Systemic Inflammation Response Index as a Predictor of Stroke Risk in Elderly Patients with Hypertension: A Cohort Study

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Objective: This study aimed to evaluate the relationship between the systemic inflammation response index (SIRI) and the risk of stroke and its subtypes in elderly patients with hypertension and to explore its predictive accuracy and any potential effect modifiers.

Methods: The study included 4749 participants with no history of stroke at baseline. Cox regression was used to estimate adjusted hazard ratios (HR) and 95% confidence intervals (CIs). Interaction tests and subgroup analyses were conducted. The predictive performance of various inflammatory indicators for stroke was compared using the area under the curve (AUC), continuous net reclassification improvement (NRI), and integrated discrimination improvement (IDI).

Results: During a median follow-up period of 3.2 years, 640 strokes were recorded, of which 526 were ischemic and the remainder hemorrhagic. After adjustment for confounders, compared to the reference group, the HRs (95% CI) of stroke were 1.28 (95% CI, 1.01–1.64) and 1.46 (95% CI, 1.14–1.88) for participants in the second and third tertiles, respectively. We observed interactions between SIRI and homocysteine levels (< 15 vs. ≥ 15 μmol/L) (p for interaction = 0.014) on ischemic stroke risk. Furthermore, the AUC, NRI, and IDI analyses demonstrated that SIRI exhibited better predictive value for stroke risk when compared to other indicators. Similar results were observed for both ischemic and hemorrhagic strokes.

Conclusion: Elevated SIRI levels were significantly associated with the risk of stroke and its subtypes in elderly patients with hypertension, suggesting its potential as a promising indicator for stroke risk in this population. However, larger prospective studies are needed to confirm these findings.

Keywords: systemic inflammation response index, stroke, elderly, hypertension, inflammation, cohort study

Introduction

Stroke is one of the leading causes of death in China and the second leading cause of death globally.1–4 It exhibits significant morbidity, mortality, and disability, imposing a substantial burden on society and families.1,5 With a rapidly aging population, the incidence of hypertension has increased annually. Several large-scale epidemiological surveys in China have shown that about 23.2–27.8% of adults suffer from hypertension, and even more than 50% of people over 60 years of age are affected.6–9 Hypertension, especially in the elderly, is a high-risk factor for stroke.10 Therefore, identifying the residual risk of stroke and early risk stratification in elderly patients with hypertension is critical to the more effective formulation of risk reduction strategies.
Inflammation is associated with a poor clinical prognosis in patients with various diseases. In recent decades, accumulating evidence has confirmed that inflammation is an integral part of the development and maintenance of hypertension, the formation of atherosclerosis, and the rupture of arterial plaques, suggesting a key role in the emergence of cardiovascular diseases (CVD). Various markers reflecting inflammation include peripheral platelets, neutrophils, lymphocytes, and monocytes, as well as indicators of inflammation constructed based on these markers, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR). Recently, two novel inflammatory indices, the systemic immune inflammation index (SII) and the systemic inflammation response index (SIRI), composed of platelets and three subtypes of white blood cells, have emerged as significant correlates of CVD. In particular, SIRI is regarded as a superior indicator of chronic inflammation and has a good prognostic predictive value for patients with acute strokes and tumors. However, little research has investigated the relationship between SIRI and stroke, especially in elderly hypertensive patients.

The aim of this study was to evaluate the relationship between SIRI and the risk of stroke and its subtypes in the elderly hypertensive population and to explore its predictive superiority and any potential effect modifiers.

Materials and Methods

Study Population

This study was a retrospective cohort study. Hypertensive patients with ≥2 visits registered at the Hypertension Center of Xinjiang Uygur Autonomous Region People’s Hospital from January 1, 2010, to December 31, 2021, were enrolled. Participants in the retrospective study were selected, as previously mentioned. There were a total of 8031 elderly hypertensive patients greater than or equal to 60 years of age. Exclusion criteria can be found in Figure S1. Ultimately, 4749 participants were included in the final analysis. The Ethics Board of the People’s Hospital of the Xinjiang Uygur Autonomous Region (KY2021031901) approved this retrospective study. Due to the retrospective design and the use of de-identified data, an exemption status for individual informed consent was provided. The Declaration of Helsinki guidelines were followed during the whole study. All data collected was kept strictly confidential and de-identified prior to analysis. Each patient’s data has an anonymous numeric code that prevents the patient from being identified in order to protect the patient’s privacy. The study adhered to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) when presenting its findings.

