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Atherogenic and Inflammatory Markers in Recent Small Subcortical Infarcts: Associations with Location, Morphology, and Short-Term Recurrence

Chaojuan Huang[1,*], Jie Geng[1,2,*], Jie Fan[1,3], Bo Tian[1], Kaigui Wang[1], Yimei Zhang[1], Xia Zhou[1], Xiaoqun Zhu[1], Zhongwu Sun[1]

[1]Department of Neurology, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, 230022, People's Republic of China; [2]Department of General Medicine, The Second Affiliated Hospital of Bengbu Medical University, Bengbu, Anhui, 233000, People's Republic of China; [3]Department of Neurology, Anqing Municipal Hospital, Anqing, Anhui, 246003, People's Republic of China

*These authors contributed equally to this work

Correspondence: Zhongwu Sun; Xiaoqun Zhu, Department of Neurology, The First Affiliated Hospital of Anhui Medical University, No. 218 Jixi Road, Shushan District, Hefei, Anhui, 230022, People's Republic of China, Email sunzhwu@126.com; zxq_ayfy@163.com

Background: Recent small subcortical infarcts (RSSIs) have emerged as a growing public health concern due to their poor long-term clinical outcomes. This study aimed to investigate the associations between the atherogenic index of plasma (AIP), systemic immune-inflammation index (SII), and systemic inflammation response index (SIRI) with the occurrence and recurrence of RSSIs.

Methods: Three hundred forty-two patients with RSSIs who met the eligibility criteria were included in the cross-sectional analysis. Comprehensive demographic, laboratory, and neuroimaging data were collected at baseline. Patients were categorized into subcortical white matter, basal ganglia, and brainstem RSSIs based on lesion location. Lesions were further classified by shape (round/oval or tubular) and diameter (≤15 mm or >15 mm). Of these, 336 patients completed follow-up at six months. Logistic regression models were established to assess the relationships between AIP, SII, and SIRI with the occurrence and recurrence of RSSIs, considering variations in lesion location and morphology. The short-term prognostic performances of individual and combined risk factors were evaluated using receiver operating characteristic curve analysis.

Results: Cross-sectional analysis revealed a significant positive correlation between AIP and basal ganglia RSSIs (OR: 3.269, 95% CI: 1.209–8.839), as well as between SIRI and brainstem RSSIs (OR: 1.472, 95% CI: 1.012–2.143) and tubular RSSIs (OR: 1.440, 95% CI: 1.043–1.989), after adjusting for potential confounders. In the longitudinal analysis, multivariate regression indicated that hypertension, periventricular white matter hyperintensities, and SII were independently associated with RSSI recurrence. The predictive model demonstrated strong performance, with an area under the curve of 0.853 (95% CI: 0.738–0.968), sensitivity of 90.9%, and specificity of 75.4%.

Conclusion: Atherogenic and inflammatory markers are associated with specific locations and morphologies of RSSIs and serve as potential predictive factors for short-term RSSI recurrence. These findings may enhance our understanding of the mechanisms underlying RSSIs and inform early prevention strategies.

Keywords: atherogenic index of plasma, systemic immune-inflammation index, systemic inflammation response index, recent small subcortical infarct, cerebral small vessel disease, recurrence

Introduction

Recent small subcortical infarcts (RSSIs) are recognized as a key hallmark of cerebral small vessel disease (CSVD), accounting for approximately 25% of acute ischemic stroke cases.[1,2] RSSIs are characterized by diffusion-weighted imaging (DWI)-positive lesions measuring ≤20 mm in diameter within the territory of a single perforating artery and are

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often accompanied by focal neurological deficits, such as pure motor or sensory impairments, sensorimotor deficits, or ataxic hemiparesis.[3] Although historically considered benign due to their small lesion size and mild clinical symptoms, recent studies have challenged this view. Specifically, long-term outcomes of RSSIs may be comparable to those of large-artery strokes. Notably, one study with a median 12-year follow-up reported a 22% recurrence rate of ischemic cerebrovascular events in patients with RSSIs,[4] underscoring their underestimated burden. These findings highlight the significant public health impact of RSSIs and the urgent need for effective prevention and management strategies.

RSSIs typically occur in the subcortical white matter, basal ganglia, and brainstem,[5] with lesion location closely associated with distinct etiologies and vascular risk profiles. For instance, Eppinger et al, in a retrospective analysis of 335 patients, reported a higher prevalence of hypertension in those with RSSIs located in the subcortical white matter or basal ganglia, whereas diabetes mellitus (DM) was more frequently associated with brainstem RSSIs.[6] Similarly, Kloppenborg et al demonstrated that hyperhomocysteinemia significantly increased the risk of basal ganglia RSSIs, while smoking and hypertension were strongly linked to subcortical white matter RSSIs over a mean follow-up period of 3.9 years.[7] Notably, RSSIs exhibit heterogeneity not only in location but also in lesion size and morphology, which may reflect underlying differences in vascular mechanisms.[6,8] Despite the identification of multiple associated risk factors, the precise mechanisms driving the development and recurrence of RSSIs remain incompletely understood. Emerging evidence implicates that both atherosclerosis and inflammation play vital roles in the pathophysiology of these lesions.[9,10]

The atherogenic index of plasma (AIP) is a well-established marker of lipid metabolism and atherosclerotic risk.[11] Additionally, the systemic immune-inflammation index (SII) and systemic inflammation response index (SIRI) have emerged as novel indicators reflecting immune-inflammation balance.[12] These indices collectively capture distinct yet interconnected aspects of vascular pathology, including atherosclerosis and inflammatory processes. Growing evidence has demonstrated that elevated levels of AIP, SII, and SIRI are associated with increased risks and poorer outcomes in both cardiovascular and cerebrovascular diseases.[13–16] Notably, associations between these markers and CSVD have also been reported. AIP, in particular, has been identified as an independent risk factor for both CSVD and its total burden score.[17] Neuroimaging-based studies further reveal that AIP and SII are closely associated with specific CSVD features, such as lacunes, white matter hyperintensities (WMHs), and enlarged perivascular spaces (EPVS).[18,19] Despite increasing evidence supporting the roles of atherosclerosis and inflammation in cerebrovascular disease, these markers - particularly AIP, SII, and SIRI - have not yet been widely incorporated into clinical risk assessment or secondary prevention strategies for patients with RSSIs. Moreover, few studies have systematically investigated the anatomical and morphological heterogeneity of RSSIs in relation to these emerging vascular biomarkers.

