

The Association Between Systemic Inflammatory Markers and Post-Stroke Depression: A Prospective Stroke Cohort

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Objective: Inflammation plays an important role in stroke. Many inflammatory markers in peripheral blood are proved to be associated with stroke severity or prognosis. But few comprehensive models or scales to evaluate the post-stroke depression (PSD) have been reported. In this study, we aimed to compare the level of systemic inflammation markers between PSD and non-PSD patients and explore the association of these inflammatory markers with PSD.

Methods: Totally, 432 ischemic stroke patients were consecutively enrolled in the study and received 1 month follow-up. We used the 17-Hamilton Rating Scale to measure depressive symptoms at 1 month after stroke. With the Hamilton Depression Scale score of >7 , patients were diagnosed with PSD. Systemic immune-inflammation index (SII), neutrophil-to-lymphocyte (NLR), platelet-to-lymphocyte (PLR) and derived neutrophil-to-lymphocyte ratio (dNLR) were calculated from the admission blood work.

Results: Finally, 129 patients (30.5%) were diagnosed with PSD at 1 month. PSD patients showed significantly higher levels of SII (501.27 (345.43–782.58) vs 429.60 (315.64–570.98), $P=0.001$), NLR (2.36 (1.77–3.82) vs 2.17 (1.56–2.80), $P=0.010$), dNLR (1.67 (1.30–2.51) vs 1.54 (1.16–1.99), $P=0.009$), PLR (124.65 (95.25–155.15) vs 109.22 (92.38–142.03), $P=0.015$), especially SII at admission as compared to non-PSD patients. In the logistic analysis, SII value (>547.30) was independently associated with the occurrence of PSD (OR=2.181, 95% CI=1.274–3.732, $p=0.004$), better than dNLR (OR=1.833, 95% CI=1.071–3.137, $p=0.027$), PLR (OR= 1.822, 95% CI=1.063–3.122, $p=0.029$) and NLR (OR=1.728, 95% CI=1.009–2.958, $p=0.046$).

Conclusion: Increased SII, PLR, dNLR, NLR, particularly SII at admission, are significantly correlated with PSD and may add some prognostic clues to find early discovery of PSD.

Keywords: inflammatory markers, post-stroke depression, systemic immune-inflammation index, neutrophil-to-lymphocyte, platelet-to-lymphocyte, derived neutrophil-to-lymphocyte ratio

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Introduction

Stroke is a multifactorial disease with high mortality and morbidity. There are approximately 3 million new strokes every year in China.^{1,2} It is well acknowledged that stroke can lead to pretty much further complications, such as cognitive impairment, disability, mental disorders and so on.^{3–5}

Post-stroke depression (PSD) is strongly associated with further worsening of physical and cognitive recovery, functional outcome and quality of life.⁶ A meta-analysis of

61 studies by Hackett and Pickles⁷ reported a pooled frequency of depression of 31% at any time up to five years following stroke, consistently with results found in a 10-year earlier review where the pooled frequency was 33%.⁸ Depression negatively affects patients' ability to engage in rehabilitation therapies. This emphasises the need of better evidence-based strategies of screening, prevention and therapy for PSD patients. Indeed, PSD remains relatively under-diagnosed, under-treated and under-researched. Despite of numerous clinical and experimental studies have been done, the pathophysiological mechanisms of PSD remain far from clear. The available evidence supports the reciprocal modulation of neurotransmitter systems, neuroinflammation, neuroendocrine activation, neuronal plasticity, vascular factors which may take effect in recognizing the disease process.^{9,10}

