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The correlation between neutrophil/lymphocyte ratio and the MRI burden and cognitive function in patients with cerebral small vessel disease

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Objective: Aims to explore the relationship between neutrophil/lymphocyte ratio (NLR) and the total burden of imaging markers and cognitive function in patients with cerebral small vessel disease (CSVD).

Methods: A retrospective study was conducted on 148 hospitalized CSVD patients at Hebei General Hospital from January 2022 to September 2024, with complete clinical and laboratory data. NLR was calculated as neutrophil count/lymphocyte count. According to the Mini-Mental State Examination (MMSE) score, patients were divided into a cognitive impairment group ($n = 89$) and a non-cognitive impairment group ($n = 59$). The total CSVD burden was assessed based on magnetic resonance imaging (MRI). We used logistic regression models, restricted cubic spline plots, Spearman correlation, and mediation analysis to evaluate the relationship between NLR in CSVD patients and CSVD burden and cognitive impairment.

Results: The results of the multivariate logistic regression showed that after adjusting for all potential confounding factors, an elevated NLR in CSVD patients was significantly associated with the risk of cognitive impairment (OR: 3.263; 95% CI: 1.577 to 6.752; $p = 0.001$) and severe CSVD burden (OR = 2.246, 95% CI: 1.346 ~ 3.750, $p = 0.002$). The restricted cubic spline plot shows that after adjusting for confounding factors, the NLR level is linearly associated with the risk of CI (P for total = 0.022, P for non-linear = 0.231) and the total burden of CSVD (P for total = 0.005, P for non-linear = 0.448). Correlation analysis shows that NLR is positively correlated with the CSVD score ($r_s = 0.246$, $p = 0.003$). Furthermore, the results of the mediation analysis indicate that after adjusting for confounding factors, the burden of CSVD has a significant mediating effect on the relationship between NLR levels and cognitive impairment ($ab = 0.028$, 95% CI: 0.004 to 0.070, $p = 0.012$); 20.9% of the total effect of NLR on cognitive impairment in CSVD patients can be attributed to the presence of CSVD burden.

Conclusion: Elevated NLR in CSVD patients is associated with the burden of CSVD and cognitive impairment. The mediating role of CSVD burden suggests that elevated NLR may lead to cognitive impairment by exacerbating the burden of CSVD.

KEYWORDS

cerebral small vessel disease (CSVD), cognitive impairment, neutrophil/lymphocyte ratio (NLR), Mini-Mental State Examination (MMSE), total burden

Introduction

With the aging population in our country, the incidence, prevalence, disability rate, and mortality rate of cognitive impairment are increasing year by year. An increasing body of evidence indicates that cerebrovascular lesions are the important triggering factors for dementia, with additive or synergistic effects in relation to neurodegenerative diseases. Dementia has long been considered untreatable, but it can be prevented and even the course might be modifiable by intervening in related risk factors. Cerebrovascular disease is one of the risk factors that can be potentially modifiable (1). Among them, cerebral small vessel disease (CSVD) is one of the important causes of vascular cognitive impairment (2).

Cerebral small vessel disease is a group of various vascular diseases with different pathological types, which can be classified by arteriosclerosis/age-related CSVD, amyloid-related CSVD, genetic CSVD distinct from amyloid angiopathy, inflammatory-immune mediated type, venous collagenosis, and other types (3). Its imaging features include recent small subcortical infarct, white matter hyperintensities (WMHs), lacune of presumed vascular origin, cerebral microbleeds (CMBs), enlarged perivascular space (EPVS), and brain atrophy (4). However, due to the diverse clinical manifestations of patients with CSVD, the potential pathophysiological mechanisms underlying cognitive impairment remain unclear. Moreover, due to the limited understanding of the potential pathophysiology of CSVD and the lack of effective treatment options, early control of risk factors and prevention of further cerebrovascular progression are the fundamental measures to prevent and treat cognitive impairment. Lacunar infarcts is one of the clinical manifestations of CSVD. Studies shown lacunar infarcts are the ischemic stroke subtype with the best functional prognosis, but that the pathophysiology, clinical features and outcome of lacunar strokes are different from other acute ischemic cerebrovascular diseases (5). Therefore, the pathophysiological mechanism of CSVD remains to be further explored.