To address this gap, our study aims to: (1) comprehensively explore the associations of AIP, SII, and SIRI with RSSIs across different anatomical locations, lesion shapes, and sizes; and (2) identify potential predictors of RSSI recurrence within six months.

Material and Methods

Study Design and Population

Initially, 445 patients diagnosed with RSSIs were enrolled from the Department of Neurology at the First Affiliated Hospital of Anhui Medical University between January 2022 and May 2024. Baseline data, including demographic characteristics, laboratory test results, and Magnetic Resonance Imaging (MRI) findings, were collected. All patients were followed for six months to determine the recurrence of RSSIs. Patients with ≤20 mm DWI-positive lesions within a single perforating artery territory, along with corresponding focal neurological deficits occurring within three weeks, were included in the analysis.[3] The exclusion criteria were as follows: (1) intracranial large artery stenosis ≥ 70%; (2) history of intracerebral hemorrhage, traumatic brain injury, vascular malformations, or brain tumors; (3) systemic malignancies or severe dysfunction of the liver, kidneys, heart, or lungs, as well as acute or chronic inflammatory diseases; (4) presence of ≥2 RSSIs in different locations; (5) missing data on complete blood count (CBC), glucose, or lipids; (6) incomplete follow-up information within six months; and (7) contraindications to MRI, including in-vivo dentures, metallic stents, or claustrophobia. A detailed flowchart of the inclusion and exclusion process is presented in Supplementary Figure 1.

After applying these stringent inclusion and exclusion criteria, a sum of 342 patients were included in the cross-sectional analysis, and 336 in the longitudinal analysis. This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was granted by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University (PJ2023-01-45), and written informed consent was obtained from all participants prior to study commencement.

Laboratory Biomarker Measurement

Fasting venous blood samples were collected from all patients after an overnight fast of at least 8 hours on the first day of admission, and within 72 hours of MRI scanning, ensuring temporal alignment between biomarker acquisition and imaging evaluation. For CBC testing, 1 mL of blood was collected in EDTA-anticoagulant tubes. Additionally, 2 mL of blood was drawn into non-anticoagulant vacuum tubes and centrifuged at 3000 rpm for 10 minutes to separate serum for biochemical analysis. All samples were transported to the hospital laboratory and analyzed within two hours of collection. CBCs were performed using a fully automated hematology analyzer (XN-20 A1+SP-50, Sysmex Corporation, Kobe, Japan), which utilizes advanced flow cytometry and fluorescence staining techniques. This system provides quantitative measurements of leukocyte subtypes (neutrophils, lymphocytes, monocytes), red blood cell counts, hemoglobin concentration, and platelet counts. Biochemical parameters, including triglycerides, high-density lipoprotein cholesterol (HDL-C), and glucose, were measured using a fully automated biochemical analyzer (5600, Johnson & Johnson, USA) based on optical colorimetry.

The AIP, SII, and SIRI were calculated using the following equation: AIP = log [triglyceride (mmol/L) / HDL-C (mmol/L)]; SII = [platelet (10^3/μL) * neutrophils (10^3/μL)] / lymphocytes (10^3/μL); SIRI = [monocytes (10^3/μL) * neutrophils (10^3/μL)] / lymphocytes (10^3/μL).

MRI Scanning

MRI scans were conducted using a GE 1.5 Tesla MR System (Discovery MR750w, Milwaukee, Wisconsin, USA). During the scanning procedure, patients were instructed to wear earplugs, keep their eyes closed, and maintain head stability. The scanning protocol included the following sequences and parameters: (1) T1 weighted images: slice thickness = 6 mm, repetition time (TR) = 2000 ms, echo time (TE) = 15 ms, inversion time (IT) =800 ms, flip angle (FA) = 90°, matrix size = 232 × 179, voxel size = 0.6 × 0.6 × 7.2 mm^3. (2) T2 weighted images: slice thickness = 6 mm, TR = 2501 ms, TE = 115 ms, FA = 90°, matrix size = 256 × 59, voxel size = 0.7 × 0.7 × 7.0 mm^3. (3) T2 Fluid-Attenuated Inversion Recovery (FLAIR): slice thickness = 6 mm, TR = 6000 ms, TE = 120 ms, IT =2000 ms, FA = 90°, matrix size = 240 × 181, voxel size = 0.9 × 0.9 × 7.0 mm^3. (4) DWI: slice thickness = 6 mm, TR = 2711 ms, TE = 86 ms, FA = 90°, matrix size = 152 × 106, voxel size = 1.0×1.0 × 7.0 mm^3, b = 1,000 s/mm^2.

Neuroimaging Assessment

In this study, RSSIs were classified according to their anatomical location into three groups: subcortical white matter, basal ganglia, and brainstem (Supplementary Figure 2). Lesions were further categorized by shape into either round/oval or tubular, and by their maximum axial diameter, which was divided into two groups: ≤15 mm and >15 mm. RSSI recurrence was determined through follow-up assessments, conducted via telephone and outpatient visits at six months. Recurrence was defined as the emergence of new clinical symptoms, confirmed by radiological evidence.

