

Residual Inflammatory Risk Is Associated with Cognitive Impairment After Acute Ischemic Stroke

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Objective: Acute ischemic stroke (AIS) may lead to varying degrees of cognitive impairment, while the inflammatory response plays a significant role in this process. This study aims to examine the relationship between residual inflammation risk (RIR) and the development of post-stroke cognitive impairment (PSCI) in patients with acute ischemic stroke.

Methods: This prospective cohort study enrolled a total of 172 patients diagnosed with AIS over the study period from January 2024 to December 2024. They were divided into four groups: RIR only [low-density lipoprotein cholesterol (LDL-C) < 2.6 mmol/L and high-sensitivity CRP (hsCRP) ≥ 2 mg/L], residual cholesterol risk (RCR) only (LDL-C ≥ 2.6 mmol/L and hsCRP < 2 mg/L), both risk or residual cholesterol and inflammatory risk (RCIR) (LDL-C ≥ 2.6 mmol/L and hsCRP ≥ 2 mg/L), and neither risk (LDL-C < 2.6 mmol/L and hsCRP < 2 mg/L). PSCI is defined as a Montreal Cognitive Assessment (MoCA) score below 22 at 6 months after stroke. The final analysis included 172 patients who completed the follow-up. The association between RIR and PSCI was analyzed by multivariable logistic regression analyses.

Results: Among the 172 enrolled patients, 58 (33.7%) developed PSCI. The proportion of patients with neither risk, RIR, RCR, and RCIR was 23.8% (n=41), 18.6% (n=32), 32.0% (n=55) and 25.6% (n=44), respectively. Compared to those without PSCI, patients with PSCI had a higher prevalence of hyperlipidemia ($P = 0.026$), a greater proportion of RIR ($P = 0.015$), and higher white blood cell count ($P = 0.042$) and neutrophil count ($P = 0.016$). Logistic regression analysis, adjusting for major confounding factors, identified RIR as an independent factor associated with PSCI occurrence (OR 4.496, 95% CI 1.571–17.477, $P = 0.030$; RCIR: OR 7.357, 95% CI 2.081–26.006, $P = 0.002$).

Conclusion: This study presents what is, to our knowledge, the first evidence that RIR is associated with PSCI among acute ischemic stroke patients.

Keywords: residual inflammatory risk, post-stroke cognitive impairment, acute ischemic stroke

Introduction

Stroke remains a leading global cause of death and disability. Acute ischemic stroke (AIS) constitutes its most common and predominant subtype.¹ While advancements in acute medical care have increased the number of stroke survivors, a notable proportion, approximately 30% to 40% experience progressive cognitive decline during recovery, ultimately developing post-stroke cognitive impairment (PSCI). PSCI significantly reduces quality of life and increases the societal care burden, presenting a major challenge in cerebrovascular disease prevention and management.^{2,3} Studies indicate that 26.1% of patients with first-ever ischemic stroke exhibit cognitive impairment at 90 days post-event, with this prevalence further increasing by 6 months.^{4,5}

Increasing evidence shows that inflammation plays a key role in the pathophysiological process of stroke and may be an important driver of the occurrence and development of PSCI. An acute ischemic stroke event triggers an intense local

and systemic inflammatory response. Ischemia-hypoxia in brain tissue leads to the release of damage-associated molecular patterns (DAMPs), which activate microglia and astrocytes, and promote the infiltration of peripheral immune cells into the brain parenchyma. These cells release large amounts of pro-inflammatory cytokines (such as IL-1 β , IL-6, TNF- α) and chemokines.^{6–9} This persistent inflammatory state not only exacerbates secondary brain injury and compromises blood-brain barrier (BBB) integrity but also directly impairs neuronal and synaptic function and adversely affects neuroplasticity.^{10–12} Multiple clinical studies have observed that elevated levels of circulating inflammatory biomarkers during the acute or recovery phase are significantly associated with subsequent cognitive decline and an increased risk of PSCI in stroke patients.^{13,14} This suggests that chronic, low-grade inflammatory responses, whether systemic or within the central nervous system, may serve as a potential biological pathway connecting acute cerebrovascular events to long-term cognitive deterioration.