In recent years, the neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and monocyte/lymphocyte ratio (MLR) have been proposed as newer systemic inflammatory biomarkers. Previous studies have shown that these indicators reflect the inflammatory state induced by various malignant tumors and have been proven to be reliable prognostic tools for different stages of the disease and treatment methods (6–8). In particular, the NLR has been shown to predict early cerebral edema and clinical deterioration after reperfusion therapy for stroke, and it is correlated with early neurological outcomes after thrombolysis in patients with acute ischemic stroke (9), cardiovascular risk in hypertensive patients (10), and cognitive impairment in patients with CSVD (11). However, the relationship between NLR, PLR, and MLR with the total imaging burden and cognitive function in CSVD patients has not been explored simultaneously.

In this study, we explored whether these indicators increase the severity of the burden of CSVD and the risk of cognitive impairment,

as well as whether the impact of cognitive impairment is mediated by the severity of the CSVD burden.

Materials and methods

Study population

This is a hospital-based retrospective study, selecting patients with CSVD who were hospitalized and completed neuropsychological assessments from January 2020 to September 2024 at Hebei General Hospital. All included subjects had detailed medical histories, physical examinations, relevant laboratory tests, and neuroimaging data. The exclusion criteria were as follows: (1) patients with active infections or antibiotic use within the last 2 weeks; (2) hematological diseases, malignant tumors, autoimmune diseases; (3) recent treatment with immunosuppressants; (4) those with brain tumors or other systemic tumors, surgery, or severe trauma; (5) non-vascular white matter injury, such as metabolic encephalopathy, multiple sclerosis, etc.; (6) cognitive impairment due to other conditions, such as carbon monoxide poisoning, hyperthyroidism, hypothyroidism, severe anxiety, or depression. Ultimately, a total of 148 eligible patients participated in the analysis. CSVD was diagnosed according to the Chinese guidelines for CSVD (12). The interval between CSVD diagnosis and blood tests was within 7 days. This study was conducted according to the declaration of Helsinki and approved by the Ethical Committees of Hebei General Hospital (No.2024-LW-0228).

Clinical characteristics

All demographic and risk factors were obtained from medical records: age, gender, years of education, body mass index (BMI), smoking status, and alcohol consumption. Medical history was also collected, including hypertension, diabetes, coronary heart disease, and stroke. Laboratory biomarkers were measured, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total homocysteine (tHcy), white blood cell count, neutrophil count, lymphocyte count, monocyte count, and platelet count. NLR was calculated as neutrophil count/lymphocyte count. PLR was calculated as platelet count/lymphocyte count. MLR was calculated as monocyte count/lymphocyte count. The SII was calculated as platelet count $\times$ neutrophil count/lymphocyte count.

Imaging acquisition and assessment

All eligible participants had completed magnetic resonance imaging (MRI) examination with adequate sequences for the assessment of CSVD. All sequence images were obtained from the medical records. MRI examination was performed in all patients with 3.0-Tesla magnetic resonance scanners (Signa, GE Healthcare of

America). The MRI protocol and detailed acquisition parameters are as follows: (1) T1-weighted imaging (T1WI), repetition time (TR)/echo time (TE) = 1909/20.2 milliseconds (ms), field of view (FOV) = $240 \times 192 \text{ mm}^2$, acquisition matrix = 320×224 , number of excitations (NEX) = 1; (2) T2-weighted imaging (T2WI), TR/TE = 5000/125 ms, FOV = $240 \times 240 \text{ mm}^2$, acquisition matrix = 352×352 , NEX = 1; (3) Fluid Attenuation Inversion Recovery (FLAIR), TR/TE = 8502/159.4 ms, FOV = $240 \times 240 \text{ mm}^2$, acquisition matrix = 256×256 , NEX = 1; (4) Sensitivity Weighted Imaging (SWI), TR/TE = 78.6/47.6 ms, FOV = $240 \times 216 \text{ mm}^2$, acquisition matrix = 384×320 , NEX = 1; (5) Diffusion Weighted Imaging (DWI), TR/TE = 4800/81.7 ms, FOV = $240 \times 240 \text{ mm}^2$, acquisition matrix = 160×160 , NEX = 1. The slice thickness for SWI is 2 mm, while the slice thickness for T1WI, T2WI, FLAIR, and DWI is 5 mm.