Furthermore, other neuroimaging markers of CSVD were evaluated. These markers included: (1) lacunes: subcortical fluid-filled cavities with a diameter of 3–15 mm, exhibiting a hypointense center and hyperintense rim on T2 FLAIR; (2) WMHs: hyperintense lesions in the centrum semiovale or periventricular on T2 FLAIR; (3) EPVS: hyperintense round, oval, or linear lesions in the centrum semiovale or basal ganglia on T2 weighted image; and (4) brain atrophy: reduction in brain parenchymal volume. A CSVD burden score was calculated, ranging from 0 to 4. One point was assigned for each of the following marker: the presence of lacunes, periventricular WMHs rated as grade 3 or deep WMHs rated as grades 2–3, >10 EPVS in the basal ganglia, and a global cortical atrophy score >1.[19,20]

Statistical Analysis

The normality of quantitative variables was assessed using the Shapiro–Wilk test. Continuous variables with a normal distribution were presented as mean ± standard deviation and compared using independent-samples t-tests or analysis of variance. Skewed continuous variables were presented as median (P25, P75) and analyzed using the rank-sum test. Categorical variables were reported as frequencies (percentages) and compared using the chi-square test. Univariate and multivariate logistic regression models were constructed to examine the independent associations between AIP, SII, SIRI, and the risk of RSSIs across different locations, shapes, and sizes. The effect sizes were expressed as odds ratios (OR) with 95% confidence intervals (95% CI). Based on a combination of clinical relevance, literature review, and univariate analysis with a *P*-value threshold of <0.05, three multivariable regression models were constructed: Model 1, which included no covariates; Model 2, which adjusted for age, time from symptom onset to MRI, National Institutes of Health Stroke Scale (NIHSS) score at admission, Modified Rankin Scale (MRS) score at admission, hypertension, DM, cardiovascular disease, body mass index (BMI), and CSVD burden score; and Model 3, which further adjusted for laboratory test results in addition to the covariates in Model 2. Partial correlation analysis, controlling for age, sex, and CSVD burden score, was used to examine the relationships between RSSI diameter and NIHSS/MRS scores at both admission and discharge.

Group comparisons were further conducted based on the recurrence of RSSIs within six months. Variables with a p-value < 0.2 in the univariate analysis were included in the multivariate logistic regression model. Those with a *P*-value < 0.05 in the regression analysis were subsequently incorporated into receiver operating characteristic (ROC) curve analysis to evaluate their predictive performance for RSSI recurrence. All statistical analyses were performed using SPSS 25.0. Bonferroni correction was applied for multiple comparisons. A *P*-value <0.05 (two-sided) was recognized as reaching statistically significant.

Results

Baseline Characteristics of Study Population

Ultimately, 342 individuals were included in the cross-sectional analysis, comprising 38 patients with subcortical white matter RSSIs, 165 with basal ganglia RSSIs, and 139 with brainstem RSSIs. The mean ages were 68.82±12.29 years for the subcortical white matter RSSIs group, 61.39±11.85 years for the basal ganglia RSSIs group, and 66.53±13.22 years for the brainstem RSSIs group, with a statistically significant difference observed (*P*<0.001). Among the three groups, the brainstem RSSIs group exhibited the most severe clinical symptoms, as reflected by significantly higher NIHSS and MRS scores (*P*<0.001). A history of hypertension and hyperlipidemia also varied significantly across the groups (*P* <0.05). The subcortical white matter RSSIs group had the smallest lesion diameter and the lowest proportion of tubular RSSIs. However, this group demonstrated the highest prevalence of neuroimaging markers, including lacunes, WMHs, EPVS, and brain atrophy, and also had the highest CSVD burden score (*P* <0.05). Regarding laboratory findings, the basal ganglia RSSIs group had the highest AIP levels, while the brainstem RSSIs group exhibited the highest levels of SII and SIRI. Detailed differences in demographic and clinical characteristics across RSSI locations, shapes, and sizes are provided in Table 1 and Supplementary Tables 1 and 2.

Table 1 Comparison of Demographic and Clinical Characteristics of RSSI Across Different Locations

	Total (n=342)	Subcortical White Matter RSSI (n=38)	Basal Ganglia RSSI (n=165)	Brainstem RSSI (n=139)	F/H/χ^2	P Value
Demographic characteristics						
Age (years)	64.30 ± 12.77	68.82 ± 12.29	61.39 ± 11.85	66.53 ± 13.22	9.18[ac]	<0.001
Male (n.%)	245 (71.64)	29 (76.32)	114 (69.09)	102 (73.38)	1.14	0.564
BMI (kg/m^2)	24.83 ± 2.96	25.12 ± 2.97	24.95 ± 2.92	24.62 ± 3.00	0.68	0.506

(*Continued*)

Table 1 (Continued).