The well-established relationship between cardio-cerebral vascular diseases and low-density lipoprotein cholesterol (LDL-C) is widely recognized. However, the PROVE IT-TIMI trial demonstrated that despite achieving significant reductions in LDL-C levels, patients receiving intensive statin therapy still exhibited residual cardiovascular risk. This residual risk may be linked to underlying inflammation.¹⁵ Consequently, residual inflammatory risk (RIR) is commonly defined based on elevated high-sensitivity C-reactive protein (hsCRP) levels, typically using a threshold of ≥ 2 mg/L.¹⁶ Current research continues to explore novel risk markers for ischemic stroke.¹⁷ However, in contrast to indicators such as the triglyceride-glucose index, the association between residual inflammatory risk (RIR)—a well-established predictor of cardiovascular events—and post-stroke cognitive impairment (PSCI) has not been sufficiently investigated. Clarifying this association could hold certain implications for personalized medicine, potentially identifying patients who would benefit most from targeted anti-inflammatory strategies to mitigate cognitive decline. This study, therefore, aims to investigate the association between elevated RIR and PSCI in patients with acute ischemic stroke.

Materials and Methods

Study Population

This prospective study enrolled patients with AIS admitted to the Department of Neurology at the First Hospital of Anhui University of Science and Technology between January 2024 and December 2024. The study protocol received approval from the hospital's Ethics Committee, and written informed consent was obtained from all participants.

Inclusion criteria comprised: (1) hospital admission within 7 days of symptom onset; and (2) age ≥ 18 years. Exclusion criteria were: (1) use of cognition-affecting medications within the preceding 2 weeks or pre-existing cognitive impairment; (2) Montreal Cognitive Assessment (MoCA) score < 22 ; and (3) severe acute/chronic infection, autoimmune disease, or malignancy.

Baseline Data Collection

Baseline clinical data, including age, sex, height, weight, educational attainment, current smoking status, current alcohol intake status, and medical history (hypertension, diabetes, hyperlipidemia, and ischemic stroke), were extracted from medical records. Educational attainment was categorized as either ≤ 9 years or > 9 years. Clinical conditions were operationally defined as follows: Hypertension was diagnosed as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on three separate resting measurements, or current antihypertensive medication use; diabetes required fasting blood glucose ≥ 7.0 mmol/L and/or 2-hour postprandial blood glucose ≥ 11.1 mmol/L, or current treatment with insulin or oral hypoglycemic agents; ischemic stroke history was documented as present or absent based on medical records; smoking status defined current smokers as those actively smoking or having quit within one month prior to admission; alcohol intake was defined as consumption at least twice monthly.

Blood Sample Collection and Measurements

Fasting venous blood should be collected within 24 hours after admission. The median time from symptom onset to blood collection was 31.6 hours. Laboratory analyses included: lipid profile [total cholesterol, triglycerides, LDL-C, high-density lipoprotein cholesterol (HDL-C)] measured using a Siemens ADVIA 1800 fully automated biochemical

analyzer; hsCRP quantified using a Mindray BC 7500 fully automated hematology analyzer; and complete blood count parameters (white blood cells, neutrophils, lymphocytes, monocytes) analyzed using a Sysmex BC 7500 fully automated hematology analyzer.

Post-Stroke Cognitive Impairment Assessment

Enrolled patients underwent baseline cognitive assessment using both the Montreal Cognitive Assessment (MoCA) at admission, with identical reassessments conducted at the 6-month follow-up. The cognitive assessments were conducted by clinicians who had received standardized training and were blinded to the patients' laboratory results, including RIR group status. The MoCA, chosen for its established superior sensitivity in detecting PSCI, served as the primary outcome. PSCI was defined as a MoCA score of <22 at the 6-month follow-up, capturing short-term cognitive outcomes.¹⁸

Statistical Analysis

Statistical analysis was carried out using software SPSS (version 26.0), and R (version 4.4.3). Continuous variables were assessed for normality via the Kolmogorov–Smirnov test. Normally distributed data are presented as mean \pm standard deviation (SD) and compared using independent samples *t*-test, non-normally distributed data are expressed as median (interquartile range) with Mann–Whitney *U*-tests for group comparisons. Categorical and ordinal variables are reported as frequencies (percentages), analyzed using chi-square tests or rank-sum tests, respectively.