Several studies proved that patients developed a storm of inflammation in the body after stroke.^{11–14} Extensive investigations also suggested that high levels of pro-inflammatory and inflammatory markers were involved in the inflammatory response to depression, including interleukin-1, interleukin-18, interleukin-6 and tumor necrosis factor- α (TNF- α), interferon- γ (IFN- γ).^{15,16} Thus, researchers suspected whether inflammation was related with the occurrence of PSD and have confirmed this by animal experiments.¹⁷ In recent years, cell counting and their combinations such as neutrophil-to-lymphocyte (NLR), platelet-to-lymphocyte (PLR), derived neutrophil-to-lymphocyte ratio (dNLR) as classic hematological markers of systemic inflammation, were reported to be able to reflect sensitively the inflammatory response.^{18,19} Those indexes, derived from peripheral blood tests are easily available, have been validated to have a certain diagnostic value in a variety of tumors, coronary atherosclerotic heart disease, stroke and so on.^{20–22} Besides, previous studies found increased NLR, PLR were associated with the prevalence and poorer outcome of post-stroke depression.^{23,24} More recently, systemic immune-inflammation index (SII), a new Inflammatory biomarker, was constructed based on neutrophil, lymphocyte, and platelet count. As an easy-to-obtain indicator, the ratio of SII has been a research hotspot in diagnosing or predicting diseases, such as cardiovascular diseases, infections, inflammatory diseases, psychosis and several types of cancers.^{25,26} SII was first developed by Hu and expected to predict prognosis of hepatocellular carcinoma after surgery.²⁷ Hu's study demonstrated that the prediction ability of SII was more sensitive than those methods that use only one or two cell subtypes on hepatocellular carcinoma. Because inflammation plays a vital role in many diseases, now, there is continued interest in the inflammatory process in cerebrovascular

disease. Hou's study showed SII was associated with severity of acute ischemic stroke and might be more reasonable and effective in the evaluation of stroke than NLR and PLR.²⁸ Gabriela reported SII predicted poor outcome after spontaneous supratentorial intracerebral hemorrhage.²⁹ There have been several studies about SII and psychiatric disorders, especially depression. Mazza found a tight correlation between baseline SII and scores of depression and anxiety in COVID-19 survivors at follow-up.³⁰ A single study revealed higher SII levels were linked to poor prognosis in major depressive disorder,³¹ suggesting that it could be a marker of the low-grade inflammation observed in mood disorder.^{32,33}

To the best of our knowledge, the relationship between SII and PSD has not been reported to date. We aimed to investigate whether the levels of SII, as well as NLR, PLR and dNLR were associated with the occurrence, development and severity of disease in patients with PSD. We hypothesized that SII could better reflect the inflammatory status than other inflammatory markers in PSD.

Materials and Methods

Subjects

All acute ischemic stroke patients were from the Stroke Ward of the First Affiliated Hospital of Wenzhou Medical University, between 2014 and 2017. Four hundred and eighty-six patients consecutively participated in our study. The inclusion standards were: (i) patients aged between 18 and 80 years old, (ii) first-ever acute ischemic stroke happening within seven days at admission, (iii) diagnosed by computed tomography (CT) or magnetic resonance imaging (MRI), (iv) patients willing to sign the written informed consent. The exclusion standards were: (i) severe psychiatric history especially depression, (ii) any central nervous system disease, such as a diagnosis of dementia, Parkinson's disease or other significant cognitive impairment before stroke, (iii) the use of depression drugs, (iv) serious aphasia or dysarthria or hearing impairment or chronic inflammatory disease that might influence examination, (v) intracerebral hemorrhage, (vi) a history of stroke, (vii) severe heart, respiration, renal disease or cancer, (viii) patients that could not cooperate with us to complete a series of assessment.

Clinical Measurement

Demographic characteristics (age, gender, education, etc.), vascular risk factor (hypertension, diabetes mellitus, hyperlipidaemia, coronary heart disease, etc.), and

TOAST subtypes. The severity of stroke was assessed by experienced neurologists using the National Institutes of Health Stroke Scale (NIHSS) within 24h of admission. Functional outcomes were evaluated by the modified Rankin Scale (mRS) and Activities of Daily Living (ADL) at 1 month.

Psychological Measurement

All patients were evaluated by the 17-item Hamilton Depression Scale (HAMD)³⁴ at 1 month. Patients with HAMD score > 7 were considered to be diagnosed post-stroke depression according to the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th edition.