Data Collection and Definitions

Data for this study was obtained from the patient’s electronic medical records. Alcohol use and smoking status were categorized as binary variables: never/former or current. Standardized procedures were used to record blood pressure, height, and weight. The body mass index (BMI) was calculated in kilograms per square meter. All baseline blood samples were collected after an overnight fast. Fasting plasma glucose (FPG), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), high-density lipoprotein (HDL-C), homocysteine (Hcy), and uric acid (UA) were measured by the automatic biochemical analyzer. Hcy level ≥ 15 mmol/L was defined as hyperhomocysteinemia. The estimated glomerular filtration rate (eGFR) was calculated by the CKD-EPI equation. Routine blood tests, including white blood cell, neutrophil, monocyte, lymphocyte, and platelet counts, were determined by a full blood count analyzer. The following inflammatory indicators were calculated: LMR = lymphocyte count/monocyte count; PLR = platelet count/lymphocyte count; NLR = neutrophil count/lymphocyte count; SII = platelet count * neutrophil count/lymphocyte count; SIRI = neutrophil count * monocyte count/lymphocyte count. Medical history was identified by the ICD-10 codes. The medical history included coronary heart disease (CHD) (I24 and I25), atrial fibrillation (AF) (I48), diabetes (E10–E14), and dyslipidemia (E78). The Charlson comorbidity index (CCI) provided a summary of the overall burden of comorbidities. Table S1 lists the drugs involved in this study.
Outcomes and Follow-Up
The primary outcome was the first stroke, whether ischemic or hemorrhagic. The supplemental materials and methods describe methods for determining an incident stroke. Medical records, interviews, contacts with regional sickness and death registries, or access to the database of basic medical insurance were all used to establish the study’s outcomes. Patients were monitored from the time of enrollment until the end of the period, which was defined as the date of the final follow-up appointment, the date the first study outcome appeared, the date of death, or the conclusion of the investigation (December 31, 2021).

Statistical Analysis
The missForest procedure based on R was employed to impute the missing covariates. Continuous variables are presented as means ± standard deviation (SD) or medians (interquartile range) as appropriate, and categorical variables as proportions. Kaplan-Meier analysis was carried out with a log rank test. The proportional hazard assumption was verified using Schoenfeld residuals (Figure S2). Collinearity was assessed using variance inflation factors (Table S2). Cox proportional hazards models were utilized to calculate hazard ratios (HRs) and 95% confidence intervals (CI) for stroke events, with adjustment for age, sex, heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), smoking status, drinking status, uric acid (UA), eGFR, triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), fasting plasma glucose (FPG), homocysteine (Hcy), platelet count, hypertension duration, CHD, diabetes, dyslipidemia, AF, and the CCI. Restricted cubic splines were used to graphically assess the dose-response correlations between SIRI and stroke risk. We tested for interactions and performed subgroup analyses. To test the robustness of the findings, several additional sensitivity analyses were conducted. Prediction performance was measured by the receiver operating characteristics curve (ROC) and area under the ROC curve (AUC). A comparison of prediction performance was assessed using the reclassification method, expressed as continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI). Further details on the statistical analysis can be found in the supplemental materials and methods. R version 4.1.1 was used for all statistical analyses. The threshold for statistical significance (p = 0.05) was applied to all two-sided p values.