Imaging markers of CSVD (WMHs, CMBs, lacune, EPVS) were evaluated independently by two readers (XX and JX) following the STRIVE criteria (4). In case of disagreement on any markers, a radiologist (CS) was involved to reach a consensus. All ratings were performed blinded to all patient data. The imaging assessment criteria are as follows: WMHs: Manifesting as abnormal signals of varying sizes in the white matter regions, appearing as high signals on T2WI and FLAIR, and as isointense or low signals on T1WI sequences. WMHs are mostly bilaterally symmetrical, primarily distributed around the lateral ventricles or in the deep white matter of the brain. WMHs are assessed using the Fazekas scale: periventricular white matter (PVWMH): 0 points, no lesions; 1 point, lesions appear as cap-like or pencil-thin layers; 2 points, lesions appear as smooth halo-like; 3 points, irregular lesions extend into the deep white matter (DWMH): 0 points, no lesions; 1 point, punctate lesions; 2 points, lesions begin to merge; 3 points, lesions merge extensively (13). Lacune: Presenting as round or oval fluid-filled spaces resembling cerebrospinal fluid signals located in the subcortical area, appearing as low signal on T1WI sequence, high signal on T2WI sequence, and central low signal with a peripheral high signal ring on FLAIR sequence, with a diameter of 3 to 15 mm (4). EPVS: Similar to lacune, presenting as low signal on T1WI and FLAIR sequences, high signal on T2WI sequence, but generally with a diameter of <3 mm, and no high signal ring on FLAIR. EPVS in the basal ganglia were coded according to following scale applied to standard axial images: grade 0 = no EPVS, grade 1 = 1–10 EPVS, grade 2 = 11–20 EPVS and grade 4 = > 40 EPVS. The numbers refer to EPVS on one side of the brain; the higher score was used if there was asymmetry between the sides and EPVS were counted in the slice with the highest number (14). CMBs: Presenting as small round or oval shapes on SWI, with clear boundaries, homogeneity, and signal loss lesions, typically with a diameter of 2–5 mm, and can be up to 10 mm. Among them, deep CMBs (basal ganglia, internal and external capsules, thalamus, corpus callosum, and periventricular white matter) are considered related to small artery atherosclerotic CSVD, thus only the number of deep CMBs is counted (15). CSVD total burden was rated on an ordinal scale from 0 to 4. 1 point is recorded when the following manifestations are present: according to the Fazekas assessment scale, DWMH score ≥ 2 points or (and) PVWMH score of 3 points; deep CMBs ≥ 1 ; lacune ≥ 1 ; EPVS grading ≥ 2 (16). The total score is 4 points; a higher score indicates a heavier total burden of CSVD, and the study subjects are divided into a mild burden group (0–2 points) and a severe burden group (3–4 points) based on the total burden (17).

Neuropsychological assessment

All eligible participants had completed neuropsychological assessments the validated Chinese version of the Mini-Mental State Examination (MMSE) and results were obtained from the medical records. Neuropsychological assessments were conducted for all eligible participants using the validated Chinese version of the Mini-Mental State Examination (MMSE). Since MMSE performance is most influenced by educational level, it is strongly recommended to consider education level when interpreting MMSE results. Therefore, in this study, the educational stratification cut-off points were selected based on population-based norms in China: 17 points for the uneducated, 20 points for those educated for 1–6 years, and 24 points for those educated for more than 7 years as the cut-off for cognitive impairment (18).

Statistical methods

First, analysis was conducted using SPSS 26.0 statistical software (IBM, Armonk, NY, United States). Continuous variables that conform to a normal distribution are expressed as mean $\pm$ standard deviation, and comparisons between the two groups were performed using a two-tailed Student's *t*-test. Data that do not conform to a normal distribution are expressed as median (interquartile range) and analyzed using the Mann–Whitney *U* test. Categorical variables are expressed as numbers (percentages), and comparisons between the two groups were performed using the χ^2 test. We applied a binary logistic regression model to assess the relationship between NLR and cognitive function and the severity of CSVD burden. The predictive value of the NLR level for cognitive impairment was identified by drawing receiver operating characteristic (ROC) curve. And the optimal cut-off point of serum NLR levels in patients with cognitive impairment was predicted according to the maximum value of the Youden Index. To evaluate the relationship between NLR and the total burden of CSVD, the Spearman correlation between NLR levels and CSVD total burden scores was calculated.

Secondly, we used R version 4.4.0 (R Foundation for Statistical Computing, Vienna, Austria) to create restricted cubic spline plots and conduct mediation analysis. Using the rms Packages in R to create restricted cubic spline plots, we further explored the relationship between NLR and the risk of cognitive impairment as well as the burden of severe CSVD. Finally, we used R's plyr and mediation Packages to determine whether the CSVD burden mediates the relationship between NLR and cognitive impairment. A simple mediation model (Model 4) was employed for the mediation analysis. The bootstrap method was used for 5,000 repeated samples to obtain more stable mediation model results.

