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ORIGINAL RESEARCH

Systemic Immune-Inflammation Index is Associated with Cerebral Small Vessel Disease Burden and Cognitive Impairment

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Objective: This study sought to explore the associations of the systemic immune-inflammation index (SII) with total cerebral small vessel disease (CSVD) burden and cognitive impairment.

Methods: We enrolled 201 patients in the retrospective study with complete clinical and laboratory data. The SII was calculated as platelet count × neutrophil count/lymphocyte count. Cognitive function was evaluated by the Mini-Mental State Examination (MMSE). Total CSVD burden was assessed based on magnetic resonance imaging. We performed logistic regression models, Spearman correlation, and mediation analysis to evaluate the associations of SII with CSVD burden and cognitive impairment.

Results: After adjustment for confounding factors in the multivariate binary logistic regression model, elevated SII (odds ratio [OR], 3.263; 95% confidence interval [CI], 1.577–6.752; $P = 0.001$) or severe CSVD burden (OR, 2.794; 95% CI, 1.342–5.817; $P = 0.006$) was significantly associated with the risk of cognitive impairment. Correlation analyses revealed that SII levels were negatively associated with MMSE scores (rs = −0.391, $P < 0.001$), and positively associated with the total CSVD burden score (rs = 0.361, $P < 0.001$). Moreover, SII was significantly related to the severity of the CSVD burden (OR, 2.674; 95% CI, 1.359–5.263; $P = 0.004$). The multivariable-adjusted odds ratios (95% CI) in highest tertile versus lowest tertile of SII were 8.947 (3.315–24.145) for cognitive impairment and 4.945 (2.063–11.854) for severe CSVD burden, respectively. The effect of higher SII on cognitive impairment development was partly mediated by severe CSVD burden.

Conclusion: Elevated SII is associated with severe CSVD burden and cognitive impairment. The mediating role of severe CSVD burden suggests that higher SII may contribute to cognitive impairment through aggravating CSVD burden.

Keywords: systemic immune-inflammation index, inflammation, cognitive impairment, cerebral small vessel disease, total burden

Introduction

As life expectancies and the aging population across the world continue to rise, cognitive impairment is a major obstacle to healthy aging.[1,2] Cerebral small vessel disease (CSVD), common in the elderly, has become a primary vascular contributor to cognitive impairment.[3] It contributes to 45% of all dementias, posing a tremendous socioeconomic burden.[4,5]

CSVD is a chronic disease caused by various etiologies affecting the small intracerebral arteries and their distal branches, arterioles, capillaries, and small veins.[6] White matter hyperintensity (WMH) and lacunes of presumed vascular origin, cerebral microbleeds (CMBs), and enlarged perivascular space (EPVS) are typical magnetic resonance imaging (MRI) features of the disease.[7] Based on these MRI markers, the total CSVD burden score can serve as a better indicator of the severity of CSVD.[8] It has been demonstrated that total CSVD burden is strongly associated with the development

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of cognitive impairment.[9] Although many studies have focused on the etiological mechanisms of CSVD, they are not yet clear. Recent studies have found that inflammation is strongly associated with CSVD.[10]

Recently, the systemic immune-inflammation index (SII) has been proposed as a relatively new systemic inflammatory biomarker. SII is calculated using neutrophil, lymphocyte, and platelet counts in the peripheral blood, more comprehensively reflecting the systemic immune response and inflammatory status.[11,12] Previous studies have revealed that SII has a very high prognostic value in various malignant tumors[13,14] and are associated with poor outcomes in cerebrovascular,[15] cardiovascular[16] and autoimmune diseases.[17] We were particularly interested in its positive correlations with basal ganglia EPVS (BG-EPVS) and modified WMH burden.[18] In addition, several population-based studies have confirmed the association between SII and cognitive impairment.[19–21] Therefore, we speculate that there may be some potential relationship among them. However, the association of SII with total CSVD burden as well as cognitive function has not been explored simultaneously.

In the current study, we explored whether a higher level of SII increases the severity of CSVD burden and the risk of cognitive impairment, as well as whether the effects of higher SII on cognitive impairment are mediated by the severe CSVD burden.