Laboratory Tests

All blood samples were collected by vacuum tubes the next morning (range: 05:00–08:00) after admission by trained nurses and tested by clinical laboratory technicians in a hospital certificated laboratory. White blood cell (WBC), neutrophil (N), lymphocyte (L), platelet (P) from the patients' first blood sampling were recorded after hospitalization. The formulas are as follows: NLR was calculated as neutrophil count/ lymphocyte count ($NLR=N/L$), PLR was calculated as platelet count/lymphocyte count ($PLR=P/L$), dNLR was calculated as neutrophil count/ (leukocyte count – neutrophil count) ($dNLR=N/N-W$) and SII was calculated as platelet count \times neutrophil count/ lymphocyte count ($SII=P \times N/L$).^{18,19,27}

Statistical Analyses

All statistical analysis was performed by SPSS 23.0. Categorical variables were represented as frequency and percentages were compared using χ^2 test. Continuous variables in normal distribution data described as means (SD) were compared using Student's *t*-test, whereas variables in non-normal distribution of data described as medians (quartiles) were compared using the Mann–Whitney *U*-test. Employing binary logistic regression analyzed the relationship between NLR, SII, PLR, dNLR and PSD when adjusted the confounding factors, such as age, gender, education, etc. $P < 0.05$ was considered statistically significant.

Results

Patients' Characteristics

A total of 423 patients with acute ischemic stroke were finally enrolled in the study (Figure 1). Among all follow-

up patients, 272 (64.3%) patients were male and the average age was 62.58 ± 10.27 years. The number of patients diagnosed with depression was 129 (30.5%) 1 month later. Meanwhile, patients in the PSD group were predominantly male (58%) and the average age was 62.0 ± 10.9 years. The proportion of current smokers was 18% and the average BMI was 24.35 ± 3.31 kg/m². The baseline characteristics of the 423 patients with PSD and those without were summarized in Table 1. We found significant difference of SII (501.27 (345.43–782.58) vs 429.60 (315.64–570.98), $P=0.001$), NLR (2.36 (1.77–3.82) vs 2.17 (1.56–2.80), $P=0.010$), dNLR (1.67 (1.30–2.51) vs 1.54 (1.16–1.99), $P=0.009$), PLR (124.65 (95.25–155.15) vs 109.22 (92.38–142.03), $P=0.015$), WBC ($p=0.012$), Neutrophil ($p=0.008$) and Lymphocyte ($p=0.022$) between patients with and without PSD. The score of HAMD in the PSD group was higher than Non-PSD group (9 (10–13) vs 3 (1–5), $p<0.001$) 1 month later. Moreover, there was a positive association between the SII levels and the HAMD scores ($r = 0.160$, $P=0.001$). The PSD group had a more severe stroke with NIHSS (3(2–6) vs.2(1–4), $p<0.001$) being higher at admission, as well as a worse functional outcome at 1 month with mRS (2(1–3) vs 1(1–2), $p<0.001$) being higher and the ADL being lower (95 (80–100) vs.100 (100–100), $p<0.001$). There was no obvious association between vascular risk factors, such as hypertension, diabetes mellitus, coronary heart disease, hyperlipidaemia and PSD. Stroke patients in small-artery occlusion seemed to be more susceptible to occur PSD.

Predictors of the Occurrence of Depression

We divided all patients into three subgroups according to tertiles of SII levels (tertile1, $<363.99 \times 10^9$ /L; tertile2, $363.99–547.30 \times 10^9$ /L; and tertile3, $>547.30 \times 10^9$ /L). The demographics and diagnostic parameters of subgroup analysis are shown in Table 2. With stroke patients taken as a whole, tertile 1 taken as the reference and the presence of PSD taken as a dependent variable for SII values in the logistic analysis, higher SII values (>547.30) remained independently associated with the occurrence of PSD (OR=2.181, 95% CI=1.274–3.732, $p=0.004$). Using the same methods, similar conclusion could be attained in Table 3 when the dNLR (OR=1.833, 95% CI=1.071–3.137, $p=0.027$) level was a continuous variable in the logistic regression analysis, as well as PLR (OR= 1.822, 95% CI=1.063–3.122,