Results

Participant characteristics

A total of 148 patients (median age: 68 years, interquartile range: 60–72 years; 100 males and 48 females) participated in the current analysis. According to MMSE scores and years of education, the cognitive impairment group included 89 patients, while the no

cognitive impairment group included 59 patients. Table 1 provides detailed information about the two groups. Compared to patients without cognitive impairment, those with cognitive impairment had higher Hcy levels ($p < 0.05$). There were statistically significant differences in NLR, MLR, SII, and total CSVD burden scores between the two groups ($p < 0.05$), while PLR showed no significant difference. There were no statistically significant differences in the remaining demographic and general clinical data between the groups.

The relationship between NLR and cognitive impairment

In this study, we used a logistic regression model to explore the relationship between NLR and cognitive impairment (Table 2). After adjusting for homocysteine and total burden of CSVD factors, the logistic regression results showed that NLR was significantly associated with the occurrence of cognitive impairment (OR: 1.625; 95% CI: 1.049 to 2.517; $p = 0.030$), while MLR and SII were not

independent risk factors for the occurrence of cognitive impairment. Additionally, the results of the restricted cubic spline graph more clearly demonstrate the dose–response curve of NLR and the risk of cognitive impairment (Figure 1). After adjusting for all confounding

TABLE 2 The logistic regression analyses of risk factors for cognitive impairment.

Factors	Multivariable analysis	
	OR(95% CI)	P-value
tHcy	1.004(0.970–1.039)	0.827
CSVD burden	1.565(1.111–2.205)	0.010*
NLR	1.625(1.049–2.517)	0.030*
MLR	45.428(0.621–3325.424)	0.081
SII	1.002(1.000–1.004)	0.097

* $P < 0.05$.

tHcy, total homocysteine; tHcy, NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; MLR, monocyte/lymphocyte ratio; SII, systemic immune-inflammation index; CSVD, cerebral small vessel disease.

TABLE 1 Characteristics of the participants between cognitive impairment group and no cognitive impairment group.

Clinical characteristics	Cognitive impairment group (n = 89)	NO cognitive impairment group (n = 59)	p-value
Age, median (IQR), years	68(59.5,74.0)	68(60.0,71.0)	0.906
Sex, female, n (%)	25(28.1)	23(39.0)	0.166
BMI, median (IQR), kg/m ²	25.25(23.01,27.73)	25.24(24.14,28.34)	0.308
Diabetes, n (%)	30(33.7)	17(28.8)	0.531
Hypertension, n (%)	63(70.8)	39(66.1)	0.547
Coronary heart disease, n (%)	7(7.9)	6(10.2)	0.628
History of stroke, n (%)	72(80.9)	45(76.3)	0.498
Current smoking, n (%)	19(21.3)	14(23.7)	0.733
Alcohol use, n (%)	7(7.9)	10(16.9)	0.090
Education, median (IQR), year	9(8,12)	9(6,12)	0.638
TC, mean (SD), mmol/L	4.26 ± 1.05	4.45 ± 1.18	0.305
TG, median (IQR), mmol/L	1.10(0.80,1.55)	1.20(0.84,1.62)	0.522
HDL-C, mean (SD), mmol/L	1.13 ± 0.26	1.18 ± 0.29	0.263
LDL-C, median (SD), mmol/L	2.59 ± 0.78	2.71 ± 0.88	0.378
tHcy, median (IQR), μmol/L	15.30(12.00,20.20)	13.50(11.10,17.20)	0.045*
NLR, mean (SD)	2.63 ± 0.80	2.25 ± 0.84	0.007*
PLR, median (IQR)	128.93(105.89,164.35)	122.88(101.46,147.59)	0.365
MLR, median (IQR)	0.23(0.18,0.28)	0.18(0.16,0.25)	0.020*
SII, median (IQR)	527(403,671)	450(315,619)	0.021*
Fazekas	5(3,6)	3(2,5)	0.003*
Total CSVD burden score			0.001*
1, n (%)	9(10.1)	7(11.9)	
2, n (%)	11(12.4)	17(28.8)	
3, n (%)	18(20.2)	21(35.6)	
4, n (%)	51(57.3)	14(23.7)	

* $p < 0.05$.

