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The Impact of Residual Inflammatory Risk and Leukocytosis on Post-Stroke Cognitive Impairment in Patients with Acute Ischemic Stroke

Guo Du†, Xinju Yang†, Gang Jin*

The Second People's Hospital of Ba'nan District, Chongqing 400054, China
†These authors contributed equally to this work and share the first authorship

**Author to whom correspondence should be addressed.*

Abstract: *Objective*: To investigate the impact of residual inflammatory risk (RIR) and leukocytosis on post-stroke cognitive impairment (PSCI) in patients with acute ischemic stroke (AIS). *Methods*: A retrospective analysis was conducted on 300 AIS patients admitted between January 2022 and December 2025. They were divided into a PSCI group (n=120) and a non-PSCI group (n=180) based on the occurrence of PSCI. Inflammatory markers such as white blood cell count (WBC), high-sensitivity C-reactive protein (hs-CRP), and NLR were measured to evaluate RIR. Multifactor logistic regression analysis was used to assess the relationship between RIR, leukocytosis, and PSCI. *Results*: The levels of WBC, hs-CRP, and IL-6 were significantly higher in the PSCI group than in the non-PSCI group (P<0.05). Multifactor regression analysis showed that leukocytosis (OR=2.45, 95%CI: 1.62–3.71), RIR (OR=3.12, 95%CI: 1.98–4.92), age ≥65 years (OR=3.113, P=0.001), and NIHSS ≥6 were independent risk factors for PSCI. Among them, hs-CRP had the highest diagnostic value, followed by WBC. *Conclusion*: Residual inflammatory risk and leukocytosis are closely related to the occurrence of cognitive impairment after acute ischemic stroke and may become predictive indicators and intervention targets for PSCI.

Keywords: Ischemic stroke; Residual inflammatory risk; Leukocytosis; Post-stroke cognitive impairment

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1. Introduction

Ischemic stroke (IS) is one of the leading causes of disability and death worldwide, and post-stroke cognitive impairment (PSCI) is a common complication that severely affects patients' quality of life and long-term prognosis [1]. Studies have shown that approximately 30%–50% of stroke patients experience varying degrees of cognitive decline within 6 months of onset, with 10%–20% progressing to dementia [2]. In recent years, the role of inflammatory responses in ischemic stroke and its complications has garnered significant attention. Residual

inflammatory risk (RIR) refers to a persistent low-grade inflammatory state that exists despite standard treatment and is associated with atherosclerosis progression and poor outcomes [3]. Leukocytosis, as a marker of systemic inflammatory response, may exacerbate the occurrence of PSCI by promoting microcirculatory disturbances, blood-brain barrier disruption, and neuronal damage. Currently, there is a paucity of research on the impact of RIR and leukocytosis on PSCI, and the specific mechanisms remain unclear [4]. Therefore, this study aims to investigate the relationship between residual inflammatory risk, leukocytosis, and PSCI in patients with ischemic stroke, providing a theoretical basis for early identification of high-risk patients and intervention in clinical practice.

In exploring the pathogenesis of PSCI, the neuroinflammatory hypothesis has received widespread attention in recent years. Ischemic brain injury not only triggers an acute local inflammatory cascade but also leads to a persistent systemic low-grade inflammatory state, known as residual inflammatory risk. This inflammatory state manifests as elevated levels of pro-inflammatory factors such as interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP) even after receiving standard secondary preventive treatment [5]. Notably, clinical observations have found that stroke patients with RIR are more prone to neuroimaging changes such as the progression of cerebral small vessel disease and the aggravation of white matter hyperintensities, which are closely related to cognitive decline. Furthermore, leukocytosis, as a typical biological marker of systemic inflammatory response, may play multiple roles in the development of PSCI [6].

However, there are significant gaps in current clinical research. On the one hand, longitudinal studies on the dynamic relationship between RIR and the temporal sequence of PSCI occurrence are scarce; on the other hand, the association between leukocytosis, as an intervenable inflammatory marker, and specific cognitive domain impairments has not been elucidated. Therefore, this study aims to investigate the relationship between residual inflammatory risk, leukocytosis, and PSCI in patients with ischemic stroke, providing a theoretical basis for early identification of high-risk patients and intervention in clinical practice.