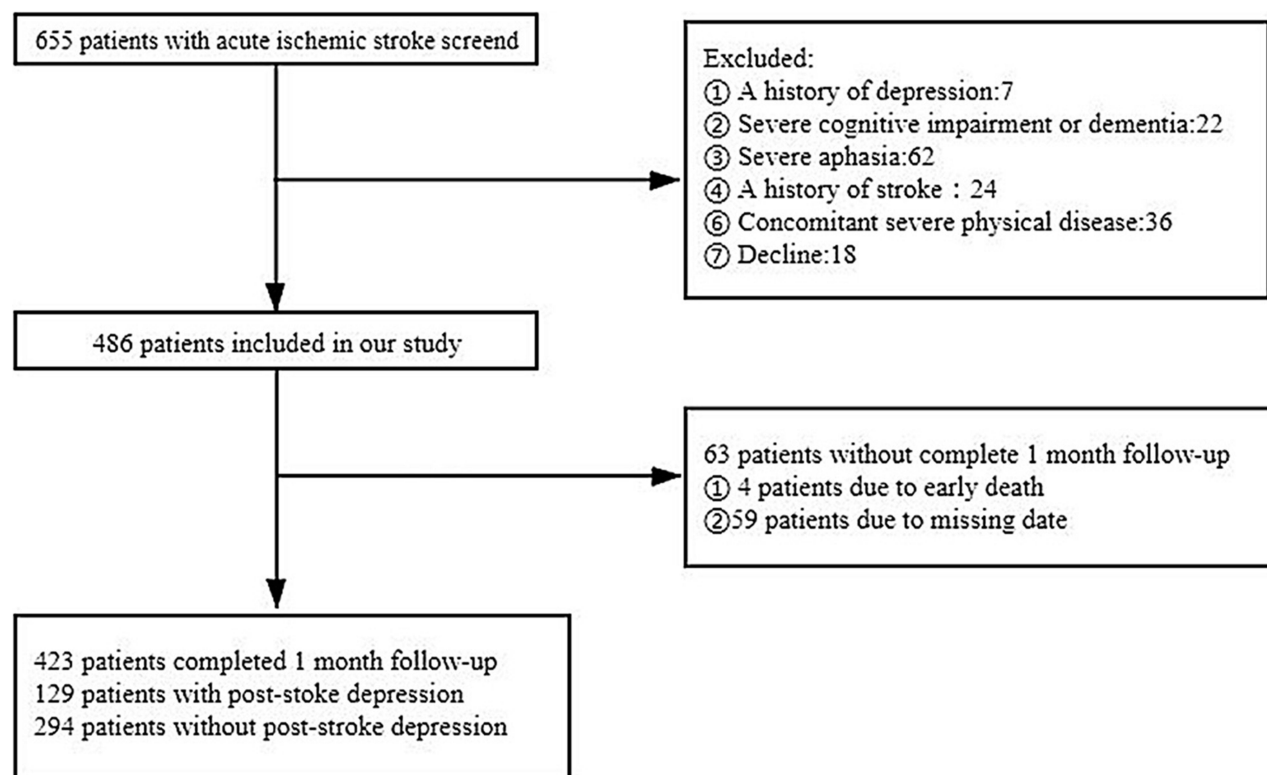


Figure 1 The process of screening patients in our study.

$p=0.029$) and NLR (OR =1.728, 95% CI=1.009–2.958, $p=0.046$) after adjustment for confounding factors that had already been established as predictors of PSD in others studies and that significantly differed between two groups on the univariate analysis, including age, gender, educational year, baseline NIHSS, Coronary heart disease (Table 4). Apparently, SII has the maximum OR value above-mentioned inflammatory indexes.

Discussion

As far as we know, this is the first study to explore the connection between early elevated SII, dNLR and the occurrence and development of PSD. In our study, patients with PSD had higher SII, dNLR, NLR, PLR than patients without PSD, respectively. Patients with acute ischemic stroke showing high SII, dNLR, PLR, NLR were more likely to develop PSD, especially high SII after adjusting for confounders. Our results demonstrated that the SII was a better indicator of risk of the development of PSD compared with dNLR, NLR, PLR.