Materials and Methods

Study Population

This cross-sectional study retrospectively analyzed data from hospitalized patients at Hebei General Hospital between January 2018 and December 2021. We enrolled patients over 50 years of age who had the blood examinations, completed the cognitive function assessment, and underwent brain MRI to evaluate CSVD markers. Exclusion criteria: (1) patients with active infection or use of antibiotics within 2 weeks; (2) hematologic disorders, malignant tumors, autoimmune diseases; (3) recent immunosuppressant treatment; (4) with tumors of the brain or other systems, surgery, or severe trauma; (5) acute ischemic/hemorrhagic stroke, myocardial infarction; (6) white matter damage of non-vascular origin, such as metabolic encephalopathy, multiple sclerosis; (7) cognitive impairment may be caused by other conditions, such as carbon monoxide poisoning, hyperthyroidism, hypothyroidism, severe anxiety, or depression. Ultimately, a total of 201 eligible patients participated in the analyses. This study was conducted according to the declaration of Helsinki and approved by the Ethical Committees of Hebei General Hospital (No.2022166).

Clinical Characterization

All demographic and risk factors were acquired from medical records: age, sex, years of education, body mass index (BMI), smoking status, and alcohol consumption. Medical history was also collected, including hypertension, diabetes mellitus, coronary heart disease and stroke. Laboratory biomarker were measured, including total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), total homocysteine (tHcy), uric acid (UA), neutrophil count, lymphocyte count, and platelet count. The SII was calculated as platelet count × neutrophil count/lymphocyte count.[11]

MRI Acquisition and Assessment

Brain MRI was performed in all eligible participants using 3.0-Tesla MRI scanners (Signa, GE Healthcare of American). The MRI protocol and detailed acquisition parameters were as follows: (1) T1-weighted imaging (T1WI), repetition time (TR)/echo time (TE) = 1909/20.2 milliseconds (ms), field of view (FOV) = 240 × 192mm^2, acquisition matrix = 320 × 224, number of excitations (NEX) = 1; (2) T2-weighted imaging (T2WI), TR/TE = 5000/125 ms, FOV = 240 × 240mm^2, acquisition matrix = 352 × 352, NEX = 1; (3) fluid-attenuated inversion recovery (FLAIR), TR/TE = 8502/159.4 ms, FOV = 240 × 240mm^2, acquisition matrix = 256 × 256, NEX = 1; (4) susceptibility weighted imaging (SWI), TR/TE = 78.6/47.6 ms, FOV = 240 × 216mm^2, acquisition matrix = 384 × 320, NEX = 1; (5) diffusion-weighted imaging (DWI), TR/TE = 4800/81.7 ms, FOV = 240 × 240mm^2, acquisition matrix = 160 × 160, NEX = 1. Slice thickness was 2 mm in SWI, and 5 mm in T1WI, T2WI, FLAIR, and DWI.

The total CSVD burden score was calculated based on the neuroimaging markers of CSVD (WMH, lacunes, CMBs, and EPVS).[8] Each component of CSVD was independently evaluated by two readers blinded to all participants' data according to STRIVE criteria.[7] Finally, a third reader assessed any images with inconsistent results. The presence and severity of periventricular and deep cerebral WMH ranged from 0 to 3 and were visually evaluated on T2WI and FLAIR images using the Fazekas scoring system.[22] Lacune was defined as a subcortical lesion of between 3 mm and 15 mm in size with cerebrospinal fluid (CSF) intensity on T1WI and FLAIR.[7] CMBs were small (less than 10 mm in diameter), homogeneous, round foci of hypointensity on SWI, distinct from vessel flow void. According to current consensus criteria and the Microbleed Anatomical Rating Scale,[23] their presence and number were assessed. EPVS, a linear or round CSF-like signal space (generally <3 mm in diameter), is visible on T1WI and T2WI.[7] BG-EPVS were rated using a validated 4-point visual rating scale: none, 0 point; 1–10 EPVS, 1 point; 11–20 EPVS, 2 point; 21–40 EPVS, 3 point; >40 EPVS, 4 point.[24] The total CSVD burden scores were computed on an ordinal scale from 0 to 4, according to a point system designed by Wardlaw's group. A point was allocated for each criterion: (1) WMH: pWMH Fazekas score = 3 or dWMH Fazekas score ≥2; (2) lacunes: one or more lacunes; (3) CMBs: one or more deep CMBs; (4) EPVS: the score ≥2 in BG-EPVS. When the score exceeded 2, we considered it a severe CSVD burden.[25]