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; UA, uric acid; tHcy, total homocysteine; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; MLR, monocyte/lymphocyte ratio; SII, systemic immune-inflammation index; CSVD, cerebral small vessel disease.

factors, NLR exhibited a linear relationship with the risk of cognitive impairment (P for total = 0.022, P for non-linear = 0.231). It is obtained by drawing ROC curve the NLR levels of patients with cognitive impairment were optimally cut-off at 2.26 (Figure 2), with an area under the curve (AUC) of 0.636 (95% CI: 0.543 to 0.728, $p < 0.05$).

The correlation between NLR and total burden of CSVD

In the univariate binary logistic regression analysis, elevated NLR levels were associated with an increased risk of severe CSVD burden (OR = 1.958, 95% CI: 1.215 ~ 3.158, $p = 0.006$). Further adjustment for age, total cholesterol, and low-density lipoprotein revealed that elevated NLR levels are an independent risk factor for severe CSVD (OR = 2.246, 95% CI: 1.346 ~ 3.750, $p = 0.002$) as shown in Table 3. Similarly, we further illustrate the dose-response curve of NLR and the total burden of CSVD by plotting the results of the restricted cubic spline (Figure 3). After adjusting for all confounding factors, a linear relationship between NLR and the total burden of CSVD was observed (P for total = 0.005, P for non-linear = 0.448). In addition, a Spearman correlation analysis between NLR levels and CSVD total burden scores (Table 4) showed a positive correlation ($r_s = 0.246$, $p = 0.003$), indicating that higher NLR levels are associated with more severe CSVD.

The mediating role of CSVD total burden

This section of the study employs a mediation model to explore whether the total burden of CSVD mediates the risk of cognitive impairment associated with increased NLR. Results of the mediation analyses are presented in Figure 4. There is a significant total effect (c) and direct effect (c') of NLR on cognitive impairment ($p < 0.05$), and when the severe CSVD total burden score is included in the model, there is a significant indirect effect ($ab = 0.025$, 95% CI: 0.002 to 0.070, $p = 0.028$). After adjusting for age, TC, LDL-C, and tHcy, the mediation effect of CSVD total burden still exists ($ab = 0.028$, 95% CI: 0.004 to 0.070, $p = 0.012$). After adjusting for confounding factors,

20.9% of the total effect of NLR on cognitive impairment can be attributed to the presence of CSVD burden (Figure 4).

Discussion

In this study, we found that NLR is an independent risk factor for the occurrence of cognitive impairment and severe CSVD burden in patients. In patients with CSVD, as NLR increases, the risk of cognitive impairment and the severity of the total CSVD burden also increase. Furthermore, the results of the mediation model suggest that the effect of NLR on the occurrence of cognitive impairment is mediated by the total burden of CSVD, meaning that an increase in NLR may exacerbate the severity of CSVD, thereby increasing the risk of cognitive impairment.