In this study, we finally found 129 (30.5%) of acute ischemic stroke patients were diagnosed as depression 1

month later, which was in accordance with the results of previous studies.⁶ Furthermore, our study showed that PSD patients had poorer functional outcome and suffered more severe strokes.⁶ The correlation between NLR, PLR and PSD was also consistent with earlier studies.^{23,24}

PSD is a heterogeneous condition, and no single pathophysiological mechanism can fully explain PSD. According to some researches,^{35,36} one of the assumptions is that PSD is a multisystem inflammatory disease, both centrally and peripherally. Abnormal inflammatory response is linked to PSD. These inflammatory biomarkers alter neurotransmission and induce severe dysfunction in the brain. When acute ischemic stroke happens, neutrophils first migrate from peripheral blood vascular to the ischemic brain within a few minutes³⁷ and release pro-inflammatory biomarkers, such as matrix metalloproteinases 9 (MMP9), cytokines (IL-6 etc), chemokines (MCP-1 etc), proteolytic enzyme, oxygen-free radicals and so on.^{38,39} These inflammatory mediators trigger a series of excitotoxic inflammatory response. At the same time, platelets aggregate in the point of lesion. Through combining with PSGL-1 and Mac-1, platelets cooperate with infiltrated neutrophils to activate platelet function and change the characteristics of endothelial cells, leading to more neutrophils to

Table 1 Clinical and Demographic Characteristics of Participants

Baseline Characteristics	Non-PSD (n=294)	PSD (n=129)	P
Demographic characteristics			
Male (%)	197(67)	75(58)	0.098
Age (y), mean±SD	62.8±10.0	62.0±10.9	0.433
Educational(y), mean ±SD	4.4±4.3	4.1±3.5	0.527
BMI(kg/m ²), mean±SD	24.25±7.85	24.35±3.31	0.919
Vascular risk factors (%)			
Hypertension	214(72)	94(73)	1.00
Diabetes mellitus	65(22)	29(22)	1.00
Coronary heart disease	20(7)	4(3)	0.171
Hyperlipidaemia	22(7)	15(14)	0.134
Alcohol consumption	122(41)	42(33)	0.084
Current smoking	56(19)	23(18)	0.892
TOAST subtypes			
LAA	202(69)	84(65)	0.499
CE	66(22)	23(18)	0.303
SAO	26(9)	22(17)	0.019
Laboratory tests			
WBC (10 ⁹ /L)	6.6±1.8	7.1±1.8	0.012
Neutrophil (%)	60.3±9.2	63.2±10.7	0.008
Platelet (10 ⁹ /L)	206.3±52.5	215.8±55.1	0.092
Lymphocyte (%)	28.9±8.4	26.4±10.4	0.022
Neuropsychological function			
NIHSS score media (IQR)	2(1–4)	3(2–6)	<0.001
mRS score at 1 month media (IQR)	1(1–2)	2(1–3)	<0.001
ADL score at 1 month media (IQR)	100(100–100)	95(80–100)	<0.001
HAMD at 1 month media (IQR)	3(1–5)	9(10–13)	<0.001
NLR media (IQR)	2.17(1.56–2.80)	2.36(1.77–3.82)	0.010
PLR media (IQR)	109.22 (92.38–142.03)	124.65 (95.25–155.15)	0.015
SII (10 ⁹ /L) media (IQR)	429.60 (315.64–570.98)	501.27 (345.43–782.58)	0.001
dNLR media (IQR)	1.54(1.16–1.99)	1.67(1.30–2.51)	0.009

Notes: Data are presented as number of patients (%) or median (interquartile range). **Abbreviations:** BMI, body mass index; LAA, large-artery atherosclerosis; CE, cardioembolism; SAO, small-artery occlusion; WBC, white blood cell; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; ADL, activities of daily living; IQR, interquartile range; SD, standard deviation.