Neurocognitive Assessment

A validated Chinese version of the Mini-Mental State Examination (MMSE) was administered to all eligible participants for assessment of cognitive function. Because MMSE performance was most strongly influenced by education, it is strongly recommended that education levels be taken into account when interpreting MMSE results. Therefore, education-stratified cut-off points were chosen in the current study according to a population-based normative in China: 17 for individuals without any education, 20 for those with 1–6 years of education, and 24 for those with more than 7 years of education.[26]

Statistical Analyses

Continuous variables with a normal distribution are presented as the mean ± standard deviation, and the 2-tailed Student's *t*-test was performed for comparisons between two groups. While non-normally distributed data were presented as the median (the interquartile range), and the Mann–Whitney *U*-test was performed. Categorical variables were expressed as number (percentage), and compared between the two groups using the $\chi 2$ test. We applied binary logistic regression models to evaluate the associations of SII with cognitive function and the severity of CSVD burden. Trend tests in ORs across SII tertiles were performed with the median within each tertile as the variable. We conducted three logistic regression models. Model 1: unadjusted; Model 2: adjusted for age, sex, and years of education; Model 3: additionally adjusted for hypertension, history of stroke, HDL-C, and tHcy. To assess the relationship between SII and cognitive performance, Spearman correlations were calculated between SII levels and the MMSE score. Similarly, the association of SII with the total CSVD burden score was also performed with Spearman correlations. The predictive value of the SII level for cognitive impairment was identified by a receiver operating characteristic (ROC) curve. Determined by Youden Index, the optimal cut-off point for SII levels was identified. Statistical significance was defined as a $P < 0.05$. All data were analyzed using the SPSS 23.0 statistical software (IBM, Armonk, NY, USA).

Finally, we performed the mediation analysis using R, version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria). The bruceR and mediation packages for R to determine whether the severe CSVD burden mediates the relationship between higher SII and cognitive impairment. Mediation analysis was conducted using the simple mediation model (Model 4). A nonparametric bootstrap with 5000 samples was employed to estimate the impact more robustly.

Results

Participants Characteristics

A total of 201 patients (median age: 66 years, interquartile range: 59–73 years; 96 men, 105 women) were enrolled in the current analysis. Based on MMSE scores and years of education, the cognitive impairment group included 68 patients, and the no cognitive impairment group included 133 patients. In Table 1, the details of the two groups are presented.

Table 1 Characteristics of the Participants Between Cognitive Impairment Group and No Cognitive Impairment Group

Clinical Characteristics	Cognitive Impairment Group (n = 133)	No Cognitive Impairment Group (n = 68)	*P*-value
Age, median (IQR), years	69.5 (64–75)	65.0 (58–72)	0.008*
Sex (male), n (%)	36 (52.9)	60 (45.1)	0.294
Education, median (IQR), year	9 (6–12)	9 (6–12)	0.005*
BMI, median (IQR), kg/m^2	24.19 (22.24–26.04)	24.80 (22.54–26.73)	0.232
Current smoking, n (%)	12 (17.6)	17 (12.7)	0.354
Alcohol use, n (%)	7 (10.2)	13 (9.7)	0.908
Hypertension, n (%)	51 (75.0)	74 (55.6)	0.008*
Diabetes, n (%)	14 (20.5)	29 (21.8)	0.843
Coronary heart disease, n (%)	12 (17.6)	23 (17.2)	0.950
History of stroke, n (%)	27 (39.7)	40 (30.0)	0.172
TC, mean (SD), mmol/L	4.33±1.02	4.52±1.03	0.996
TG, median (IQR), mmol/L	1.25 (0.95–1.61)	1.21 (0.855–1.756)	0.862
HDL-C, median (IQR), mmol/L	1.06 (0.93–1.29)	1.19 (1.02–1.39)	0.003*
LDL-C, median (IQR), mmol/L	2.59 (2.27–3.17)	2.88 (2.25–3.39)	0.251
VLDL-C, median (IQR), mmol/L	0.40 (0.28–0.53)	0.41 (0.26–0.64)	0.531
UA, median (IQR), μmol/L	270.37 (207.57–339.55)	299.4 (257.4–348.1)	0.089
tHcy, median (IQR), μmol/L	14.66 (12.08–22.95)	12.8 (10.85–16)	0.002*
SII, median (IQR), $\times 10^9/L$	617.5 (466.19–1016.95)	424.8 (331.44–550.79)	< 0.001*
Total CSVD burden score			< 0.001*
0, n (%)	4 (5.8)	40 (30.0)	
1, n (%)	6 (8.8)	30 (22.5)	
2, n (%)	17 (25.0)	34 (25.5)	
3, n (%)	16 (23.5)	16 (12.0)	
4, n (%)	25 (36.7)	13 (9.7)	

Note: *$P < 0.05$.