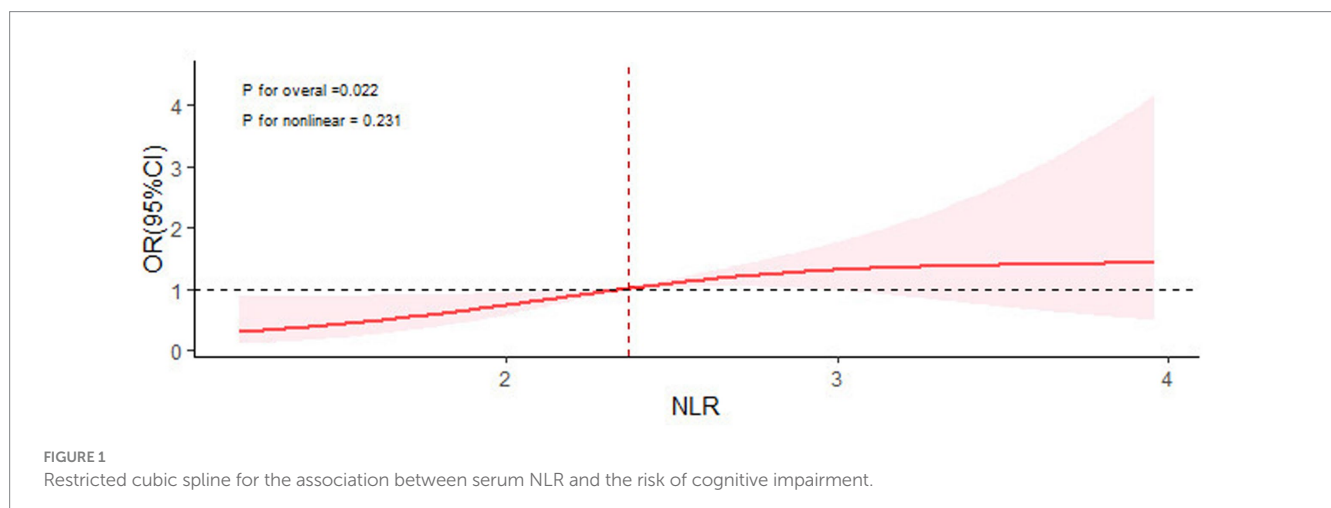
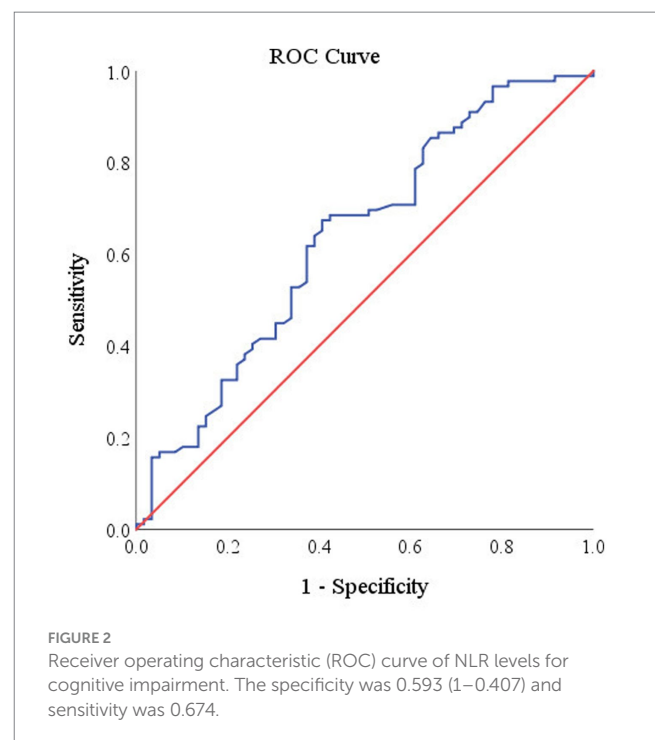


TABLE 3 The logistic regression analysis of risk factors for severe CSVD burden.

Factors	Univariable analysis		Multivariable analysis ^a	
	OR(95% CI)	P-value	OR(95% CI)	P-value
Age	1.067(1.025,1.112)	0.002*	1.081(1.029,1.135)	0.002*
Sex	1.708(0.818,3.564)	0.154	—	—
Education	0.990(0.893,1.096)	0.842	—	—
BMI	0.920(0.832,1.-16)	0.100	—	—
Diabetes	0.743(0.353,1.564)	0.434	—	—
Hypertension	1.410(0.668,2.974)	0.367	—	—
History of stroke	1.162(0.496,2.726)	0.729	—	—
Coronary heart disease	0.324(0.102,1.026)	0.055	—	—
Current smoking	0.805(0.351,1.844)	0.608	—	—
Alcohol use	0.426(0.153,1.190)	0.104	—	—
TC	0.466(0.320,0.679)	<0.001*	1.124(0.323,3.906)	0.855
TG	0.944(0.623,1.429)	0.786	—	—
LDL-C	0.351(0.213,0.578)	<0.001*	0.279(0.052,1.491)	0.136
HDL-C	0.377(0.102,1.394)	0.144	—	—
tHcy	1.045(0.933,1.099)	0.091	—	—
NLR	1.958(1.215,3.158)	0.006*	2.246(1.346,3.750)	0.002*
PLR	1.004(0.995,1.012)	0.374	—	—
MLR	45.994(0.397,5327.384)	0.114	—	—
SII	1.002(1.000,1.003)	0.132	—	—

* $P < 0.05$. ^aAdjusted with $P < 0.05$ for age, TC, LDL-C, and NLR.
BMI, body mass index; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; tHcy, total homocysteine; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; MLR, monocyte/lymphocyte ratio; SII, systemic immune-inflammation index.