Based on current guidelines defining LDL-C <2.6 mmol/L as the treatment target for high-risk populations and hsCRP \geq 2 mg/L indicating high inflammatory status,^{19,20} patients were stratified using these thresholds into four mutually exclusive groups: RIR only (LDL-C <2.6 mmol/L and hsCRP \geq 2 mg/L), residual cholesterol risk (RCR) only (LDL-C \geq 2.6 mmol/L and hsCRP <2 mg/L), both risk or residual cholesterol and inflammatory risk (RCIR) (LDL-C \geq 2.6 mmol/L and hsCRP \geq 2 mg/L), and neither risk (LDL-C <2.6 mmol/L and hsCRP <2 mg/L). The relationship between RIR and PSCI was evaluated using multivariable logistic regression. Three progressively adjusted models were constructed: Model 1 accounted for age and sex; Model 2 additionally adjusted for education level, smoking history, alcohol intake, hypertension, diabetes, hyperlipidemia, prior stroke, and baseline NIHSS scores; Model 3 further incorporated white blood cell and neutrophil counts. Statistical significance was defined as $p < 0.05$.

Results

Baseline Characteristics

A total of 204 patients with AIS were initially enrolled in this study. Of these, 13 patients developed pulmonary infections, 9 lacked part of the laboratory data, and 10 were lost to follow-up. Consequently, 172 patients completed the 6-month post-discharge follow-up (Figure 1).

Among them, there were 101 men and 71 women. The median age was 70 (60.25–77.75) years and the median duration of education was 6 (3–10) years. Comorbidities among these AIS patients included hypertension (65.7%), diabetes mellitus (34.9%), hyperlipidemia (22.1%), and a history of stroke (27.9%).

Based on the 6 months follow-up assessments, PSCI was diagnosed in 58 patients (33.7%), with the proportions of PSCI varying across different residual risk groups as shown in Figure S1 (Supplementary Figure S1). Comparative data between the PSCI and post-stroke non-cognitive impairment (PSNCI) groups are presented in Table 1. Compared to the PSNCI group, patients in the PSCI group were significantly older ($P < 0.001$), had fewer years of education ($P = 0.004$), and exhibited higher white blood cell counts ($P = 0.042$), neutrophil counts ($P = 0.016$), and RIR ratio ($P < 0.001$).

Baseline characteristics stratified by LDL-C and hsCRP levels are shown in Table 2. The proportions of patients categorized as having no residual risk, RIR, RCR, and RCIR were 23.8%, 18.6%, 32.0%, and 25.6%, respectively. Significant differences were observed among the four groups for years of education ($P = 0.035$), smoking status ($P = 0.038$), total cholesterol ($P < 0.001$), HDL-C ($P = 0.002$), white blood cell count ($P < 0.001$), neutrophil count ($P < 0.001$), lymphocyte count ($P = 0.015$), and monocyte count ($P = 0.003$).

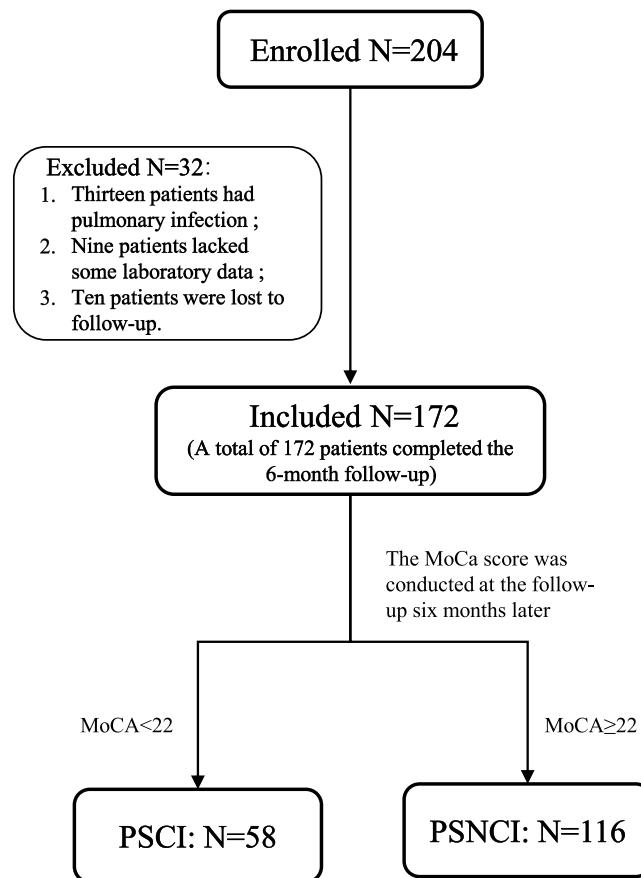


Figure 1 Study enrollment flow chart.