Table 2 Baseline Characteristics of the Three Groups of SII

	Tertile1 (n=141)	Tertile2 (n=141)	Tertile3 (n=141)	P
SII (10 ⁹ /L)	<363.99	363.99–547.30	>547.30	<0.001
Male (%)	84(60)	97(69)	91(65)	0.270
Age (y), mean±SD	62.2±10.6	61.3±11.0	64.3±8.9	0.087
Educational (y), mean±SD	4.6±4.2	4.6±4.5	3.7±3.4	0.143
BMI (kg/m ²), mean ±SD	25.18 ±10.84	24.21 ±2.89	23.40 ±3.51	0.143
Vascular risk factors (%)				
Hypertension	100(71)	106(75)	102(72)	0.716
Diabetes mellitus	33(23)	37(26)	24(17)	0.162
Coronary heart disease	10(7)	10(7)	10(7)	1.00
Hyperlipidaemia	13(10)	12(9)	11(8)	0.913
Alcohol consumption	50(35)	56(40)	58(41)	0.596
Current smoking	18(13)	25(18)	36(26)	0.021
TOAST subtypes				0.094
LAA	103(73)	95(67)	88(62)	
CE	27(19)	33(23)	29(21)	
SAO	11(8)	13(10)	24(17)	
NIHSS score media (IQR)	2(1–4)	2(1–4)	3(1–5)	0.193

assemble in the brain edema region.⁴⁰ Consecutive inflammatory reaction finally destroys the blood–brain barrier. Once the blood–brain barrier is damaged, our body will turn down the immune response in order to reduce the potential inflammation in the lesion. Lymphocytes also play an important role in inflammation, although the pathogenesis of lymphocytes might be controversial. Lymphocytes consisting of B and T cells, particularly CD4⁺, CD8⁺ T cells, can produce several cytotoxic substances and pro-inflammatory cytokines, nevertheless some researches report that lymphocytes have a protective effect towards inflammation.⁴¹ Stroke can also activate the pathway of the sympathetic nervous system, parasympathetic nervous system and hypothalamus pituitary adrenal axis, which induces the apoptosis of lymphocytes or transforms the percentage of lymphocytes.⁴² Those inflammatory and pro-inflammatory cytokines are thought to play an important role in the etiology of depression at the same time.^{15,16} It has been found that patients with

Table 3 Factors Associated with PSD by Multivariate Logistic Regression Analysis

		Model1		Model2		Model3	
		OR(95% CI)	p	OR(95% CI)	p	OR(95% CI)	p
SII	Int vs low	0.927(0.540–1.591)	0.783	0.948(0.550–1.637)	0.849	0.977(0.556–1.717)	0.935
	High vs low	2.099(1.266–3.478)	0.004*	2.236(1.336–3.744)	0.002*	2.181(1.274–3.732)	0.004*
NLR	Int vs low	0.573(0.346–0.951)	0.031	1.052(0.617–1.791)	0.853	0.942(0.542–1.639)	0.833
	High vs low	0.594(0.359–0.984)	0.043*	1.820(1.083–3.056)	0.024*	1.728(1.009–2.958)	0.046*
PLR	Int vs low	1.115(0.657–1.892)	0.686	1.096(0.644–1.864)	0.735	1.055(0.607–1.833)	0.850
	High vs low	1.810(1.089–3.010)	0.022*	1.845(1.101–3.091)	0.020*	1.822(1.063–3.122)	0.029*
dNLR	Int vs low	1.076(0.633–1.829)	0.787	1.136(0.664–1.944)	0.642	1.080(0.620–1.881)	0.787
	High vs low	1.865(1.123–3.099)	0.016*	1.993(1.190–3.341)	0.009*	1.833(1.071–3.137)	0.027*

Notes: Model 1 was not adjusted for any variables. Model 2 was adjusted for age, gender and education years. Model 3 was adjusted for age, gender, education years, baseline NIHSS, Coronary heart disease. *Indicates statistically significant.

schizophrenia have increased levels of pro-inflammatory cytokines, such as IL1B, IL-6 and IL-8.⁴³ In another study, pro-inflammatory cytokine levels were improved after anti-depressant therapy.⁴⁴ Depression increased leukocyte and neutrophil levels, while they decreased lymphocytes.⁴⁵ Our research also testified that patients with depression after stroke had significantly higher level of white blood cell, neutrophils, platelets and lower lymphocytes than patients without depression.

However, there are still no exact biomarker to reflect inflammation in PSD up to now.