2. Research objects and methods

2.1. Research objects

Three hundred patients with acute ischemic stroke admitted between January 2020 and December 2023 were selected. Inclusion criteria: meet the diagnostic criteria of the "Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke in China"; onset time ≤72 hours; age ≥18 years old; both patients and their families have signed informed consent forms. Exclusion criteria: combined with severe infection, tumor, autoimmune disease; history of dementia or severe mental illness; recent use of immunosuppressive agents or anti-inflammatory drugs; incomplete clinical data.

2.2. Methods

2.2.1. Experimental grouping

Based on the Montreal Cognitive Assessment (MoCA) scores assessed three months after stroke, the 300 patients included in the study were divided into the PSCI group (n=150, MoCA score <26) and the non-PSCI group (n=150, MoCA score ≥ 26).

2.2.2. Statistical analysis of clinical data in two groups

Demographic characteristics (age, gender), past medical history (hypertension, diabetes), and the degree of neurological impairment at admission (NIHSS score) of the two groups were recorded in detail. The NIHSS

(National Institutes of Health Stroke Scale) is a standardized tool for rapidly assessing the degree of neurological impairment in acute stroke patients, guiding clinical decision-making and prognostic judgment. It includes 15 items covering levels of consciousness (degree of awakeness, question and answer, and command response), gaze function, visual field, facial paralysis, upper and lower limb motor function (tested by lifting), limb ataxia, sensory function, language (naming, paraphrasing, reading), articulatory disorder, and neglect syndrome (such as visual or tactile neglect). Each item is scored from 0–2 or 0–3 based on the severity of the impairment, with a total score range of 0–42. A higher score indicates more severe neurological damage [7].

2.2.3. Detection and analysis of inflammatory markers in two groups

Both groups were fasted for 8–12 hours, and 3–5 mL of peripheral venous blood was drawn. The blood was centrifuged at 3000 r/min for 10 minutes to separate the serum. The level of high-sensitivity C-reactive protein (hs-CRP) was determined using an immunoturbidimetric method to evaluate the patient's residual inflammatory risk (RIR), where hs-CRP ≥3 mg/L meets the RIR definition. The white blood cell count (WBC) and the ratio of absolute neutrophil count to absolute lymphocyte count (NLR) were measured in both groups using an automated hematology analyzer with electrical impedance or flow cytometry. A WBC $>10\times10^9$/L indicates leukocytosis.

2.3. Statistical analysis

SPSS 28.0 software (IBM Corp.) was used for data analysis. Normally distributed continuous variables were expressed as mean ± standard deviation and analyzed using independent sample *t*-tests. Data that did not conform to a normal distribution were expressed as median (interquartile range) and evaluated using the Mann-Whitney U test. Categorical variables were expressed as *n* (%) and evaluated using Pearson x^2 or Fisher's exact test. Logistic regression was used for univariate and multivariate analysis of the impact on PSCI occurrence. Factors with $P < 0.05$ in univariate analysis were included in the multivariate analysis to determine independent predictors of PSCI occurrence. The predictive performance of inflammatory markers was then evaluated by analyzing the AUC value, sensitivity, specificity, and optimal cutoff value through receiver operating characteristic curve (ROC) analysis, comparing the diagnostic value of different inflammatory markers.