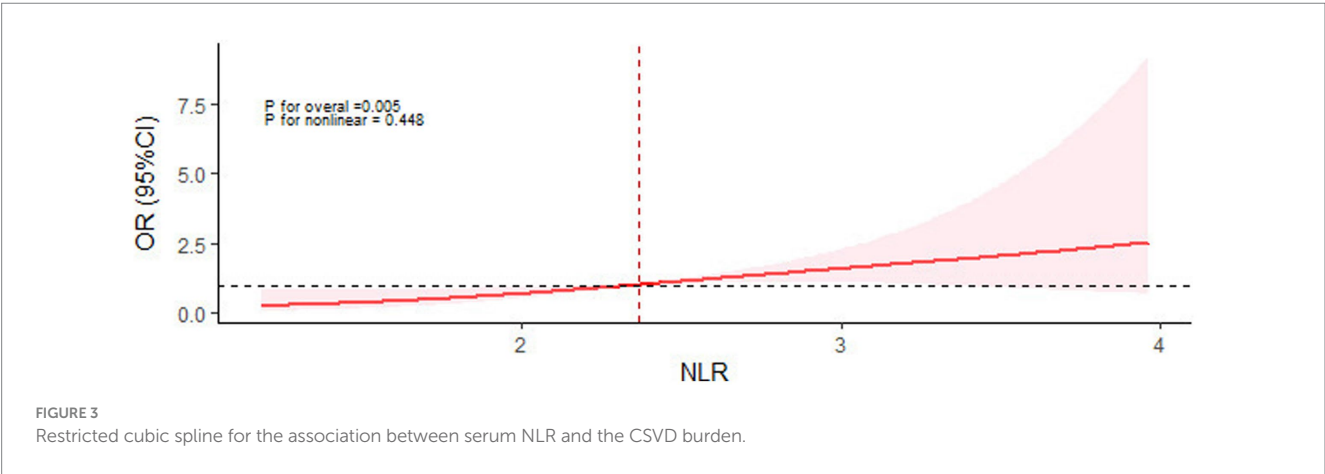


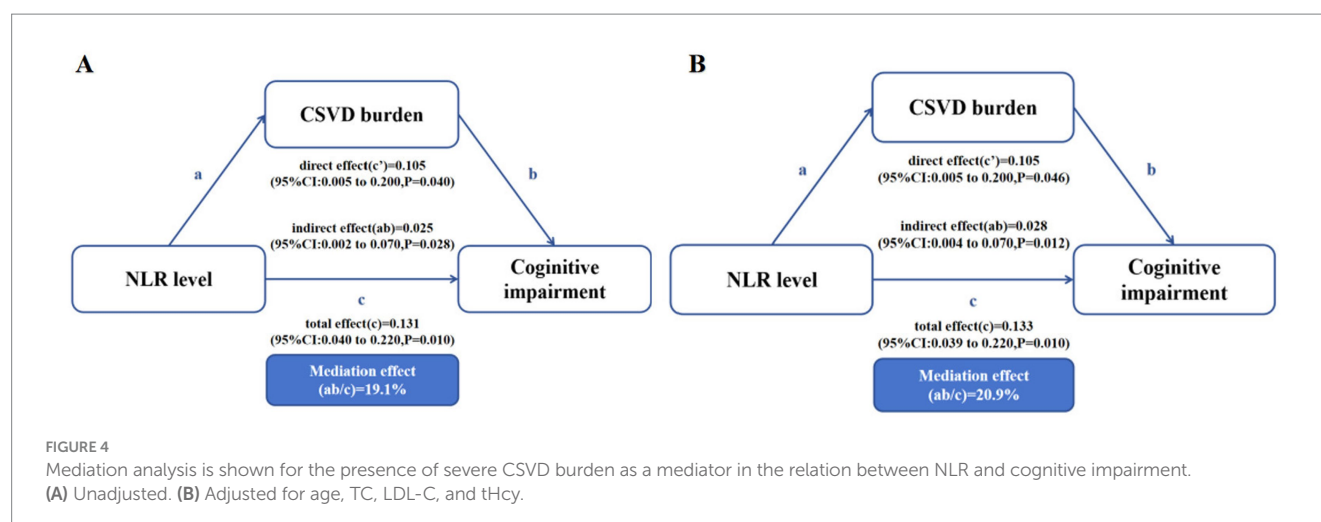
TABLE 4 Spearman correlation analysis of NLR and total CSVD burden score.

Factors	rs	P-value
CSVD burden score	0.246	0.003*

* $p < 0.05$.
CSVD, cerebral small vessel disease.