	Total (n=342)	Subcortical White Matter RSSI (n=38)	Basal Ganglia RSSI (n=165)	Brainstem RSSI (n=139)	F/H/χ^2	P Value
Clinical symptoms						
Time of the initial MRI	4.00 (2.00, 6.00)	5.00 (3.00, 8.25)	3.00 (2.00, 5.00)	4.00 (2.00, 7.00)	8.02[a]	0.018
NIHSS score at admission	2.00 (1.00, 4.00)	2.00 (1.00, 4.25)	2.00 (1.00, 3.00)	3.00 (2.00, 6.00)	25.59[bc]	<0.001
NIHSS score at discharge	1.00 (1.00, 3.00)	1.00 (0.00, 2.25)	1.00 (0.00, 2.00)	2.00 (1.00, 4.00)	26.71[bc]	<0.001
MRS score at admission	2.00 (1.00, 3.00)	1.00 (1.00, 3.00)	1.00 (1.00, 2.00)	2.00 (1.00, 4.00)	30.43[bc]	<0.001
MRS score at discharge	1.00 (1.00, 2.00)	1.00 (0.00, 2.00)	1.00 (1.00, 2.00)	2.00 (1.00, 3.00)	32.45[bc]	<0.001
Vascular risk factors						
Hypertension (n.%)	225 (65.79)	26 (68.42)	95 (57.58)	104 (74.82)	10.10[c]	0.006
Diabetes mellitus (n.%)	145 (42.40)	15 (39.47)	64 (38.79)	66 (47.48)	2.49	0.289
Hyperlipidemia (n.%)	152 (44.44)	9 (23.68)	75 (45.45)	68 (48.92)	7.83[ab]	0.020
Cardiac disease (n.%)	20 (5.85)	5 (13.16)	7 (4.24)	8 (5.76)	4.46	0.107
Smoking (n.%)	140 (40.94)	17 (44.74)	71 (43.03)	52 (37.41)	1.24	0.538
Drinking (n.%)	145 (42.40)	18 (47.37)	70 (42.42)	57 (41.01)	0.50	0.781
Neuroimaging markers						
Diameter of RSSI (mm)	10.53 (7.63, 14.74)	8.00 (4.50, 10.79)	10.60 (7.93, 15.23)	11.34 (7.80, 14.97)	19.09[ab]	<0.001
Tubular RSSI (n.%)	147 (43.00)	10 (26.32)	81 (49.09)	56 (40.29)	7.23[a]	0.027
Lacune (n.%)	137 (40.06)	26 (68.42)	58 (35.15)	53 (38.13)	14.60[ab]	<0.001
Periventricular WMHs (n.%)	111 (32.46)	24 (63.16)	42 (25.45)	45 (32.37)	20.03[ab]	<0.001
Deep WMHs (n.%)	106 (31.00)	20 (52.63)	41 (24.85)	45 (32.37)	11.36[a]	0.003
Moderate to severe EPVS (n.%)	96 (28.07)	21 (55.26)	38 (23.03)	37 (26.62)	16.14[ab]	<0.001
Brain atrophy (n.%)	128 (37.43)	25 (65.79)	37 (22.42)	66 (47.48)	34.91[ac]	<0.001
CSVD burden score	1.00 (0.00, 3.00)	3.00 (1.75, 3.25)	1.00 (0.00, 2.00)	1.00 (0.00, 3.00)	36.73[abc]	<0.001
Laboratory tests						
Neutrophils (10^9/L)	4.17 (3.40, 5.32)	3.93 (3.10, 5.40)	3.90 (3.16, 4.75)	4.50 (3.82, 5.63)	19.64[c]	<0.001
Lymphocyte (10^9/L)	1.69 (1.29, 2.16)	1.76 (1.32, 2.45)	1.75 (1.35, 2.16)	1.59 (1.22, 2.08)	5.78	0.056
Monocyte (10^9/L)	0.43 (0.34, 0.54)	0.43 (0.34, 0.54)	0.40 (0.31, 0.49)	0.46 (0.39, 0.57)	21.44[c]	<0.001
Red blood cell (10^{12}/L)	4.53 ± 0.55	4.39 ± 0.58	4.59 ± 0.54	4.50 ± 0.53	2.38	0.094
Hemoglobin (g/L)	137.42 ± 16.96	133.39 ± 18.93	138.93 ± 16.91	136.73 ± 16.34	1.85	0.159
Platelet (10^9/L)	205.50 (171.75, 238.00)	217.00 (166.75, 247.25)	203.00 (166.00, 237.00)	208.00 (181.00, 236.00)	1.65	0.439
Triglyceride (mmol/L)	1.53 (1.21, 2.07)	1.13 (0.85, 1.62)	1.60 (1.31, 2.16)	1.50 (1.14, 2.04)	14.99[ab]	<0.001
HDL-C (mmol/L)	0.98 (0.84, 1.13)	0.99 (0.74, 1.19)	0.97 (0.83, 1.09)	0.98 (0.84, 1.18)	2.01	0.366
Glucose (mmol/L)	5.76 (5.07, 7.85)	5.54 (5.00, 6.89)	5.76 (5.06, 7.80)	5.97 (5.14, 8.49)	3.87	0.144
AIP	0.19 (0.07, 0.36)	0.10 (−0.12, 0.29)	0.22 (0.09, 0.37)	0.18 (0.01, 0.39)	10.62[a]	0.005
SII	493.84 (377.67, 712.13)	454.24 (336.86, 673.06)	455.92 (323.90, 597.08)	597.50 (414.29, 801.21)	22.32[bc]	<0.001
SIRI	1.06 (0.76, 1.50)	1.01 (0.66, 1.51)	0.89 (0.63, 1.34)	1.27 (0.99, 1.75)	43.37[bc]	<0.001

Notes: [a] indicates a significant difference between the subcortical white matter RSSI and basal ganglia RSSI; [b] indicates a significant difference between the subcortical white matter RSSI and brainstem RSSI; [c] indicates a significant difference between the basal ganglia RSSI and brainstem RSSI.

Abbreviations: RSSI, recent small subcortical infarct; BMI, body mass index; MRI, magnetic resonance imaging; NHISS, National Institutes of Health Stroke Scale; MRS, Modified Rankin Scale; WMHs, white matter hyperintensities; EPVS, enlarged perivascular space; CSVD, cerebral small vessel disease; HDL-C, high-density lipoprotein cholesterol; AIP, atherosclerosis index of plasma; SII, systemic immune inflammation index; SIRI, system inflammation response index.

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Baseline Association Between AIP, SII, SIRI, and RSSI Risk

As outlined in Table 2, logistic regression analysis revealed that AIP levels were positively related to the risk of basal ganglia RSSIs after adjusting for confounding factors, with an OR of 3.269 (95% CI: 1.209–8.839) in Model 3. In parallel, SIRI levels consistently demonstrated a detrimental effect on brainstem RSSI risk across all models. Specifically, the effect sizes were as follows: OR 1.823 (95% CI: 1.360–2.444, $P<0.001$) in the crude Model 1, OR 1.569 (95% CI: 1.178–2.091, $P=0.002$) in the minimally adjusted Model 2, and OR 1.472 (95% CI: 1.012–2.143, $P=0.043$) in the fully adjusted Model 3. Additionally, an increase in SIRI levels was also linked to a higher risk of tubular RSSIs. The OR in the unadjusted model was 1.324 (95% CI: 1.068–1.640, $P=0.010$). While the association became weaker after adjusting for covariates, it remained significant in both Model 2 (OR=1.319, 95% CI: 1.050–1.658, $P=0.017$) and Model 3 (OR=1.440, 95% CI: 1.043–1.989, $P=0.027$). The full results of the regression models are detailed in Supplementary Tables 3–5 However, no significant correlations were noticed between AIP, SII, or SIRI levels and the risk of subcortical white matter RSSIs, nor was there any association with the diameter of RSSIs.