Abbreviations: SD, standard deviation; IQR, interquartile range; BMI, body mass index; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; VLDL-C, very low density lipoprotein cholesterol; UA, uric acid; tHcy, total homocysteine; SII, systemic immune-inflammation index; CSVD, cerebral small vessel disease.

Compared to patients without cognitive impairment, those with cognitive impairment were more older (median age: 69.5 years, interquartile range: 64–75 years), with lower level of education, higher frequencies of hypertension ($P < 0.05$). Patients with cognitive impairment also had lower HDL-C, higher tHcy, SII and total CSVD burden score ($P < 0.05$).

Association of SII with Cognitive Impairment

In the current study, we performed logistic regression models to explore the relationship between SII and cognitive impairment (Table 2). Unadjusted binary logistic regression results showed that higher level of SII was associated with cognitive

Table 2 The Logistic Regression Analyses of Risk Factors for Cognitive Impairment

Factors	Univariable Analysis		Multivariable Analysis[a]	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age	1.050 (1.014–1.087)	0.006*	1.031 (0.990–1.073)	0.146
Education	0.894 (0.831–0.961)	0.002*	0.895 (0.823–0.972)	0.009*
Hypertension	2.392 (1.253–4.576)	0.008*	1.603 (0.740–3.474)	0.232
HDL-C	0.266 (0.085–0.830)	0.023*	0.484 (0.133–1.755)	0.269
tHcy	1.070 (1.031–1.111)	<0.001*	1.052 (1.008–1.097)	0.019*
SII (<468.27 vs ≥468.27)	4.466 (2.350–8.489)	<0.001*	3.263 (1.577–6.752)	0.001*
Severe CSVD burden	5.446 (2.881–10.294)	<0.001*	2.794 (1.342–5.817)	0.006*

Notes: *$P < 0.05$. [a]Adjusted with $P < 0.05$ in the univariable analysis (age, education, hypertension, HDL-c, tHcy, and severe CSVD burden).
Abbreviations: HDL-C, high density lipoprotein cholesterol; tHcy, total homocysteine; SII, systemic immune-inflammation index; CSVD, cerebral small vessel disease.

impairment (odds ratio [OR]: 4.466; 95% confidence interval [CI]: 2.350 to 8.498; $P < 0.001$). After adjusting for age, education, hypertension, HDL-C, tHcy, and severe CSVD burden, the multivariate binary logistic regression results demonstrated that SII was an independent risk factor for cognitive impairment (OR: 3.263; 95% CI: 1.577 to 6.752; $P = 0.001$).

Based on SII tertiles, the eligible patients were divided into 3 groups (tertile 1: <414.06, tertile 2: 414.06–571.37, tertile 3: >571.37). Table 3 shows a significant trend between tertiles of SII levels and the risk of cognitive impairment. Higher levels of SII were significantly associated with cognitive impairment (OR for tertile 2: 4.572, 95% CI: 1.740 to 12.015, *P* for trend <0.001; OR for tertile 3: 10.829, 95% CI: 4.119 to 28.473, *P* for trend <0.001) after adjustment for age, sex, and education. The association remained significant but strengthened in tertile 2 and weakened in tertile 3 (OR for tertile 2: 4.493, 95% CI: 1.671 to 12.083, *P* for trend <0.001; OR for tertile 3: 8.947, 95% CI: 3.315 to 24.145, *P* for trend <0.001) after further adjustment for hypertension, history of stroke, HDL-C, and tHcy. Furthermore, we explored the correlation of SII levels and MMSE scores using correlation analysis (Figure 1). SII level was negatively associated with MMSE score ($rs = -0.391$, $P < 0.001$).

