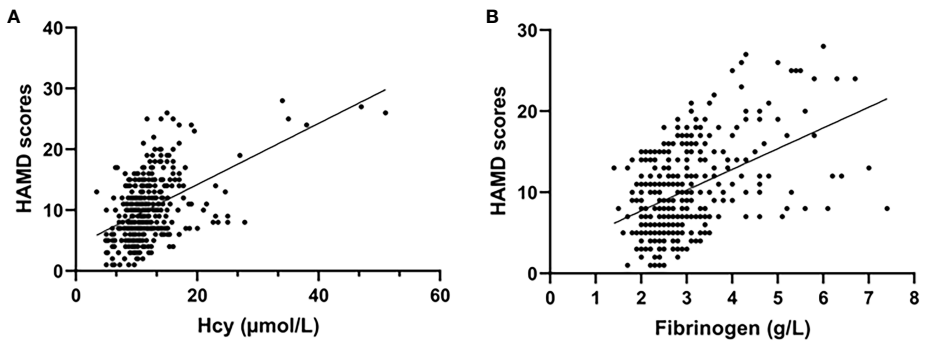

FIGURE 3
Correlation analysis between the plasma Hcy, fibrinogen and the HAMD scores in all patients. Scatter plots showing the plasma Hcy [r=0.441, p<0.001; **(A)**] and fibrinogen [r=0.407, P<0.001; **(B)**] were positively correlated with HAMD scores.

TABLE 2 Logistic regression analysis for risk factors associated with early-onset PSD.

Variable	OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Age < 65 years	Reference		Reference	
≥ 65 years	1.342(1.136–1.571)	0.135	1.012(0.993–1.032)	0.213
gender	0.561(0.329–0.957)	0.034	0.698(0.359–1.356)	0.288
Current smoking	0.585(0.368–0.929)	0.023	0.589(0.323–1.074)	0.084
NIHSS score	1.215(1.076–1.373)	0.002	1.001(0.812–1.235)	0.992
mRS score	1.483(0.840–1.632)	0.004	1.487(0.941–2.349)	0.089
BI score	1.142(1.041–1.255)	0.005	1.003(0.989–1.017)	0.523
fibrinogen	1.626(1.412–1.998)	<0.001	1.576(1.302–1.985)	<0.001
Hcy	1.405(1.270–1.555)	<0.001	1.344(1.209–1.494)	<0.001

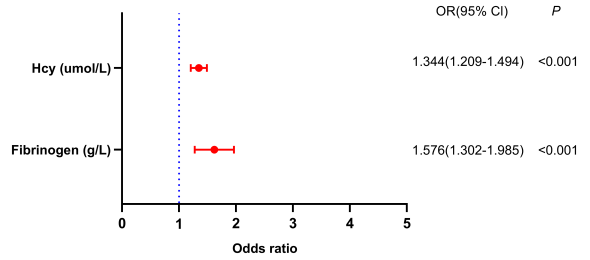

FIGURE 4
Binary logistic analysis of independent variables associated with early-onset PSD.

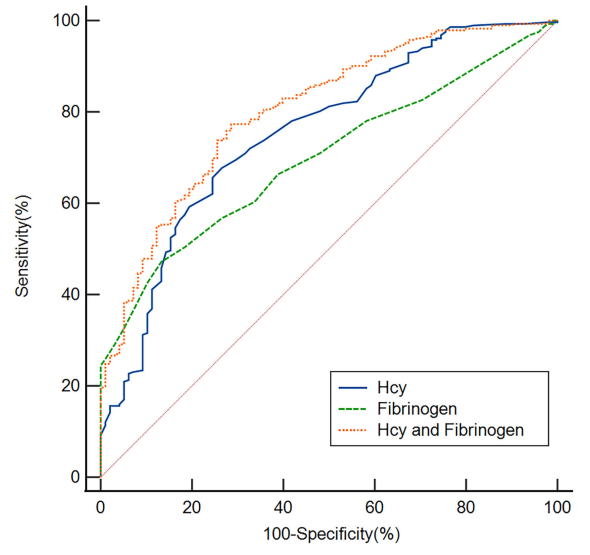

FIGURE 5
Based on ROC analysis, the Hcy, fibrinogen and Hcy combine fibrinogen exhibited respectable early-onset PSD discriminating power with AUC values of 0.754, 0.698 and 0.803, respectively.