Correlation Between RSSI Diameters and Clinical Symptoms

Partial correlation analysis revealed a significant association between the diameter of RSSIs and the severity of clinical symptoms, even after adjusting for age, sex, and the CSVD burden score (Table 3 and Figure 1). In the overall patient cohort, RSSI diameter was positive correlated with NIHSS scores at both admission (r=0.254, $P<0.001$) (Figure 1A) and discharge (r=0.274, $P<0.001$) (Figure 1B), as well as with MRS scores at admission (r=0.243, $P<0.001$) (Figure 1C) and

Table 2 Logistic Regression Analysis of Risk Factors for RSSIs Across Different Locations and Shapes

	RSSI		
	OR	**95% CI**	***P* Value**
AIP ~ Basal ganglia RSSI			
Model 1	3.276	1.418–7.571	0.005
Model 2	3.003	1.132–7.968	0.027
Model 3	3.269	1.209–8.839	0.020
SIRI ~ Brainstem RSSI			
Model 1	1.823	1.360–2.444	<0.001
Model 2	1.569	1.178–2.091	0.002
Model 3	1.472	1.012–2.143	0.043
SIRI ~ Tubular RSSI			
Model 1	1.324	1.068–1.640	0.010
Model 2	1.319	1.050–1.658	0.017
Model 3	1.440	1.043–1.989	0.027

Notes: Model 1: no covariates were adjusted; **Model 2**: age, time from symptom onset to MRI, NIHSS score at admission, MRS score at admission, hypertension, diabetes mellitus, cardiac disease, BMI, and CSVD burden score were adjusted. **Model 3**: age, time from symptom onset to MRI, NIHSS score at admission, MRS score at admission, hypertension, diabetes mellitus, cardiac disease, BMI, CSVD burden score, and laboratory tests were adjusted.

Abbreviations: RSSI, recent small subcortical infarct; OR, odds ratio; CI, confidence Interval; AIP, atherosclerosis index of plasma; SIRI, system inflammation response index; MRI, magnetic resonance imaging; NHISS, National Institutes of Health Stroke Scale; MRS, Modified Rankin Scale; BMI, body mass index; CSVD, cerebral small vessel disease.

Table 3 Partial Correlation Analysis Between the Diameter of RSSIs and the Severity of Clinical Symptoms Across Different Locations, After Controlling for Age, sex, and the CSVD Burden Score

Diameter of RSSI	NIHSS Score at Admission		NIHSS Score at Discharge		MRS Score at Admission		MRS Score at Discharge	
	r	*P*	r	*P*	r	*P*	r	*p*
Total	0.254	**<0.001**	0.274	**<0.001**	0.243	**<0.001**	0.249	**<0.001**
Subcortical white matter	0.098	0.574	0.046	0.794	0.151	0.386	0.190	0.275
Basal ganglia	0.176	0.025	0.331	**<0.001**	0.182	0.021	0.189	0.016
Brainstem	0.373	**<0.001**	0.276	**0.001**	0.309	**<0.001**	0.284	**<0.001**

Note: Significant differences were indicated in bold ($p < 0.05/16=0.003$).
Abbreviations: RSSI, recent small subcortical infarct; CSVD, cerebral small vessel disease; NHISS, National Institutes of Health Stroke Scale; MRS, Modified Rankin Scale.

discharge (r=0.249, $P<0.001$) (Figure 1D). When stratified by anatomical location, the diameter of RSSIs in the brainstem exhibited the strongest association with clinical severity. Specifically, brainstem lesions were positively correlated with NIHSS scores at admission (r=0.373, $P<0.001$) and discharge (r=0.276, $P=0.001$), as well as MRS scores at admission (r=0.309, $P<0.001$) and discharge (r=0.284, $P<0.001$). These associations remained statistically significant after adjusting for multiple comparisons. In contrast, RSSIs in the basal ganglia exhibited weaker correlations with clinical severity. No statistically significant correlations were observed for RSSIs in the subcortical white matter.

ROC Analysis for RSSI Recurrence

A sum of 336 patients were followed for six months, with 11 experiencing RSSI recurrence and 325 without recurrence. The mean ages of the recurrence and non-recurrence groups were 69.18±9.38 and 63.98±12.83 years, respectively (Table 4). No