Associations of RCR, RIR, and RCIR with PSCI

Logistic regression analysis revealed that patients with RIR (OR 4.286, 95% CI 1.471–12.488, $P = 0.008$) and RCIR (OR 5.829, 95% CI 4.129–15.954, $P = 0.001$) had a significantly higher risk of developing PSCI compared with patients without

Table 1 Baseline Characteristics of the Follow-up Patients by Cognitive Status

Variables	Total (n=172)	PSCI (n=58)	PSNCI (n=114)	P-value
Demographic characteristics				
Age(years)	70(60.25–77.75)	74(66.75–80.25)	67(58–74.25)	<0.001
Male (%)	101(58.7)	28(48.3)	73(64.0)	0.047
BMI (kg/m ²)	24.21(2.26)	24.07(2.39)	24.28(2.21)	0.451
Smoking (%)	55(32.0)	24(41.4)	31(27.2)	0.059
Drinking (%)	44(25.6)	11(19.0)	33(28.9)	0.156
Education(years)	6(3–10)	4(3–9.25)	9(4–12)	0.004
Education level				
0–9y (%)	109(63.4)	44(75.9)	65(57.0)	0.021
>9y (%)	63(36.6)	14(24.1)	49(43.0)	
Clinical characteristics				
Hypertension (%)	113(65.7)	42(72.4)	71(62.3)	0.186
Diabetes (%)	60(34.9)	24(41.4)	36(31.6)	0.202
Hyperlipidemia (%)	38(22.1)	12(20.7)	26(22.8)	0.752
Prior stroke (%)	48(27.9)	20(34.5)	28(24.6)	0.170

(Continued)

Table 1 (Continued).

Variables	Total (n=172)	PSCI (n=58)	PSNCI (n=114)	P-value
Laboratory data				
Total cholesterol(mmol/L)	4.66(4.02–5.67)	4.76(3.92–5.24)	4.64(4.04–5.43)	0.819
Triglyceride (mmol/L)	1.31(0.92–1.77)	1.34(0.99–1.79)	1.29(0.91–1.77)	0.837
HDL-C(mmol/L)	1.02(0.88–1.25)	0.99(0.87–1.18)	1.05(0.89–1.25)	0.440
LDL-C (mmol/L)	2.81(0.82)	2.76(0.91)	2.84(0.77)	0.192
hsCRP, (mg/L)	1.78(0.89–4.60)	2.93(1.95–8.22)	1.33(0.64–2.47)	<0.001
WBC, 10 ⁹ /L	6.58(5.38–7.98)	7.04(5.80–8.85)	6.36(5.09–7.82)	0.042
Neutrophils, 10 ⁹ /L	4.06(3.24–5.78)	4.69(3.57–6.35)	3.82(3.18–5.21)	0.016
Lymphocytes, 10 ⁹ /L	1.56(1.16–2.06)	1.56(1.16–2.06)	1.55(1.16–2.11)	0.689
Monocytes, 10 ⁹ /L	0.39(0.31–0.48)	0.38(0.30–0.47)	0.39(0.32–0.49)	0.773
NIHSS				
Groups according to LDL-C and hsCRP levels	2(1–3)	2(1–3)	2(1–3)	0.156
Neither risk (%)	41(23.8)	7(12.1)	34(29.8)	<0.001
RIR (%)	32(18.6)	15(25.9)	17(14.9)	
RCR (%)	55(32.0)	12(20.7)	43(37.7)	
RCIR (%)	44(25.6)	24(41.4)	20(17.5)	

Notes: All $p < 0.05$ values are bolded.

Abbreviations: PSCI, post-stroke cognitive impairment; PSNCI, post-stroke no cognitive impairment; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; WBC, white blood cell; NIHSS, national institutes of health stroke scale; RIR, residual inflammatory risk; RCR, residual cholesterol risk; RCIR, residual cholesterol and inflammatory risk.