Association of SII with Severe CSVD Burden

We next performed logistic regression models to explore the relationship between SII and the severity of CSVD burden (Table 4). In univariable analyses, higher SII displayed a significant relationship between severe CSVD burden (OR: 3.545; 95% CI: 1.908 to 6.587; $P < 0.001$). When we adjusted for age, sex, hypertension, history of stroke, and tHcy in the multivariable analyses, the relationship remains significant (OR: 2.674; 95% CI: 1.359 to 5.263; $P = 0.004$).

Similarly, we explored the trend between tertiles of SII levels and severe CSVD burden (Table 5). The results showed that the highest level of SII was strongly associated with severe CSVD burden compared with the lowest (OR: 7.228, 95% CI: 3.265 to 15.999, *P* for trend <0.001). No significant association was observed between the tertile 1 and tertile 2 groups. The association remained significant but weakened in tertile 3 (OR: 6.235, 95% CI: 2.691 to 14.443, *P* for trend <0.001) after adjustment for age,

Table 3 ORs (and 95% CIs) of Cognitive Impairment According to Tertiles of SII

	SII Levels			
	Tertile 1 (<414.06)	Tertile 2 (414.06–571.37)	Tertile 3 (>571.37)	*P* value for Trend[a]
Cognitive impairment				
Model 1	1.0 (reference)	4.481 (1.766–11.370)	11.232 (4.476–28.183)	<0.001*
Model 2	1.0 (reference)	4.572 (1.740–12.015)	10.829 (4.119–28.473)	<0.001*
Model 3	1.0 (reference)	4.493 (1.671–12.083)	8.947 (3.315–24.145)	<0.001*

Notes: *$P < 0.05$. [a]Tests for trend were conducted by treating the tertiles as a continuous variable and assigning the median for each quintile. Model 1: Unadjusted; Model 2: Adjusted for age, sex and education; Model 3: Model 2 plus additional adjustment for hypertension, history of stroke, HDL-C, tHcy.

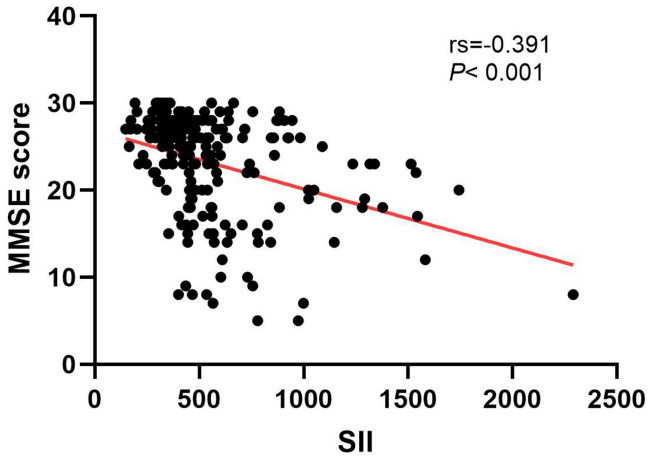

Figure 1 Correlation between SII and cognitive function. Scatterplot of SII and MMSE score (rs = −0.391, $P < 0.001$).

sex, and education. After further adjustment for hypertension, history of stroke, HDL-C, and tHcy, the association also remained significant but weakened in tertile 3 (OR: 4.945, 95% CI: 2.063 to 11.854, P for trend <0.001), with no significant association between the tertile 1 and tertile 2 groups. In addition, there was a positive association between SII levels and total CSVD burden scores (rs = 0.361, $P < 0.001$) as shown in Table 6.

Mediation by Severe CSVD Burden

Figure 2 shows that rates of severe CSVD burden and cognitive impairment increase as SII levels increase. We performed mediation models to explore whether severe CSVD burden was a mediator for higher SII and cognitive