The blood routine test is a must-check examination for all patients admitted to the hospital. Inflammatory indexes can be obtained by simple calculation using existing items in the blood routine test. Thanks to the convenience and low price, inflammatory index have the potential to be widely used in clinic and have become a hot research field in recent year. A series of novel inflammatory factors measured in peripheral blood have provided useful information for predicting future events in several different clinical settings, mainly including NLR, dNLR, PLR, and SII. There is Chen's study

Table 4 Univariate Logistic Regression Analysis Factors Related to Severity of PSD

Univariate Analysis				
Variables	B	HR	95% CI	P-value
Sex	−0.380	0.684	0.447–1.047	0.080
Age	−0.008	0.992	0.972–1.012	0.432
Educational	−0.017	0.983	0.933–1.036	0.527
BMI	0.001	1.001	0.971–1.033	0.937
Hypertension	−0.004	0.996	0.625–1.586	0.987
Diabetes mellitus	−0.021	0.979	0.596–1.608	0.933
Coronary heart disease	1.109	3.302	1.306–8.873	0.043*
Hyperlipidaemia	−0.537	0.585	0.291–1.175	0.132
Alcohol consumption	0.385	1.469	0.951–2.271	0.083
Current smoking	0.081	1.084	0.634–1.855	0.767
NIHSS score	0.197	1.218	1.123–1.321	<0.001*
SII	0.390	1.478	1.140–1.915	0.003*
NLR	0.252	1.287	0.997–1.662	0.053*
dNLR	0.321	1.379	1.066–1.783	0.014*
PLR	0.304	1.355	1.048–1.752	0.020*

Notes: *Indicates statistically significant.

showing the increased NLR at admission correlates with PSD and may help doctors get some prognostic information for the early discovery of PSD.²³ Huang indicates PLR is a significant and independent biomarker to predict the development of PSD.²⁴ In order to describe inflammatory reaction more comprehensively, SII adds platelet counts into the formula of NLR and could be more rational and extensive in the evaluation of PSD. Higher SII generally showed that inflammatory response of patients enhanced and the immune response decreased.

Platelets are not a result of inflammation, but also a predictor of inflammation. Activated platelets increase the risk of cardio-cerebrovascular diseases and mental disorders, including depression.⁴⁶ Inflammation induces dense granules within activated platelets releasing 5-hydroxytryptamine (5-HT) and other proinflammatory molecules such as cytokines, metalloprotein TF, P-selectin, CD40L that play an important role in the occurrence of depression.⁴⁷ In addition, pro-inflammatory factors and activated platelets may have a negative effect on phosphorylation and expression of brain-derived neurotrophic factor (BDNF) and BDNF receptor (TrkB) involved in the pathogenesis of depression.⁴⁸

Our study primarily certified that higher SII was independently associated with higher risk of developing PSD. To diagnose and treat PSD, monitoring their changes over time, regular follow-up of PLR, dNLR, NLR, especially SII may be a cheap, easy and effective strategy for PSD screening and management. High-level SII at admission could give physicians some diagnostic and prognostic clues to detect early PSD for stroke patients, which may lead to a better treatment. This will also help investigate how the immune-inflammatory reaction translates into psychiatric illness promoting our knowledge in the etio-pathogenesis of these mental disorders.

This study also had some inevitable limitations. First, it was a single-center study with 423 cases enrolled. Second, we only recorded the SII, NLR, PLR, dNLR once at a time at admission. It is indispensable to take routine blood tests constantly in order to investigate the association of dynamic changes in blood index after stroke. Third, we failed to check the medication history before hospitalization of participants such as Aspirin, which may affect the results.

Conclusion

In conclusion, higher levels of SII, dNLR, NLR and PLR were associated with an increased prevalence of PSD. At the

same time, SII was a more effective indicator superior to other inflammatory markers in the development of PSD.

Ethics Statement

This study obtained the approval by the Medical Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University. Patients all signed the written informed consents before participating in our study. The study project conforms to the ethical guidelines of the Declaration of Helsinki. The data was kept confidential and not shared.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships and a potential conflict of interest.

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