Table 2 Baseline Characteristics According to LDL-C and hsCRP Levels

Variables	Neither Risk (n=41)	RIR (n=32)	RCR (n=55)	RCIR (n=44)	P-value
Demographic characteristics					
Age(years)	70(58.5–79)	73.5(64–77)	67(59–73)	72.5(60.25–80)	0.140
Male (%)	24(58.5)	22(68.8)	27(49.1)	28(63.6)	0.276
BMI (kg/m ²)	23.86(2.29)	24.00(1.66)	24.17(2.02)	24.73(2.83)	0.318
Smoking (%)	8(19.5)	16(50)	15(27.3)	15(34.1)	0.038
Drinking (%)	11(26.8)	8(25)	15(27.3)	11(25)	0.992
Education(years)	6(3.5–12)	6(3–10)	9(4–12)	4(3–9)	0.035
Education level					
0–9y (%)	23(56.1)	20(62.5)	31(56.5)	36(81.8)	0.036
>9y (%)	18(43.9)	12(37.5)	24(43.6)	8(18.2)	
Clinical characteristics					
Hypertension (%)	23(56.1)	22(68.8)	36(65.5)	32(72.7)	0.428
Diabetes (%)	12(29.3)	16(50)	19(34.5)	13(29.5)	0.227
Hyperlipidemia (%)	6(14.6)	5(15.6)	13(23.6)	14(31.8)	0.204
Prior stroke (%)	11(26.8)	15(46.9)	12(21.8)	10(22.7)	0.062
Laboratory data					
Total cholesterol(mmol/L)	4.04(3.54–4.50)	3.67(3.04–4.16)	5.24(4.68–6.14)	5.00(4.69–5.53)	<0.001
Triglyceride (mmol/L)	1.52(0.87–1.99)	1.10(0.83–1.56)	1.28(0.86–1.75)	1.44(1.07–2.20)	0.073
HDL-C (mmol/L)	0.96(0.82–1.19)	0.88(0.776–1.10)	1.16(0.97–1.29)	1.02(0.89–1.16)	0.002
WBC, 10 ⁹ /L	5.72(4.68–6.63)	7.83(6.66–9.32)	5.92(5.07–7.61)	7.57(6.00–8.78)	<0.001
Neutrophils, 10 ⁹ /L	3.35(2.66–3.83)	5.93(4.64–7.70)	3.72(3.06–5.07)	5.10(3.76–6.45)	<0.001
Lymphocytes, 10 ⁹ /L	1.64(1.28–2.26)	1.28(0.90–1.75)	1.70(1.33–2.27)	1.37(1.12–1.95)	0.015
Monocytes, 10 ⁹ /L	0.34(0.28–0.40)	0.44(0.35–0.54)	0.38(0.30–0.46)	0.44(0.32–0.50)	0.003

(Continued)

Table 2 (Continued).

Variables	Neither Risk (n=41)	RIR (n=32)	RCR (n=55)	RCIR (n=44)	P-value
Cognitive status					
PSCI (%)	7(17.1)	15(46.9)	12(21.8)	24(54.5)	<0.001
PSNCI (%)	34(82.9)	17(53.1)	43(78.2)	20(45.5)	

Notes: All $p < 0.05$ values are bolded.

Abbreviations: RIR, residual inflammatory risk; RCR, residual cholesterol risk; RCIR, residual cholesterol and inflammatory risk; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; WBC, white blood cell; PSCI, post-stroke cognitive impairment; PSNCI, post-stroke no cognitive impairment.

residual risk. This association remained significant even after adjusting for gender, age, years of education, smoking status, alcohol consumption, hypertension, diabetes, hyperlipidemia, prior stroke history, white blood cell count, and neutrophil count (RIR: OR 4.496, 95% CI 1.157–17.477, $P = 0.030$; RCIR: OR 7.357, 95% CI 2.081–26.006, $P = 0.002$) (Figure 2).

Discussion

According to the findings of our investigation into the association between RIR and PSCI, RIR and cognitive decline in patients suffering from acute ischemic stroke were substantially positively connected. Furthermore, the robust positive connection between RIR and PSCI persisted even after controlling for potential confounding variables.