Table 4 The Logistic Regression Analyses of Risk Factors for Severe CSVD Burden

Factors	Univariable Analysis		Multivariable Analysis[a]	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age	1.070 (1.032–1.109)	<0.001*	1.061 (1.021–1.104)	0.003*
Sex (male)	1.954 (1.084–3.520)	0.026*	1.533 (0.772–3.046)	0.222
Education	0.938 (0.875–1.005)	0.070	—	—
BMI	0.935 (0.854–1.023)	0.140	—	—
Current smoking	1.933 (0.873–4.282)	0.104	—	—
Alcohol use	1.009 (0.383–2.656)	0.986	—	—
Hypertension	3.195 (1.641–6.220)	0.001*	2.414 (1.142–5.102)	0.021*
Diabetes	1.878 (0.945–3.732)	0.072	—	—
Coronary heart disease	0.972 (0.451–2.093)	0.941	—	—
History of stroke	3.416 (1.841–6.337)	<0.001*	2.262 (1.135–4.510)	0.020*
TC	0.811 (0.607–1.083)	0.155	—	—
TG	0.847 (0.566–1.266)	0.418	—	—
HDL-C	0.354 (0.118–1.055)	0.062	—	—
LDL-C	0.772 (0.518–1.151)	0.204	—	—
VLDL-C	0.376 (0.114–1.241)	0.108	—	—
UA	1.001 (0.997–1.004)	0.679	—	—
tHcy	1.044 (1.010–1.079)	0.010*	1.032 (0.993–1.071)	0.107
SII (<468.27vs.≥468.27)	3.545 (1.908–6.587)	<0.001*	2.674 (1.359–5.263)	0.004*

Notes: *$P < 0.05$. [a]Adjusted with $P < 0.05$ for age, sex, hypertension, history of stroke, tHcy, and SII.
Abbreviations: BMI, body mass index; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; VLDL-C, very low density lipoprotein cholesterol; UA, uric acid; tHcy, total homocysteine; SII, systemic immune-inflammation index.

Table 5 ORs (and 95% CIs) of Severe CSVD Burden Score According to Tertiles of SII

	SII Levels			
	Tertile 1 (<414.06)	**Tertile 2 (414.06–571.37)**	**Tertile 3 (>571.37)**	***P* value for Trend[a]**
Severe CSVD burden score				
Model 1	1.0 (reference)	1.558 (0.678–3.582)	7.228 (3.265–15.999)	<0.001*
Model 2	1.0 (reference)	1.478 (0.617–3.539)	6.235 (2.691–14.443)	<0.001*
Model 3	1.0 (reference)	1.444 (0.582–3.581)	4.945 (2.063–11.854)	<0.001*

Notes: *$P < 0.05$. [a]Tests for trend were conducted by treating the tertiles as a continuous variable and assigning the median for each quintile.Model 1: Unadjusted; Model 2: Adjusted for age, sex and education; Model 3: Model 2 plus additional adjustment for hypertension, history of stroke, HDL-C, tHcy.

Table 6 Spearman Correlation Analysis of SII and Total CSVD Burden Score

Factors	**rs**	***P*-value**
CSVD burden score	0.361	<0.001*

Note: *$P < 0.05$.
Abbreviation: CSVD, cerebral small vessel disease.

impairment. First of all, the SII levels of patients with cognitive impairment were optimally cut-off at 434.49 (Figure 3), with an area under the curve (AUC) of 0.766 (95% CI: 0.698 to 0.834, $P < 0.001$). In accordance with the optimal cut-off point, we divided the cohort into two groups: those with higher and lower SII levels. Mediation analysis showed a significant total effect (c) and direct effect (c') between higher SII and cognitive impairment (all $P < 0.001$), with a significant indirect effect (ab) when the severe CSVD burden score was included in the model ($P = 0.044$). And severe CSVD burden mediated 12.1% of the total effect after adjusting for age, hypertension, and tHcy (Figure 4). These results demonstrated that the presence of severe CSVD burden partly mediated the effect of higher SII levels on cognitive impairment.

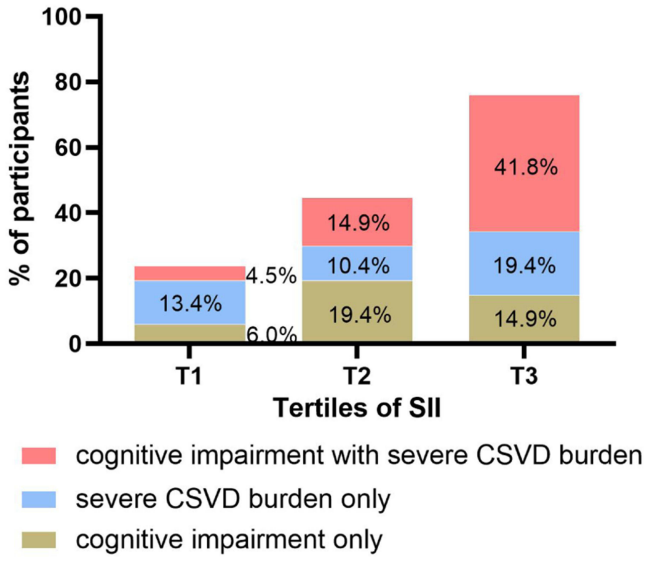

Figure 2 Increasing rates of severe CSVD burden and cognitive impairment with increase in SII.