by which elevated fibrinogen levels cause post-stroke depressive symptomology remains inconclusive, accumulating evidence supports the role of fibrinogen in the inflammatory response (56). Fibrinogen can increase during any inflammatory event and serves to control systemic inflammatory signals (57, 58). According to a study, fibrinogen might accumulate in inflammatory foci, and extravascular deposits would make inflammation worse (56). Moreover, *in vitro* experiments revealed the important role of fibrinogen in driving inflammation and identified the mechanism by which fibrinogen controls leukocyte function (56). Additionally, several studies have suggested that fibrinogen might be involved in the expression of proinflammatory cytokines IL-6, IL-1β, TNF-α, and IFN-γ (59, 60), and these inflammatory factors are involved in the pathogenesis of PSD (8).

In summary, our study indicates that Hcy and fibrinogen were associated with early-onset PSD. The results of our ROC curve analysis showed that the Hcy and fibrinogen levels had appropriate sensitivity and specificity to discriminate early-onset PSD. Clearly, the Hcy level is more discriminating than the fibrinogen, suggesting that the Hcy level at admission may be a useful tool to predict early-onset PSD. Finally, we found that the combination of Hcy and fibrinogen had a better ability to discriminate early-onset PSD with an AUC of 0.803, suggesting the combination of these two markers has a greater value in predicting early-onset PSD.

This study has the following limitations: (1) it was a single-center study with a relatively small sample size; therefore, the study findings still need to be further confirmed by multi-center and large-sample clinical studies; (2) patients with severe aphasia, unconsciousness, or dementia during hospitalization were excluded from the research, which would have resulted in biases in the prevalence of early-onset PSD; (3) our study did not include several risk variables that may impact depressive episodes, such as social support, educational background, and increasing life stress; (4) we observed PSD only 2 weeks after stroke onset. Short-term observational study conclusions might not be thorough enough; (5) patients were not tested for the vitamin B and folates levels. Future research needs to consider the effect of vitamins B and folate on Hcy levels; and (6) we did not collect homocysteine metabolism genes, and taking genetic factors into account will be important research in the future. To completely understand how Hcy and fibrinogen levels impact the incidence of early-onset PSD, more clinical research with large-scale, long-term intervention and follow-up is required.

Conclusion

In conclusion, our study indicated that elevated serum levels of Hcy and fibrinogen may be independent risk factors for early-onset PSD and can be used as predictive indicators for early-onset PSD. The combination of Hcy and fibrinogen may provide greater predictive value. Therapies that reduce serum Hcy and fibrinogen levels may be potential targets for intervention and prevention of early-onset PSD.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of the Affiliated Changsha Central Hospital, Hengyang Medical School, University of South China. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin because this is a retrospective study. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article because this is a retrospective study.

Author contributions

FL: Data curation, Formal analysis, Investigation, Methodology, Software, Writing – original draft. KS: Data curation, Formal analysis, Funding acquisition, Writing – review & editing. ZW: Data curation, Project administration, Supervision, Visualization, Writing – review & editing. WZ: Data curation, Investigation, Writing – original draft. JG: Data curation, Investigation, Writing – review & editing. SC: Data curation, Formal analysis, Methodology, Writing – review & editing. YT: Data curation, Validation, Writing – review & editing. WX: Project administration, Software, Supervision, Writing – review & editing. NZ: Conceptualization, Supervision, Validation, Writing – review & editing. MD: Conceptualization, Methodology, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2024.1371578/full#supplementary-material

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