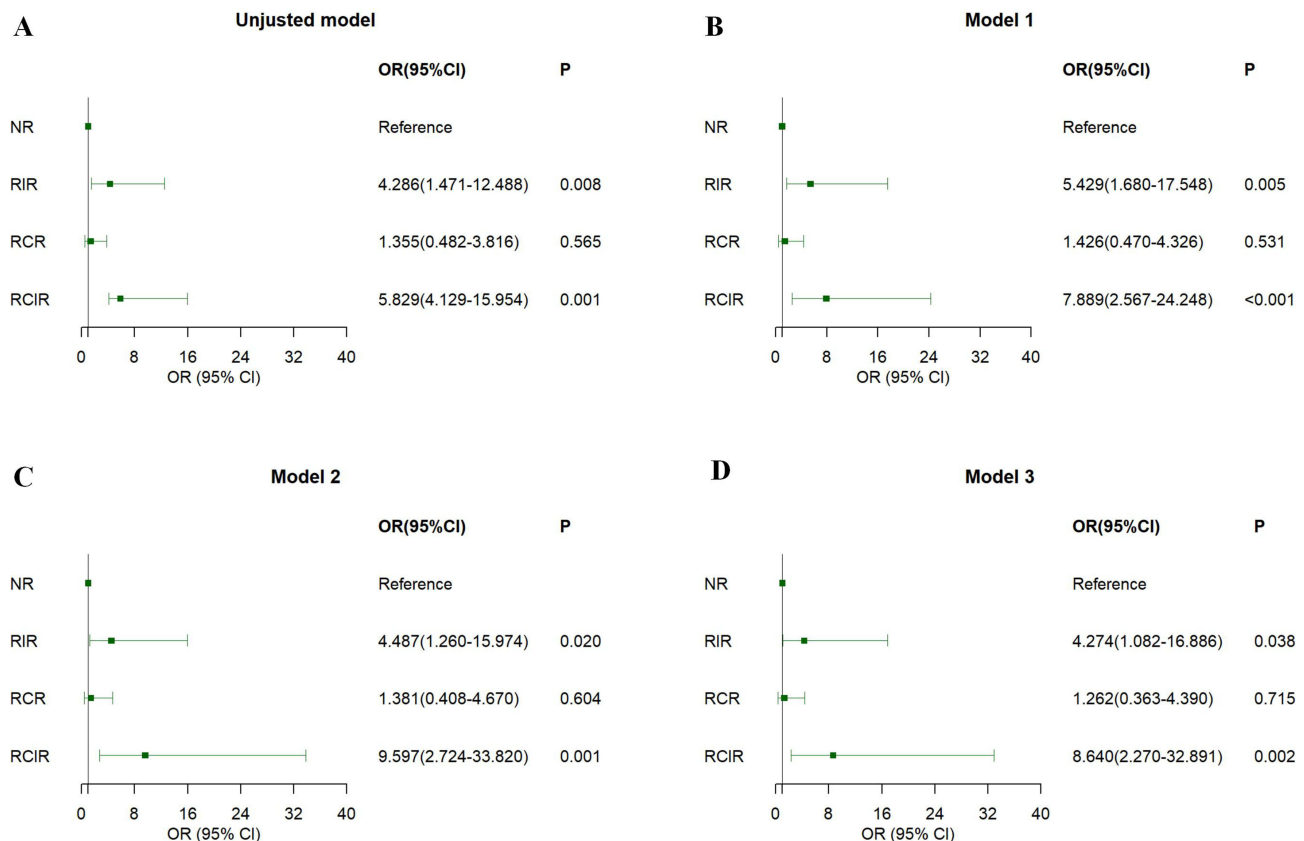


Figure 2 Logistic regression analysis for exploring the association between RIR, RCR and RCIR with PSCI (A) Unjusted model (B) Model 1 accounted for age and sex; (C) Model 2 additionally adjusted for education level, smoking history, alcohol intake, hypertension, diabetes, hyperlipidemia, and prior stroke; (D) Model 3 further incorporated white blood cell and neutrophil counts.

Abbreviations: PSCI, post-stroke cognitive impairment; OR, odds ratios; CI, confidence interval; NR, neither risk; RIR, residual inflammatory risk; RCR, residual cholesterol risk; RCIR, residual cholesterol and inflammatory risk.

Prior studies on PSCI have employed heterogeneous definitions, assessment methods, and study populations, leading to considerable variation in reported epidemiology and associated risk factors. In our cohort of AIS patients, the incidence of PSCI at 6 months was 33.7%. This finding aligns with several previous reports,^{21,22} but is slightly lower than that reported by Zhao et al.²³ This discrepancy may stem from our inclusion criteria, which encompassed only AIS patients and excluded those with transient ischemic attack (TIA). Consistent with earlier research, our study confirms that advanced age and lower educational attainment are significant risk factors for PSCI.²⁴ Mechanistically, aging contributes to cumulative neurobiological damage,²⁵ while lower education levels are associated with reduced cognitive reserve—the brain's capacity to compensate for damage through alternative neural pathways and adaptive mechanisms.^{26,27}