Results
Baseline Characteristics
As shown in the flow chart (Figure S1), a total of 4749 participants were included in the study. The study participants had an average age of 66.39 (SD, 4.67) years, and their average SIRI was 1.04 (SD, 0.50). Table 1 presents the baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Tertile 1 (&lt; 0.77)</th>
<th>Tertile 2 (0.77–1.20)</th>
<th>Tertile 3 (&gt; 1.20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants, N</td>
<td>1581</td>
<td>1585</td>
<td>1583</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>66.64 ± 4.73</td>
<td>66.18 ± 4.58</td>
<td>66.37 ± 4.69</td>
<td>0.021</td>
</tr>
<tr>
<td>Male, %</td>
<td>808 (51.11%)</td>
<td>827 (52.18%)</td>
<td>835 (52.75%)</td>
<td>0.644</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>79.90 ± 9.63</td>
<td>80.09 ± 9.61</td>
<td>80.58 ± 10.04</td>
<td>0.132</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>142.56 ± 19.17</td>
<td>143.41 ± 19.86</td>
<td>143.84 ± 20.47</td>
<td>0.182</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>87.46 ± 13.45</td>
<td>88.86 ± 14.17</td>
<td>89.17 ± 14.00</td>
<td>0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>22.68 ± 2.91</td>
<td>24.50 ± 3.05</td>
<td>25.78 ± 2.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>405 (25.62%)</td>
<td>463 (29.21%)</td>
<td>482 (30.45%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Current drinker, %</td>
<td>380 (24.04%)</td>
<td>414 (26.12%)</td>
<td>438 (27.67%)</td>
<td>0.065</td>
</tr>
<tr>
<td>Laboratory data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uric acid, µmol/L</td>
<td>320.34 ± 87.85</td>
<td>335.40 ± 88.39</td>
<td>343.32 ± 93.80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR, mL/min per 1.73 m²</td>
<td>84.04 ± 15.66</td>
<td>81.62 ± 15.13</td>
<td>79.26 ± 14.85</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

(Continued)
characteristics of the study participants categorized into SIRI tertiles. Participants with higher SIRI levels tended to have higher BMI, UA, DBP, TG, HLD-C, blood cell counts, and higher rates of diabetes compared with participants in the lowest tertile group. Similarly, they were more likely to receive antiplatelet, lipid-lowering, and glucose-lowering treatments. For SBP, TC, LDL-C, and Hcy, no discernible trend was observed.

Association Between SIRI and Total Stroke and Its Subtypes

The mean duration of follow-up time was 3.67 years, with a median duration of 3.20 years. During this period, 640 strokes were identified, of which 526 were ischemic strokes (IS) and the remainder were hemorrhagic strokes (HS). The Kaplan–Meier curves showed the participants in the highest tertile of SIRI had a higher cumulative incidence of total stroke, IS, and HS compared to those in other groups over the follow-up period (Log rank test, all p < 0.05; Figure 1).

Table 2 presents the relationships between SIRI and the risk of stroke and its subtypes. Overall, there were significant positive correlations between SIRI and the risk of total stroke (per SD increment; HR, 1.26, 95% CI: 1.15–1.38); IS (per SD increment; HR, 1.19, 95% CI: 1.07–1.32); and HS (per SD increment; HR, 1.51, 95% CI: 1.25–1.81) (Figure 2).
After multivariable adjustment, compared to the reference group (the first tertile), the HRs of total stroke were 1.28 (95% CI, 1.01–1.64) in the second tertile and 1.46 (95% CI, 1.14–1.88) in the highest tertile. SIRI showed a positive and dose-dependent association with total stroke risk in Model 3 (p for trend = 0.003). The same patterns were observed for the risks of IS and HS.

Subgroup and Sensitivity Analysis
The results of subgroup analyses are shown in Figure 3. There was a significant interaction for patients with compared with patients without hyperhomocysteinemia (p for interaction = 0.014; Figure 3B) when looking at IS as an outcome. For total stroke and HS, there were no interactions for any of the subgroups (all p for interactions > 0.05; Figure 3A and C). In the sensitivity analyses, we excluded participants with less than 1 year of follow-up, and the results remained consistent (Table S3).

Figure 1 Kaplan-Meier survival curves for total stroke and individual outcomes based on SIRI tertiles. (A) Total stroke, (B) ischemic stroke, and (C) hemorrhagic stroke.
Additionally, participants with AF at baseline were excluded, and the results still showed a strong correlation (Table S4). Furthermore, we adjusted for multiple drugs used based on Model 3, and the results remained consistent (Table S5). The analysis using competing-risks models yielded similar results (Table S6). We also excluded participants with missing values, and the results remained stable (Table S7). Ultimately, the E-value indicated that unmeasured confounding was unlikely to account for the results (Table S8).