Currently, several studies have explored the relationship between NLR and cognitive impairment in different populations. A meta-analysis found that compared to healthy individuals, the NLR was

significantly elevated in patients with mild cognitive impairment and Alzheimer's disease (19). Additionally, a prospective study on Alzheimer's disease also confirmed the above viewpoint. However, the study found no significant difference in NLR levels between aMCI patients and AD patients, suggesting that NLR cannot predict the transition of patients from mild cognitive impairment to Alzheimer disease (20). But a prospective study on amnesic mild cognitive impairment found that, at the end of follow-up, the NLR of patients who progressed to dementia from those who remained in mild cognitive impairment was significantly elevated (21). There are also



studies (22) exploring the correlation between NLR and cognitive, neuroimaging, and pathological aspects in Alzheimer's disease patients, finding that elevated NLR is significantly associated with total cognitive function, memory function, and executive ability levels in patients. Moreover, elevated NLR is associated with increased levels of β -amyloid and total T-tau protein in the cerebrospinal fluid of Alzheimer's disease patients. In terms of neuroimaging, elevated NLR is associated with reduced hippocampal volume and decreased thickness of the entorhinal cortex. The above study suggests that NLR may mediate the cognitive imaging in Alzheimer's disease patients through A β and T-tau. In a follow-up study on acute ischemic stroke, it was found that NLR, as a categorical variable, is an independent risk factor for post-stroke cognitive impairment, with patients in the higher NLR group showing significantly poorer total cognitive function (23, 24). A study using brain FDG PET to predict post-stroke cognitive impairment found that higher metabolic cognitive feature scores in FDG PET of stroke patients were positively correlated with NLR. Moreover, the predictive model for post-stroke cognitive impairment is more accurate when NLR is considered as an auxiliary factor (25). Therefore, we have reason to believe that NLR, as a peripheral blood inflammatory marker, is a feasible tool for assessing cognitive impairment.

An increasing number of research findings indicate that NLR is associated with the development of different imaging characteristics in CSVD patients, which is also very important for the occurrence of cognitive impairment. A study conducted on a community population found that higher NLR levels were significantly associated with moderate to severe basal ganglia EPVS (26). Interestingly, some studies suggest that NLR may also affect the brain electrical activity of CSVD patients through imaging, thereby leading to or exacerbating cognitive impairment (27). Compared to previous studies, the innovation of this research lies in the discovery of a significant mediating effect of the total burden of CSVD on the relationship between NLR and cognitive impairment. It is worth noting that previous studies have found a common mechanism between severe total burden of CSVD and the occurrence of cognitive impairment (28), including endothelial dysfunction, blood-brain barrier disruption, oxidative stress response, and chronic neuroinflammation (29–32). Therefore, when studying the relationship between NLR and cognitive impairment, the severity of CSVD should be considered. In

our study, it was confirmed that the elevated NLR levels in CSVD patients may exacerbate the progression of CSVD, thereby increasing the risk of cognitive impairment.

Although we have some new findings regarding the relationship between NLR, CSVD, and cognitive impairment, there are still some limitations: first, this study is a retrospective study and cannot confirm the causality between the variables. Although the results of the mediation analysis support the hypothesis that the burden of CSVD mediates, to some extent, the association between NLR in CSVD patients and the occurrence of cognitive impairment, further prospective studies are needed to confirm this. Second, this is a study with a small sample size, which may lead to selection bias. For example, in a large sample study, gender was found to have an effect on the prognosis of patients with cerebrovascular disease (33), which was not found in this study. Third, the severity of cognitive impairment was not categorized; the MMSE scale was used for cognitive assessment, which did not allow for a detailed evaluation of cognitive domains. Therefore, we will expand the sample size to verify the effect of relevant risk factors on outcomes and use broader neuropsychological testings to explore the relationship between NLR and different cognitive domains in future studies. Furthermore, we will conduct prospective studies to explore the causal relationship between variables.

Conclusion

In summary, our study indicates that in CSVD patients, NLR is associated with the total burden severity and cognitive impairment. The mediation analysis results show that an increase in NLR raises the risk of cognitive impairment, partly due to its impact on the severity of the total burden in CSVD. However, the causal relationship of this association needs to be further established through prospective studies.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the Hebei General Hospital Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin due to the retrospective nature of the study.

Author contributions

MZ: Writing – original draft, Writing – review & editing. XX: Data curation, Writing – review & editing. ZH: Writing – review & editing. MR: Data curation, Writing – review & editing. ZT: Writing – review & editing. JX: Writing – review & editing. CS: Writing – review & editing. YD: Writing – review & editing. PL: Methodology, Funding acquisition, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Gen AI was used in the creation of this manuscript.

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