Multiple clinical studies indicate that RIR is relatively prevalent in clinical practice, with reported incidence rates ranging from 29% to 37%.^{28–30} In our study, the RIR incidence rate was 18.6%. This comparatively lower rate may be attributable to the limited sample size of this study and differences in the included population. Previous research on RIR has primarily focused on its association with cardiovascular disease, stroke, and their prognoses. For instance, Liao et al demonstrated that RIR is associated with poor postoperative outcomes in patients with acute coronary syndrome,³¹ while Yu et al found that RIR predicts poor outcomes in patients with symptomatic intracranial atherosclerotic stenosis.³² Furthermore, residual inflammation increases the risk of stroke recurrence, and each recurrent stroke event may cause additional cognitive impairment.³³ In this study, we observed that six months after stroke onset, patients with RIR had a significantly higher incidence of PSCI compared to those without RIR. This association persisted even after adjusting for a series of confounding factors. This finding suggests that RIR may serve as a potential predictive biomarker for PSCI, thereby offering a rationale for its use in risk stratification and for enriching patient selection in trials of targeted anti-inflammatory interventions.

Persistent neuroinflammation may underlie the potential mechanism through which RIR contributes to PSCI. First, persistent inflammatory mediators in the circulation can directly cross the compromised blood-brain barrier or activate microglia and astrocytes within the central nervous system (CNS) through signaling pathways. This leads to chronic neuroinflammation, and this sustained inflammatory state causes multiple forms of neural damage.^{34–36} Second, this sustained neuroinflammation can directly damage neurons and impair synaptic function. Inflammatory cytokines, such as TNF- α and IL-1 β , interfere with the expression of synaptic plasticity-associated molecules, including brain-derived neurotrophic factor (BDNF), and compromise neurotransmission as well as learning and memory processes in cognition-critical regions such as the hippocampus.^{37–39} Third, the inflammatory response further compromises the blood-brain barrier, creating a vicious cycle that allows increased infiltration of peripheral inflammatory mediators and immune cells into the brain parenchyma. These infiltrating components directly impair the neurovascular unit (NVU).^{34,40–42} Fourth, the chronic inflammatory environment also impairs oligodendrocyte function and impedes remyelination, leading to a decline in white matter integrity and damaged brain network connectivity efficiency.^{43–45} Finally, the persistent inflammatory state suppresses the survival, proliferation, and differentiation of neural stem cells (NSCs), severely compromising the brain's intrinsic capacity for self-repair and compensation after stroke.⁴⁶ Therefore, the sustained, low-level inflammatory state represented by RIR significantly increases the risk of PSCI through synergistic effects on neurons, synapses, blood-brain barrier, white matter and nerve regeneration.

This study has several limitations. First, the single-center design with a specific regional cohort and the modest sample size may introduce selection bias and limit the generalizability of our findings. Second, the relatively short follow-up period precludes assessment of the long-term trajectory of RIR and cognitive impairment development; consequently, the current results may underestimate the true magnitude of long-term effects. Third, the number of outcome events was limited relative to the number of covariates in the model (ie, low event-variable ratios), which reflected mainly the wide confidence intervals in the multivariate models, implying uncertainty in the estimation of the precise value of the effect size. Fourth, as an observational cohort study, it demonstrates a significant association between RIR and PSCI but cannot establish causality. Crucially, we lacked data from prospective interventional studies, such as randomized controlled trials of anti-inflammatory therapies, to determine whether reducing RIR effectively prevents PSCI. Finally, although we adjusted for major known confounders, potential unmeasured factors influencing inflammation and cognition (eg, novel biomarkers, detailed lifestyle factors, or subclinical comorbidities) were not evaluated and should be addressed in future investigations.

Conclusion

This study suggests that RIR may serve as a predictor of PSCI in patients with AIS, laying the groundwork for future hypothesis-driven research. Our findings highlight the potential for clinical translation, such as screening for RIR in stroke survivors to identify those at high risk for cognitive decline. The essential next step is the large-scale, multi-center validation of RIR to robustly confirm its value for clinical stratification and intervention.

Ethics Statement

The study was approved by the ethics committee of the First Hospital of Anhui University of Science and Technology (2023-KY-B113-001).

Consent

Informed consent was obtained from all patients.

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Disclosure

The authors report no conflicts of interest in this work.

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