**Comparative Analysis of Five Inflammatory Indicators in Predicting Stroke**

ROC curve analysis was performed to determine the value of LMR, PLR, NLP, SII, and SIRI for predicting total stroke and its subtypes (Figure S3). Among all inflammatory parameters, the SIRI consistently exhibited the highest AUC value for total stroke and its subtypes. Furthermore, the cNRI and IDI for total stroke and its subtypes were significantly improved by the addition of SIRI to the basic model (Table S9). Nevertheless, adding other inflammatory parameters (LMR, PLR, NLR, and SII) did not significantly enhance the prediction.

**Discussion**

Currently, most studies investigating the relationship between inflammation and cerebrovascular disease primarily focus on the cellular level. These studies indicate that multiple cellular inflammatory factors are crucial to stroke occurrence and prognosis. However, our study aims to fill this research gap by investigating the association between inflammation, specifically SIRI, and the risk of total stroke and its subtypes in hypertensive elderly patients. We found that elevated levels of SIRI substantially increase the risk of stroke, even after adjusting for multiple confounders. The dose-response curve analysis further supports a significant positive correlation. Furthermore, in comparisons of various inflammatory indicators, we observed that SIRI consistently showed significant and stable results in assessing stroke risk.

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**Table 2** Hazard Ratios (95% Confidence Intervals) of Incident Stroke According to the SIRI

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Unadjusted model</th>
<th>Adjusted Model 1</th>
<th>Adjusted Model 2</th>
<th>Adjusted Model 3</th>
<th>Bootstrapping*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Per 1 SD increase</td>
<td>1.26 (1.16, 1.37)</td>
<td>1.27 (1.17, 1.38)</td>
<td>1.27 (1.17, 1.38)</td>
<td>1.26 (1.15, 1.38)</td>
<td>1.25 (1.15, 1.37)</td>
</tr>
<tr>
<td>Tertile of SIRI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 (lowest)</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>T2</td>
<td>1.33 (1.05, 1.68)</td>
<td>1.34 (1.06, 1.70)</td>
<td>1.34 (1.06, 1.70)</td>
<td>1.28 (1.01, 1.64)</td>
<td>1.29 (1.01, 1.64)</td>
</tr>
<tr>
<td>T3 (highest)</td>
<td>1.55 (1.23, 1.95)</td>
<td>1.56 (1.24, 1.96)</td>
<td>1.56 (1.24, 1.96)</td>
<td>1.46 (1.14, 1.88)</td>
<td>1.47 (1.14, 1.89)</td>
</tr>
<tr>
<td>P for trend &lt;0.001</td>
<td>1.20 (1.09, 1.31)</td>
<td>1.20 (1.09, 1.32)</td>
<td>1.20 (1.09, 1.32)</td>
<td>1.19 (1.07, 1.32)</td>
<td>1.19 (1.07, 1.32)</td>
</tr>
<tr>
<td><strong>Ischemic stroke</strong></td>
<td></td>
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<tr>
<td>Per 1 SD increase</td>
<td>1.20 (1.09, 1.31)</td>
<td>1.20 (1.09, 1.32)</td>
<td>1.20 (1.09, 1.32)</td>
<td>1.19 (1.07, 1.32)</td>
<td>1.19 (1.07, 1.32)</td>
</tr>
<tr>
<td>Tertile of SIRI</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>T1 (lowest)</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>T2</td>
<td>1.28 (0.99, 1.66)</td>
<td>1.29 (1.00, 1.68)</td>
<td>1.30 (1.00, 1.68)</td>
<td>1.25 (0.96, 1.64)</td>
<td>1.26 (0.96, 1.64)</td>
</tr>
<tr>
<td>T3 (highest)</td>
<td>1.43 (1.11, 1.85)</td>
<td>1.44 (1.12, 1.86)</td>
<td>1.44 (1.11, 1.86)</td>
<td>1.38 (1.05, 1.82)</td>
<td>1.39 (1.05, 1.83)</td>
</tr>
<tr>
<td>P for trend &lt;0.001</td>
<td>1.20 (1.09, 1.31)</td>
<td>1.20 (1.09, 1.32)</td>
<td>1.20 (1.09, 1.32)</td>
<td>1.19 (1.07, 1.32)</td>
<td>1.19 (1.07, 1.32)</td>
</tr>
<tr>
<td><strong>Hemorrhagic stroke</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Per 1 SD increase</td>
<td>1.56 (1.31, 1.85)</td>
<td>1.56 (1.31, 1.85)</td>
<td>1.56 (1.31, 1.85)</td>
<td>1.51 (1.25, 1.81)</td>
<td>1.51 (1.26, 1.82)</td>
</tr>
<tr>
<td>Tertile of SIRI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 (lowest)</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>T2</td>
<td>1.57 (0.89, 2.79)</td>
<td>1.58 (0.89, 2.81)</td>
<td>1.59 (0.89, 2.83)</td>
<td>1.44 (0.79, 2.59)</td>
<td>1.43 (0.79, 2.59)</td>
</tr>
<tr>
<td>T3 (highest)</td>
<td>2.18 (1.26, 3.77)</td>
<td>2.19 (1.27, 3.79)</td>
<td>2.19 (1.27, 3.79)</td>
<td>1.89 (1.05, 3.40)</td>
<td>1.88 (1.04, 3.39)</td>
</tr>
<tr>
<td>P for trend &lt;0.001</td>
<td>0.05</td>
<td>0.04</td>
<td>0.05</td>
<td>0.03</td>
<td>0.034</td>
</tr>
</tbody>
</table>