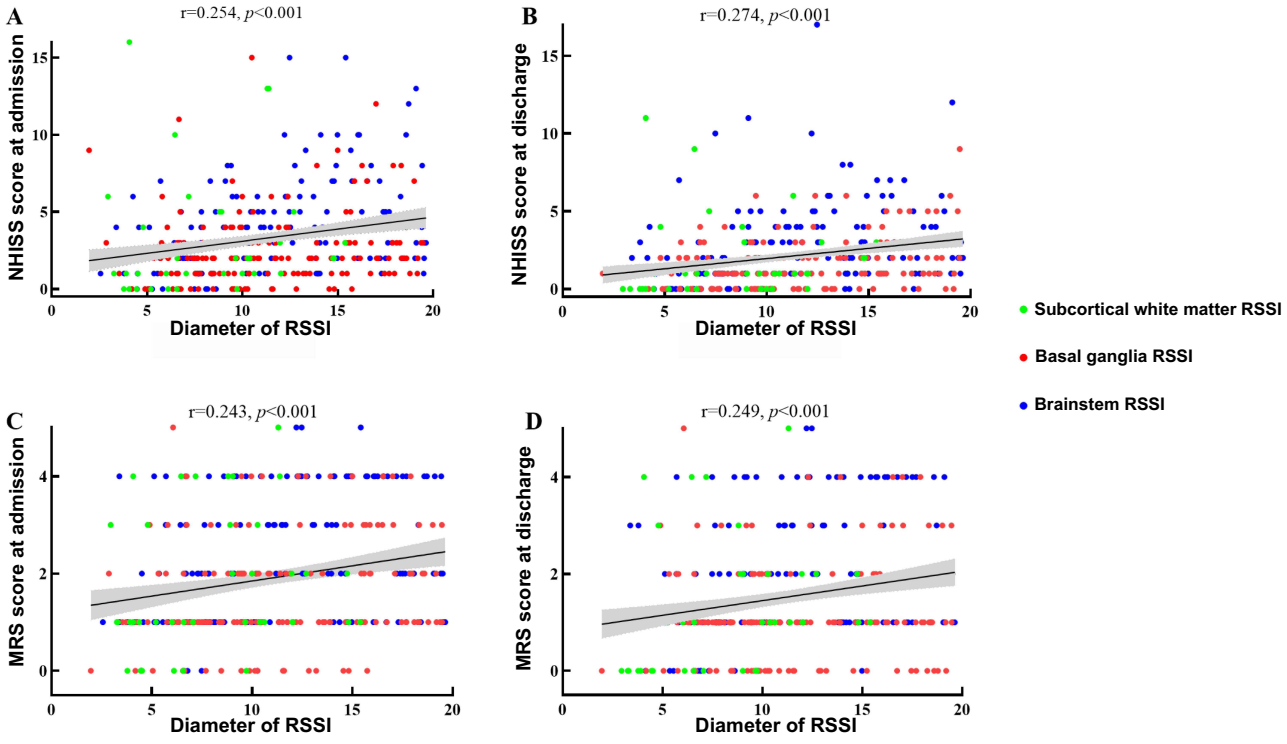

Figure 1 Partial correlation analysis between the diameter of RSSIs and the NHISS score at admission (**A**), discharge (**B**), and MRS score at admission (**C**), discharge (**D**), after controlling for age, sex, and CSVD burden score.
Abbreviations: RSSI, recent small subcortical infarct; NHISS, National Institutes of Health Stroke Scale; MRS, Modified Rankin Scale; CSVD, cerebral small vessel disease.

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Table 4 Comparison of Demographic and Clinical Characteristics of RSSIs With or Without RSSI Recurrence Within Six months

	Without RSSI Recurrence (n=325)	With RSSI Recurrence (n=11)	T/Z/χ^2	*P* Value
Demographic characteristics				
Age (years)	63.98 ± 12.83	69.18 ± 9.38	−1.33	0.183
Male (n.%)	233 (71.69)	6 (54.55)	0.80	0.370
BMI (kg/m^2)	24.86 ± 3.00	24.82 ± 1.59	0.05	0.964
Clinical symptoms				
Time of the initial MRI	4.00 (2.00, 6.00)	5.00 (3.00, 8.00)	−0.98	0.326
NIHSS score at admission	2.00 (1.00, 4.00)	4.00 (1.00, 8.00)	−0.80	0.423
NIHSS score at discharge	1.00 (1.00, 3.00)	1.00 (0.00, 5.00)	−0.26	0.793
MRS score at admission	2.00 (1.00, 3.00)	1.00 (1.00, 4.00)	−0.26	0.792
MRS score at discharge	1.00 (1.00, 2.00)	1.00 (0.00, 3.00)	−0.21	0.833
Vascular risk factors				
Hypertension (n.%)	217 (66.77)	5 (45.45)	2.16	0.142
Diabetes mellitus (n.%)	135 (41.54)	5 (45.45)	0.07	0.796
Hyperlipidemia (n.%)	148 (45.54)	3 (27.27)	0.79	0.374
Cardiac disease (n.%)	19 (5.85)	1 (9.09)	0.20	0.496
Smoking (n.%)	136 (41.85)	1 (9.09)	3.47	0.063
Drinking (n.%)	138 (42.46)	4 (36.36)	0.01	0.926
Neuroimaging markers				
RSSI location			2.64	0.245
Subcortical white matter	33 (10.15)	2 (18.18)		
Basal ganglia	160 (49.23)	3 (27.27)		
Brainstem	132 (40.62)	6 (54.55)		
Diameter of RSSI (mm)	10.60 (7.67, 14.78)	9.22 (4.57, 11.54)	1.36	0.174
Tubular RSSI (n.%)	140 (43.08)	2 (18.18)	1.78	0.182
Lacune (n.%)	131 (40.31)	4 (36.36)	0.07	0.793
Periventricular WMHs (n.%)	100 (30.77)	8 (72.73)	6.77	0.009
Deep WMHs (n.%)	98 (30.15)	5 (45.45)	0.56	0.453
Moderate to severe EPVS (n.%)	91 (28.00)	2 (18.18)	0.14	0.709
Brain atrophy (n.%)	118 (36.31)	5 (45.45)	0.09	0.763
CSVD burden score	1.00 (0.00, 3.00)	2.00 (1.00, 3.00)	−0.91	0.366
Laboratory tests				
Neutrophils (10^9/L)	4.16 (3.37, 5.28)	5.76 (4.03, 6.38)	−2.27	0.023
Lymphocyte (10^9/L)	1.70 (1.30, 2.17)	1.68 (1.24, 1.98)	0.89	0.373
Monocyte (10^9/L)	0.42 (0.34, 0.54)	0.48 (0.41, 0.54)	−1.15	0.250
Red blood cell (10^{12}/L)	4.55 ± 0.54	4.34 ± 0.44	1.28	0.203
Hemoglobin (g/L)	137.98± 16.82	132.27 ± 13.54	1.11	0.266
Platelet (10^9/L)	206.00 (171.50, 238.00)	219.00 (181.00, 295.00)	−0.77	0.442
Triglyceride (mmol/L)	1.55 (1.24, 2.10)	1.06 (1.01, 2.07)	1.49	0.136
HDL-C (mmol/L)	0.98 (0.84, 1.12)	0.90 (0.78, 1.14)	0.46	0.648
Glucose (mmol/L)	5.75 (5.07, 7.80)	6.40 (5.15, 11.30)	−1.22	0.223
AIP	0.20 (0.07, 0.37)	0.13 (−0.02, 0.29)	0.74	0.461
SII	482.01 (375.62, 707.72)	738.75 (464.00, 1385.45)	−2.26	0.024
SIRI	1.04 (0.76, 1.47)	1.69 (1.16, 2.45)	−2.50	0.013

Abbreviations: RSSI, recent small subcortical infarct; BMI, body mass index; MRI, magnetic resonance imaging; NHISS, National Institutes of Health Stroke Scale; MRS, Modified Rankin Scale; WMHs, white matter hyperintensities; EPVS, enlarged perivascular space; CSVD, cerebral small vessel disease; HDL-C, high-density lipoprotein cholesterol; AIP, atherosclerosis index of plasma; SII, systemic immune inflammation index; SIRI, system inflammation response index.