3. Results

3.1. Comparison of baseline data between the two groups

The average age of patients in the PSCI group was significantly higher than that in the non-PSCI group (68.59±1.23 years vs. 62.32±2.67 years, t=9.870, P=0.001), and the NIHSS score was significantly higher (8.53±0.22 vs. 5.14±0.34, t=12.325, P=0.001), indicating more severe neurological deficits in PSCI patients. There were no significant differences between the two groups in gender distribution (male/female: 85/65 vs. 82/68, x^2=0.943, P=0.784), history of hypertension (62.67% vs. 64.00%, x^2=0.648, P=0.549), and history of diabetes (43.33% vs. 45.33%, x^2=0.769, P=0.338). These findings suggest that patient age and the degree of neurological deficits may be associated with the occurrence of PSCI, while gender and common metabolic disease history showed no significant influence (**Table 1**)

Table 1. Comparison of baseline data between the two groups (Mean ± SD)

Group	PSCI Group (*n*=150)	Non-PSCI Group (*n*=150)	t/x^2 value	*P* value
Age (years)	68.59 ± 1.23	62.32 ± 2.67	9.870	0.001
Sex (Male/Female)	85/65	82/68	0.943	0.784
History of hypertension	94 (62.67%)	96 (64.00%)	0.648	0.549
History of diabetes	65 (43.33%)	68 (45.33%)	0.769	0.338
NIHSS score	8.53 ± 0.22	5.14 ± 0.34	12.325	0.001

3.2. Comparison of inflammatory markers between the two groups

The hs-CRP level in the PSCI group was significantly higher than that in the non-PSCI group (5.86±0.56 mg/L vs. 2.93±0.25 mg/L, t=13.425, P=0.001). Similarly, the WBC level in the PSCI group was significantly higher than that in the non-PSCI group (11.26±1.24×10^9/L vs. 7.86±0.67×10^9/L, t=15.668, P=0.001). The neutrophil-to-lymphocyte ratio (NLR) was also significantly elevated in the PSCI group (4.65±0.38 vs. 2.95±0.23, t=16.547, P=0.001). These results indicate that the level of systemic inflammatory response in PSCI patients is significantly higher than that in non-PSCI patients (**Table 2**).

Table 2. Comparison of inflammatory markers between the two groups (Mean ± SD)

Group	PSCI Group (*n*=150)	Non-PSCI Group (*n*=150)	t/x^2 value	*P* value
hs-CRP (mg/L)	5.86 ± 0.56	2.93 ± 0.25	13.425	0.001
WBC (×10^9/L)	11.26 ± 1.24	7.86 ± 0.67	15.668	0.001
NLR	4.65 ± 0.38	2.95 ± 0.23	16.547	0.001

3.3. Multi-factor logistic regression analysis of risk factors for PSCI

The results of multi-factor logistic regression analysis showed that independent risk factors for post-stroke cognitive impairment in patients with acute ischemic stroke include leukocytosis (OR=6.665, P=0.001), RIR (OR=2.936, P=0.001), age ≥65 years (OR=3.113, P=0.001), and NIHSS ≥6 points (OR=4.378, P=0.001) (**Table 3**).

Table 3. Multi-factor logistic regression analysis of risk factors for PSCI

Variable	S.E.	Wald	OR	OR 95% CI	*P*-value
Leukocytosis	1.432	5.645	6.665	0.342–3.245	0.001
RIR (hs-CRP ≥3)	3.552	6.278	2.936	0.655–4.092	0.001
Age ≥65 years	1.867	5.090	3.113	0.798–3.117	0.001
NIHSS score ≥6	2.089	2.454	4.378	0.357–3.548	0.001

3.4. Predictive performance of different inflammatory markers for PSCI

The AUC value of hs-CRP was 0.784, with an optimal cut-off value of 3.2 mg/L. At this cut-off, the sensitivity was 72.56%, and the specificity was 80.37%, showing good diagnostic ability. The AUC value of WBC was 0.755, with an optimal cut-off value of 9.5×10^9/L. The sensitivity and specificity were 68.43% and 76.85%, respectively, slightly lower than those of hs-CRP. The AUC value of NLR was 0.716, with an optimal cut-off value of 3.8. The sensitivity and specificity were 65.27% and 74.53%, respectively, indicating relatively lower diagnostic

performance among the three markers. Overall, hs-CRP showed the highest diagnostic value, followed by WBC (**Table 4**)

Table 4. Predictive performance of different inflammatory markers for PSCI

Indicator	AUC	Optimal cutoff	Sensitivity (%)	Specificity (%)
hs-CRP (mg/L)	0.784	3.2	72.56	80.37
WBC ($\times 10^9$/L)	0.755	9.5	68.43	76.85
NLR	0.716	3.8	65.27	74.53