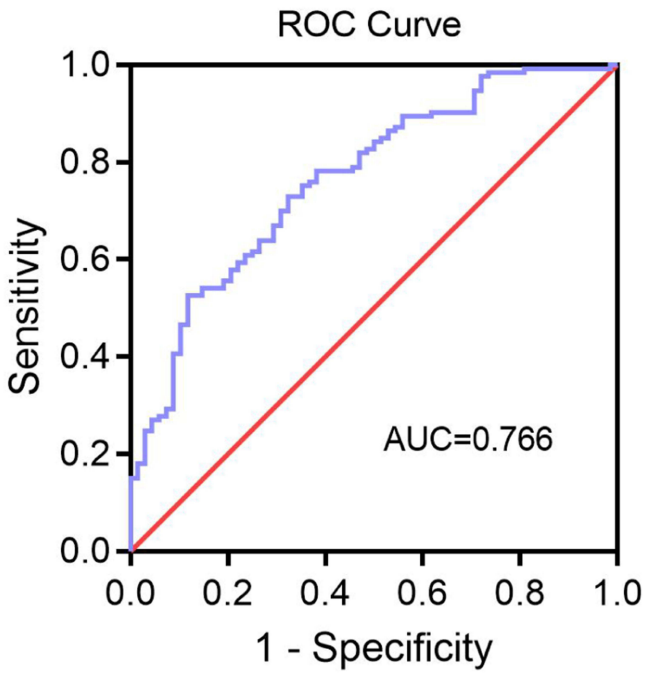

Figure 3 Receiver operating characteristic (ROC) curve of SII levels for cognitive impairment. The specificity was 0.526 (1–0.474) and sensitivity was 0.882.

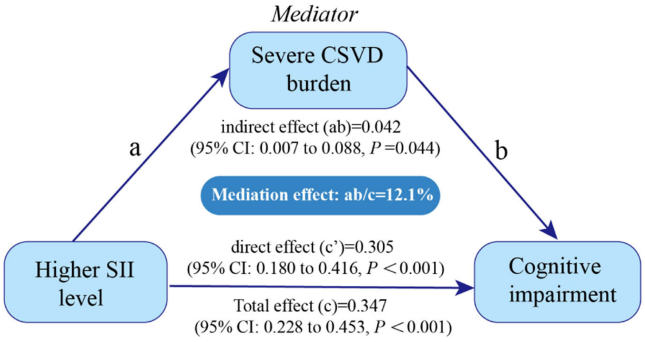

Figure 4 Mediation analysis is shown for the presence of severe CSVD burden as a mediator in the relation between higher SII and cognitive impairment.

Discussion

In this retrospective study, we evaluated the associations of SII levels with cognitive impairment and CSVD burden. Our study revealed the following findings: First, patients with cognitive impairment had higher SII levels than those without cognitive impairment. Elevated SII was found to be significantly associated with the risk of cognitive impairment and severe CSVD burden. With a higher SII level, these associations were more prominent. Second, there was a significant negative correlation between SII and MMSE scores and a positive correlation with total CSVD burden scores. Third, the effect of higher SII on the development of cognitive impairment was partly mediated by severe CSVD burden, supporting the hypothesis that increased SII may aggravate CSVD, which in turn increases cognitive impairment risk.