Table 5 The AUC, Sensitivity, and Specificity at Youden's Cut-off for Identifying RSSI Recurrence at Six months

	AUC (95% CI)	Youden's Cut Point	Sensitivity (%)	Specificity (%)	*P* Value
Hypertension	0.607 (0.433 ~ 0.781)	0.213	0.545	0.668	0.229
Periventricular WMHs	0.710 (0.555 ~ 0.865)	0.419	0.727	0.692	0.018
SII	0.700 (0.536 ~ 0.865)	0.327	0.727	0.600	0.024
Combined model	0.853 (0.738 ~ 0.968)	0.663	0.909	0.754	<0.001

Abbreviations: AUC, area under the curve; RSSI, recent small subcortical infarct; CI, confidence interval; WMHs, white matter hyperintensities; SII, systemic immune inflammation index.

statistically significant differences were observed between the groups in terms of demographic characteristics, clinical symptoms, or vascular risk factors. However, the recurrence group exhibited a significantly higher burden of periventricular WMHs (72.73% vs 30.77%, *P*=0.009), as well as elevated levels of the SII [738.75 (464.00, 1385.45) vs 482.01 (375.62, 707.72), *P*=0.024] and the SIRI [1.69 (1.16, 2.45) vs 1.04 (0.76, 1.47), *P*=0.013]. Variables with a *P*-value ≤0.20 were selected for inclusion in the logistic regression model. The final model included age, hypertension, smoking, periventricular WMHs, diameter of RSSI, tubular RSSI, SII, and SIRI. Multivariate regression analysis (Supplementary Table 6) identified hypertension, periventricular WMHs, and SII as independent risk factors for RSSI recurrence. Subsequent ROC analysis revealed that the AUC for periventricular WMHs in predicting RSSI recurrence was 0.710 (95% CI: 0.555–0.865, *P*=0.018), while the AUC for SII was 0.700 (95% CI: 0.536–0.865, *P*=0.024). A combined model incorporating hypertension, periventricular WMHs, and SII demonstrated the best predictive performance, with an AUC of 0.853 (95% CI: 0.738–0.968, *P*<0.001), sensitivity of 0.909, and specificity of 0.754 (Table 5 and Figure 2).

Discussion

In summary, our findings emphasize that RSSIs in different locations and shapes are associated with specific risk factors. Specifically, AIP levels are significantly linked to basal ganglia RSSIs, whereas SIRI is associated with brainstem and tubular RSSIs. RSSI diameter is positively correlated with the severity of clinical symptom, with the strongest

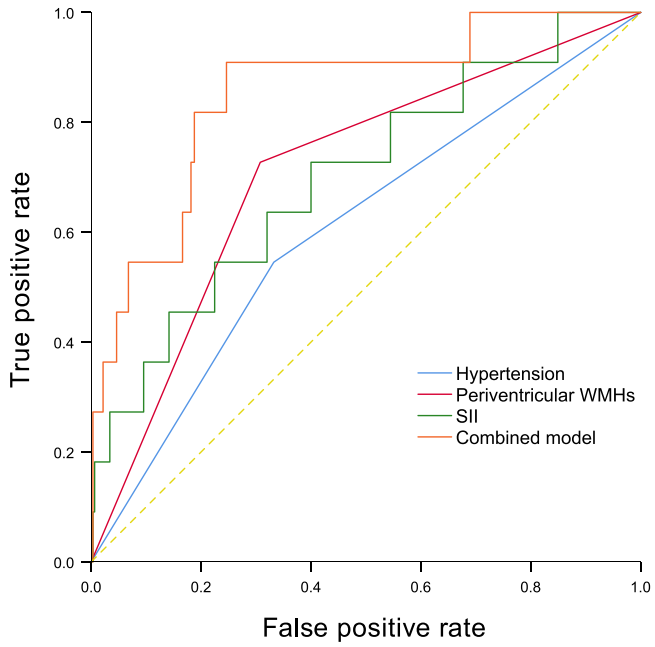

Figure 2 Receiver operating characteristic curve analysis for predicting RSSI recurrence within six months.
Abbreviations: RSSI, recent small subcortical infarct; WMHs, white matter hyperintensities; SII, systemic immune inflammation index.

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association observed in the brainstem RSSI subgroup. Additionally, a predictive model that incorporates hypertension, periventricular WMHs, and SII demonstrated excellent performance in predicting RSSI recurrence within six months.

Previous studies have extensively explored the relationship between vascular risk factors and the occurrence of RSSIs in various brain regions. Although these findings are highly heterogeneous,[21–23] they suggest that the mechanisms underlying RSSIs may vary across different brain regions. In light of these inconsistencies, the present study aims to further investigate the pathophysiological mechanisms of RSSIs. Our results show that RSSIs in the basal ganglia are more strongly associated with perforating artery atherosclerosis, as indicated by the AIP index. This finding aligns with the research by Yuan et al,[24] which identified independent associations between total cholesterol, HDL-C levels, and RSSI occurrence, further supported by lipidomic analyses.[25] We hypothesize that the relationship between AIP and RSSIs in the basal ganglia may involve the following mechanism: elevated AIP levels are often accompanied by a reduction in the size of low-density lipoprotein particles, leading to an increase in the number of small, dense low-density lipoprotein particles.[26] These smaller particles are more prone to deposit in the walls of perforating arteries, compromising both their structure and function. Moreover, elevated AIP levels reflect a reduced protective effect of HDL-C, exacerbating atherosclerosis and ultimately leading to lumen narrowing or occlusion, which promotes the formation of RSSI lesions.[27] In contrast, the lack of significant findings for subcortical white matter RSSIs in our study may be primarily attributed to the relatively small sample size in this subgroup. Previous studies consistently report a lower incidence of RSSIs in subcortical white matter compared to other brain regions.[8,28] The subcortical white matter consists mainly of conduction nerve fibers, and although infarctions in this area can disrupt communication between the cortex and deeper brain regions, the resulting motor and sensory deficits are often mild. These deficits may be under-reported by patients, increasing the likelihood of missed diagnoses.[29]