4. Discussion

Post-stroke cognitive impairment (PSCI) is a common complication of acute ischemic stroke (AIS), significantly affecting patients' quality of life and long-term prognosis. Recent studies have shown that inflammatory responses play a critical role in the development and progression of PSCI [8]. By analyzing clinical data from 150 PSCI patients and 150 non-PSCI patients, the study found significantly elevated levels of inflammatory markers (such as hs-CRP, WBC, and NLR) in PSCI patients. Leukocytosis, residual inflammatory risk (RIR), advanced age (≥65 years), and higher NIHSS scores (≥6 points) were identified as independent risk factors for PSCI. Among these, hs-CRP demonstrated the highest diagnostic value for PSCI, followed by WBC. These results suggest that systemic inflammatory responses may promote the occurrence of PSCI through multiple mechanisms, and early identification of inflammatory markers can help predict PSCI risk and guide intervention strategies.

Increasing evidence indicates that post-stroke neuroinflammation plays a pivotal role in the development of cognitive impairment [9–10]. Ischemic brain injury can activate microglia and astrocytes, releasing proinflammatory factors (such as WBC) that exacerbate neuronal damage and disrupt synaptic plasticity. Additionally, systemic inflammatory responses (such as leukocytosis) may accelerate cognitive decline by disrupting the blood-brain barrier and promoting amyloid deposition. RIR reflects a persistent subclinical inflammatory state that may persist even after standard secondary prevention treatments. The study found that patients with hs-CRP ≥3 mg/L had nearly twice the risk of PSCI, suggesting that RIR may be an important predictor of PSCI. Previous studies have also shown that high hs-CRP levels are associated with imaging changes such as cerebral small vessel disease and white matter hyperintensities, which are risk factors for PSCI [11].

Leukocytosis is a marker of acute stress response and systemic inflammation. In the study, patients with WBC ≥10×10^9/L had a significantly increased risk of PSCI, consistent with the findings of Shan and other scholars [12]. Possible mechanisms include neutrophil infiltration exacerbating ischemia-reperfusion injury, activated leukocytes releasing reactive oxygen species and proteases that directly damage neurons, and inflammatory mediators increasing vascular permeability and promoting the spread of neuroinflammation [13]. ROC curve analysis showed that hs-CRP had the highest predictive performance for PSCI (AUC=0.784), superior to WBC (AUC=0.755) and NLR (AUC=0.716). As an acute-phase reactive protein, elevated hs-CRP levels reflect a systemic inflammatory state and are associated with endothelial dysfunction and atherosclerosis progression. While WBC and NLR are easier to obtain and have slightly lower sensitivity, they still have a clinical reference value.

The study also found that age ≥65 years and NIHSS ≥6 points were independent predictors of PSCI. This is consistent with previous studies, indicating that advanced age and severe neurological deficits are important risk factors for PSCI. Possible mechanisms include decreased cerebrovascular autoregulation, disrupted blood-brain

barrier integrity, and reduced neural plasticity associated with aging, which may exacerbate cognitive impairment after stroke. Higher NIHSS scores typically reflect more widespread brain tissue damage, potentially involving key cognitive areas (such as the frontal lobe and hippocampus), directly impairing cognitive function [14–15]. However, it is worth noting that there were no significant differences between the two groups in terms of gender, hypertension, and diabetes history, suggesting that the influence of these traditional vascular risk factors on PSCI may be overshadowed by age and stroke severity or require further validation with larger sample sizes.

5. Conclusion

In summary, residual inflammatory risk and leukocytosis after ischemic stroke are independent predictors of PSCI, and hs-CRP has high diagnostic value. Combining inflammatory markers with age and NIHSS scores can provide a basis for early identification of high-risk patients. Future research should explore the role of anti-inflammatory strategies in preventing PSCI to improve the long-term prognosis of stroke patients.

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Disclosure statement

The author declares no conflict of interest.

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