Existing studies have investigated the relationship between SII and cognitive function in different pathological states. In a retrospective study, higher SII levels were associated with lower cognitive performance in breast cancer survivors who had ceased chemotherapy 20 years ago.[21] There was also evidence that a higher level of SII was found to be an independent risk factor for cognitive decline postoperatively.[20] Another retrospective study found that the elderly with a higher level of SII were at higher risk of developing mild cognitive impairment.[19] A significant inverse association between SII and cognitive function was also found in the present study, and the association was stronger in the highest

tertile compared with the lowest tertile, suggesting increased SII levels may accelerate cognitive impairment progression. However, the underlying mechanisms for the association remain unclear. Increasing evidence from studies in systemic inflammation and cognitive impairment may explain the association between higher SII and cognitive impairment, such as endothelial dysfunction, BBB disruption, vagal nerve stimulation, and oxidative stress.[6,27]

Growing evidence is showing that elevated SII is linked to the development of different imaging features of CSVD, which is important for the increased risk of cognitive impairment. It has been reported that higher SII levels were associated with greater WMH volume in a health check-up population.[28] A prospective cohort study in a community population suggested that elevated SII was positively associated with moderate-to-severe BG-EPVS and modified WMH burden, with no significant differences between SII and the total CSVD burden score.[18] Different from the previous study, we found the total CSVD burden score had a significant negative correlation with SII level, possibly due to older hospitalized patients, an increase in CSVD lesions and vascular risk factors. In addition, we extended previous research focusing on the CSVD burden severity. We found that SII was an independent risk factor for severe CSVD burden. However, only patients with the highest level of SII were significantly statistically associated with severe CSVD burden, suggesting elevated SII may increase the severity of CSVD. There were several possible explanations for the relationship between SII and CSVD. Neutrophils, lymphocytes, and platelets play vital roles in immune and inflammatory responses.[29,30] Alterations in those blood cells were associated with immune-regulatory dysfunction.[31] A sustained inflammatory stimulus induces endothelial dysfunction, leading to BBB disruption. On the one hand, the leakage of plasma constituents into the perivascular tissues might promote thickening and stiffening of arteriole walls, restricting vasodilation, and impairing further vasodilatation, oxygenation, and nutrient delivery.[32] On the other hand, peripheral inflammatory cells migrate to the central nervous system (CNS) and microglia are activated.[33,34] The chronic inflammatory microenvironment created in the CNS contributes to brain damage.

Interestingly, CSVD and cognitive impairment may share underlying mechanisms.[3] Endothelial dysfunction, BBB disruption, and microglia activation also play critical roles in the development of cognitive impairment.[35–37] It has been reported that higher CSVD burden was associated with cognitive impairment.[9] The current study also observed that severe CSVD burden was positively related to a higher risk of cognitive impairment after adjusting for potential confounding factors. As SII levels increase, so do the rates of severe CSVD burden and cognitive impairment. Consequently, when investigating the relationship between SII and cognitive impairment, CSVD severity should be considered. This is also an important strength of our study. Our findings revealed a partial mediating role of severe CSVD burden on the association between SII and cognitive impairment, supporting the hypothesis that higher SII levels could aggravate the development of CSVD and then increase the risk of poor cognitive function.

Although we have some novel findings in the relationships among SII, CSVD, and cognitive impairment, there are several limitations that deserve consideration. First, due to the limitations of the retrospective study, no causal conclusions can be drawn from SII with severe CSVD burden and cognitive impairment. Although mediation analysis proved the causal hypothesis that severe CSVD burden partly mediated the association between higher SII levels and cognitive impairment, future prospective studies remain needed. Second, this is a small sample size study with only one center enrolling patients, which may contribute to selection bias. A longitudinal study with a larger sample size would be beneficial. Third, the average SII over time might be more appropriate for evaluating chronic inflammation. Fourth, although we adjusted for several potential confounding factors in our analyses, unmeasured covariates cannot be fully ruled out. Fifth, MMSE cannot adequately represent some intricacy of particular cognitive domains, more cognitive screening tool should be used. Continuous measures of CSVD biomarkers, such as volume of WMH, would present more strongly associated with cognition. Finally, dementia and mild cognitive impairment were not distinguished in the current study. These issues should require further follow-up studies to address them.

Conclusions

In summary, our study demonstrated that SII levels are associated with total CSVD burden severity and cognitive impairment. Results of mediation analysis revealed that higher SII increased the risk of cognitive impairment in part due to its influence on CSVD burden severity. However, the causality of this association needs to be further determined by prospective studies.

Ethics Statement

This study was reviewed and approved by Ethical Committee of Hebei General Hospital (No.2022166). The data of participants would be anonymized or kept confidential, and no rights or interests of participants would be violated. According to the national legislation and the institutional requirements, this study did not require written informed consent.

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Disclosure

The authors have no conflicts of interest to declare in this work.

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