The SII and SIRI have emerged as novel immune-inflammatory biomarkers, and their associations with CSVD have been explored in previous studies. Recent research has indicated that SII is closely related to WMH burden and basal ganglia EPVS, but not with lacunes or cerebral microbleeds (CMBs).[19,30,31] Elevated SII has also been implicated in the exacerbation of cognitive dysfunction through the worsening of CSVD burden.[32] Additionally, a study by Yuan et al demonstrated that increased neutrophil count, reflecting systemic inflammation, is an independent risk factor for the development of RSSIs.[24] However, to date, no studies have systematically examined the roles of SII and SIRI in different brain regions or various morphological forms of RSSIs. In this study, we present the first evidence linking SIRI to brainstem and tubular RSSIs. Chronic inflammatory may promote leukocyte adhesion to the vascular endothelium, triggering the release of inflammatory cytokines, and initiate an inflammatory cascade, ultimately disrupting endothelial cells.[33,34] The penetrating arteries in the brainstem are relatively thin and lack sufficient collateral circulation, which makes the blood-brain barrier more permeable and vulnerable to systemic inflammation. Notably, during acute ischemic stroke, there is a significant increase in the release of inflammatory mediators.[35] Consequently, the exact causal relationship between systemic inflammation and RSSIs remains unclear and warrants further investigation through experimental and longitudinal studies. Interestingly, we also observed an association between SIRI and irregular tubular infarcts. These tubular RSSIs may result from the occlusion of large penetrating arteries, leading to the fusion of multiple infarcts, whereas round or oval-shaped RSSIs might indicate the involvement of terminal small vessels.[36] However, given that this study assessed RSSI morphology solely using axial imaging sequences, the interpretation of these findings should be approached with caution.

Consistent with previous studies,[5] we found that the subcortical white matter RSSI group exhibited the highest CSVD burden, whereas the brainstem RSSI group displayed the most severe clinical symptoms. Rudilosso et al also reported a positive correlation between subcortical white matter RSSIs and a higher CSVD burden, particularly with the presence of WMHs, which aligns with our findings.[28] Despite its small volume, the brainstem serves as a crucial relay station for both ascending and descending pathways, and plays a crucial role in regulating functions such as respiration, heart rate, blood pressure, and consciousness.[37] The brainstem's blood supply primarily relies on a limited number of major arteries, and its vascular structure is relatively fragile, with insufficient collateral circulation. Therefore, even small infarctions in this region can lead to substantial neurological deficits,[38] which helps explain the stronger correlation between infarct diameter and clinical severity observed in the brainstem RSSI group. Our findings elucidate the complex relationship between the clinical manifestations of RSSIs, their anatomical locations, lesion extent, and underlying pathological burden.

After six months of follow-up, the recurrence rate of RSSIs in our study was 3.3%, which is consistent with findings from previous short-term follow-up studies.[39] In our analysis, hypertension, periventricular WMHs, and SII were identified as independent predictors of RSSI recurrence. These results align with those of a recent observational study, which reported that baseline CSVD imaging markers - particularly CMBs and severe WMHs - were significantly associated with an increased risk of recurrent ischemic stroke in patients with RSSI.[40] However, our study did not include susceptibility-weighted imaging, and therefore, we were unable to assess the burden of CMBs. The linkage between inflammatory factors and RSSI recurrence risk has been well-established in the literature. Specifically, prospective cohort studies have demonstrated that elevated levels of tumor necrosis factor receptor 1[41] and high-sensitivity C-reactive protein[42] are associated with an increased risk of recurrent RSSIs. Despite these findings, the role of antihypertensive treatment in preventing RSSI recurrence remains a topic of ongoing debate. For instance, the Secondary Prevention of Small Subcortical Strokes trial identified a J-shaped relationship between blood pressure control and stroke recurrence risk in RSSI patients.[43] Additionally, RSSI patients with a higher burden of WMH appeared to benefit more from intensive blood pressure control (systolic BP <130 mmHg), as this intervention significantly reduced stroke recurrence.[44] While SII was significantly associated with RSSI recurrence, its predictive value was enhanced when combined with traditional risk factors such as hypertension and periventricular WMHs. This finding suggests that a multifactorial risk model more accurately reflects the underlying pathophysiology of RSSIs than single markers alone. Early identification of high-risk individuals through accessible blood biomarkers, in combination with MRI-based CSVD markers, may facilitate clinical risk stratification and guide personalized preventive strategies. However, the relatively short follow-up period and the limited number of recurrent RSSI cases (n = 11) restricted our ability to perform subgroup analyses. Therefore, further validation in larger, long-term prospective cohorts is warranted.

Our study has several notable strengths. To the best of our knowledge, this is the first study to comprehensively investigate the relationship between AIP, SII, SIRI and RSSI risk across different anatomical locations and morphologies, combining both a baseline cross-sectional analysis with a six months longitudinal follow-up. The AIP, SII, and SIRI utilized in this study are readily accessible, cost-effective, and easy to measure, making them highly valuable for clinical application and widespread implementation. Additionally, all imaging biomarkers were independently assessed by two neuroimaging experts, with final determinations made following discussion, ensuring the reliability of the results. However, several limitations must also be acknowledged. First, baseline age was not matched among the groups. Nonetheless, we controlled for age in all subsequent analyses to mitigate its potential confounding effect. Second, the AIP, SII, and SIRI were measured only at baseline, providing a snapshot of these indices at a single time point. As such, these measures do not reflect the dynamic changes in atherosclerosis and inflammation over time. Third, this study was a single-center, retrospective analysis with a relatively short follow-up period of six months, which may limit the generalizability of the findings and hinder the establishment of causal relationships, particularly given the small number of recurrent cases. Finally, the lack of detailed information on the use of antiplatelet agents and plaque-stabilizing drugs may have influenced the development of the risk factor model for RSSI recurrence. Future investigation, incorporating multi-center, large-scale, long-term follow-up data, is necessary to verify and expand upon our findings.

Conclusion

Our research demonstrated a significant positive correlation between the AIP and basal ganglia RSSIs, as well as between SIRI and brainstem and tubular RSSIs, highlighting the regional and morphological differences in the pathogenesis of RSSIs. Additionally, baseline SII levels, in conjunction with hypertension and periventricular WMHs, were identified as strong predictors of RSSI recurrence within six months. These findings may provide clinically relevant insights for individualized risk stratification and the development of early screening and preventive strategies for RSSIs, particularly in Asian settings. Future large-scale, multicenter studies are warranted to validate the predictive value of these biomarkers and to establish cost-effective, regionally adapted screening protocols aimed at reducing the burden of RSSIs and broader CSVD.

Data Available Statement

The datasets generated during the current study are available from the corresponding author (Zhongwu Sun) upon reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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