**Notes:** Data are hazard ratios (95% confidence intervals). Adjusted Model 1: Adjusted age and sex. Adjusted Model 2: Adjusted Model 1 + heart rate, systolic blood pressure, diastolic blood pressure, body mass index, smoking status, and drinking status. Adjusted Model 3: Adjusted Model 2 plus uric acid, eGFR, homocysteine, platelet count, hypertension duration, coronary heart disease, diabetes, dyslipidemia, atrial fibrillation, and the Charlson comorbidity index. *Bootstrapping was conducted with 1000 bootstrap samples via Adjusted Model 3.

**Abbreviations:** SD, standard deviation; SIRI, systemic inflammatory response index; eGFR, estimated glomerular filtration rate.
Traditional indicators, such as LMR, PLR, and NLR, have been widely used to quantify the inflammatory state. In contrast, two novel indicators, SII and SIRI, integrate information from three immune pathways, including the sustained inflammatory response of monocytes and neutrophils as well as immune regulation by lymphocytes. These novel indicators offer a more comprehensive assessment of the inflammatory state.

Previous studies have demonstrated the validity of SII and SIRI in assessing the level of inflammation and its association with metabolic disorders, CVD, cancer, and acute stroke prognosis, particularly SIRI. In this cohort study, we investigated the association between SIRI and stroke risk in elderly patients with hypertension. Our findings revealed that increasing SIRI levels were associated with an elevated risk of stroke. Consistent with our results, several previous studies have shown that chronic inflammation increases the risk of CVD and stroke.

In a study of SIRI and SII dynamic status and the risk of CVD, subjects with a significantly higher risk of CVD were found to have higher levels of SIRI, and in particular, SIRI levels significantly increased the risk of stroke. Huang et al found that SIRI could predict the severity and functional outcome of stroke patients. The higher SIRI was correlated with a greater risk of stroke severity, and it may be a predictor of the early functional outcome of stroke. Additionally, SIRI has been identified as an independent risk factor for stroke prognosis and outcomes in patients with acute ischemic stroke.

A substantial body of evidence indicates that inflammation plays a significant role in cerebrovascular disease and is a key mechanism contributing to the risk of stroke. To date, no randomized controlled trials have been completed on the use of anti-inflammatory drugs for stroke prevention. However, there have been a number of heart disease-related studies...
randomized controlled trials reported. Indirectly, these studies offer significant proof-of-concept data for the contribution of inflammation to stroke etiology and support the need for randomized controlled studies of anti-inflammatory medicines in the prevention of stroke. In conclusion, our findings may, in part, help with risk stratification and better clinical

Figure 3 Subgroup analyses of the relationship between SIRI and risk of stroke events. (A) Total stroke, (B) ischemic stroke, and (C) hemorrhagic stroke.
identification of elderly patients with hypertension who need primary prevention or personalized medicine approaches to management, such as anti-inflammatory therapy for high-risk patients who need to start primary prevention.

Meanwhile, subgroup analyses showed that the SIRI increased the risk of incident IS, especially in patients with hyperhomocysteinemia. The exact mechanisms linking inflammation, hyperhomocysteinemia, and IS remain to be determined. Several studies have shown a significant correlation between HCy levels and the severity of inflammation.\textsuperscript{55,56} A previous study suggested that inflammatory monocytes could be a potential target for treating inflammation and cardiovascular complications in hyperhomocysteinemia patients.\textsuperscript{57} Youssef et al\textsuperscript{58} also suggested the involvement of inflammation-related mechanisms in the association between Hcy and CVD risk. However, further investigations are needed to fully understand the underlying mechanisms.

Strong evidence exists that inflammatory processes in hypertension are dominated by innate and adaptive immune responses, and this relationship is particularly evident in elderly patients with hypertension.\textsuperscript{59,60} Through the excessive release of cytokines and chemokines, activated immune cells can infiltrate target tissues, resulting in the promotion of end-organ injuries.\textsuperscript{61,62} Furthermore, an increasing number of studies have demonstrated the relevance of inflammation in the pathogenesis of stroke. Firstly, inflammation of the cerebrovascular system triggers an oxidative stress response, leading to the occlusion of blood vessels. This triggers an immediate immune response in the ischemic brain, promoting the chemotaxis of inflammatory cells into brain tissue, resulting in brain tissue damage.\textsuperscript{63–65} Additionally, proinflammatory signals from immune mediators also promptly activate permanent cells and affect the infiltration of inflammatory cells into the ischemic zone, exacerbating the brain injury.\textsuperscript{66} Secondly, cerebral ischemia not only activates both innate immunity and adaptive immunity but also releases a large amount of indiscriminate humoral and cellular inflammation factors to damage brain cells and tissues, thus forming a vicious cycle.\textsuperscript{66,67} Thirdly, high inflammatory stimulation can lead to the activation of the complement system, causing a large number of active complement components produced in the blood vessels to enter the brain parenchyma and damage the brain tissue.\textsuperscript{68,69} Meanwhile, the activation of complement also promotes the phagocytosis of microglia on stressed neurons, leading to impairment of the corresponding nerve function.\textsuperscript{70,71} Finally, inflammation is also involved in all stages of atherosclerotic plaque, leading to thrombotic events.\textsuperscript{46,72,73}

To our knowledge, this study represents the first exploration of the association between SIRI levels and the risk of stroke and its subtypes in elderly hypertensive patients. This study has several strengths worth noting. Firstly, it boasts a relatively large sample size and a prolonged follow-up duration. Secondly, the confidence interval for continuous NRI and IDI was generated through 1000 repeated samplings to minimize the impact of sampling error. Other advantages include multiple sensitivity analyses to confirm the robustness of the findings. Nevertheless, certain limitations should be acknowledged. Firstly, SIRI measurements were only obtained at baseline and did not account for dynamic changes during the follow-up period. Secondly, while multivariable adjustment and multiple sensitivity analyses were performed, unmeasured confounding remains. Thirdly, being an observational study, it can only report on associations but cannot attribute causality. Lastly, given that this study was conducted solely on a Chinese population, the external generalizability of the findings remains uncertain. Thus, further validation of these results in future studies is warranted.

**Conclusion**

Elevated SIRI levels were significantly associated with the risk of stroke and its subtypes in elderly hypertensive patients. Consequently, larger-scale, multicenter cohort studies are warranted to validate these initial findings.

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**Disclosure**

The authors report no conflicts of interest in this work.
References


