Blood Neutrophil-to-Lymphocyte Ratio as a Predictor of Cerebral Small-Vessel Disease

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Financial support: This work was supported by the National Natural Science Foundation of China (grant numbers: 81971111, 81771259)

Conflict of interest: We declare that we have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Background: In recent studies, neutrophil-to-lymphocyte ratio (NLR) was reported to be a good predictor of acute ischemic stroke (AIS), but its role in cerebral small-vessel disease (CSVD) is still controversial. We aimed to explore the value of NLR to identify CSVD.

Material/Methods: We enrolled 466 CSVD patients and 413 controls. The total burden score of CSVD was calculated according to MRI results, and imaging subgroups were divided according to MRI. The 90-day outcome was evaluated using the modified Rankin scale (mRS). NIHSS score, mRS, clinical information, biochemical parameters, and NLR were recorded, and we analyzed the relationship between NLR and CSVD.

Results: NLR was a risk factor for CSVD (OR 1.58, 95%CI 1.015–1.322; \( P = 0.029 \)). NLR was positively correlated with CSVD (\( r = 0.259, P = 0.001 \)). The AUC was 0.774, with a cut-off value of 1.89 (95% CI 0.742–0.806), \( P = 0.000 \). NLR was significantly different among the different total burden score groups of CSVD (\( P = 0.009 \)). NLRs were significant different among enlarged perivascular space (EPVS) groups (\( P = 0.017 \)), periventricular white matter high signal (PWMHS) groups (\( P = 0.028 \)), and deep white matter high signal (DWMHS) groups (\( P = 0.004 \)), but no significant difference was found among cerebral microbleeds (CMBs) groups (\( P = 0.118 \)). NLR was correlated with short-term outcome of CSVD (\( P = 0.000 \)). The AUC was 0.732 (95% CI 0.684–0.779), with a cut-off value of 2.413 for predicting a poor CSVD prognosis.

Conclusions: NLR has potential diagnostic value for CSVD, and it can predict the short-term outcome of CSVD. Therefore, NLR may be a useful biomarker to predict CSVD and its outcome.

Keywords: Cerebral Small Vessel Diseases • Ischemic Stroke • Prognosis • Severity of Illness Index • Outcome Assessment, Health Care

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/935516
Background

Cerebral small-vessel disease (CSVD) is a chronic systemic and whole-brain disease caused by the occlusion of small perforating arteries or arterioles in the elderly brain [1,2]. On brain imaging, CSVD usually presents as silent lacunar infarction (SLI), cerebral white matter hyperintensities (WMHs), enlarged perivascular space (EPVS), cerebral microbleeds (CMBs), and encephalatrophy. In the older population, the overall incidence of CSVD is much higher compared with other types of stroke. Cohort studies in community-living older people have shown that the prevalence of visible WMHs is 50-98% [3]. It also causes serious and lasting damage to cognitive, emotional, sleep, and motor function [4,5]. The pathogenesis of CSVD has not yet been fully elucidated. In recent studies, CSVD had been linked to inflammation [6,7].

Most CSVD cases are initially asymptomatic. Diagnosis of CSVD requires the use of magnetic resonance imaging (MRI), which is not available in rural areas. Efforts should be directed to find inexpensive tests that help to identify CSVD candidates. In this view, the neutrophil-to-lymphocyte ratio (NLR) had been reported as a more useful marker of inflammation [8], and an increased NLR has been associated with cardiac and cerebrovascular diseases and could help identify candidates [9-11]. However, its role in CSVD was still controversial [12-14].

Therefore, we aimed to clarify the relationship between NLR and CSVD, investigate the relationship between NLR and imaging subgroups of CSVD, and determine the value of NLR as a biomarker to predict the occurrence and outcome of CSVD.

Material and Methods

There were 1643 participants recruited in our research who were seen between January 2018 and June 2020 at the Affiliated Hospital of Qingdao University, including 466 CSVD patients (Figure 1). Inclusion criteria were: (1) age ≥18 years; (2) onset time ≤72 h; (3) brain MRI met the diagnostic criteria for CSVD [15], according to brain imaging (CSVD included LI, WMHs, EPVS, CMBs, and cerebral atrophy); and (4) signed informed consent.

Exclusion criteria were: (1) confirmed other types of stroke; (2) infection 2 weeks before onset; (3) a history of malignancy or autoimmune disease; (4) recent hormone/immunosuppressant treatment; (5) AIS with a lesion diameter of >20 mm on diffusion-weighted imaging (DWI); (6) contraindications to MRI (eg, claustrophobia); (7) confirmed neurodegenerative disease; (8) presence of definite non-vasogenic white matter lesions, such as multiple sclerosis, adult white matter dysplasia, or metabolic encephalopathy; and (10) inability to complete follow-up due to geographic or other reasons.

We selected 413 subjects as the control group, who underwent a physical examination in the Physical Examination Center of the Affiliated Hospital of Qingdao University during the same period and underwent head MRI. They were excluded from the diagnosis of CSVD, and they were sex- and age-matched with the case group.

This study was reviewed and approved by the Medical Ethics Committee of the Affiliated Hospital of Qingdao University, and all subjects provided written informed consent before participation.

Figure 1. Flowchart of the selection of CSVD patients.
Radiological Evaluation

All subjects underwent brain magnetic resonance imaging (MRI), which included the sequences of T1-weighted image, T2-weighted image, FLAIR (fluid-attenuated inversion recovery), DWI (diffusion-weighted imaging), ADC (apparent diffusion coefficient), MRA (magnetic resonance angiography), and SWI (susceptibility-weighted imaging) using 1 of 3 MR systems (GE Discovery MR750; Siemens: Siemens Skrya 3.0T; Philips Achieva 1.5T, The Netherlands). Brain and cervical computed tomography angiography (CTA) (GE Optima CT660) and digital subtraction angiography of the whole brain were performed if necessary. Image evaluation was performed by neuroimaging specialists without knowledge of clinical and laboratory data, according to the standards for reporting vascular changes on neuroimaging (STRIVE) [15]. The total burden score of CSVD ranged from 0 to 4 points, and patients were divided into 5 groups [16,17].

Clinical Assessment

The following data were collected once patients were enrolled in the study: (1) general information, including age and sex; (2) past medical history, including hypertension (defined as higher than baseline blood pressure [140 mmHg systolic or 90 mmHg diastolic]) or a history of antihypertensive treatment), hyperlipidemia (defined as a fasting total cholesterol [TC] concentration of ≥220 mg/dL or a history of statin therapy), diabetes mellitus (defined as a fasting blood glucose [FBG] concentration of ≥126 mg/dL or a history of hypoglycemic treatment), and coronary heart disease; and (3) personal history (eg, smoking history, defined as a current smoker at the time of examination). Coronary artery occlusion disease (CAOD) was defined as a history of CAOD and percutaneous coronary intervention or coronary artery bypass grafting. History of drinking was considered to be generally more than 5 years, with more than 3 drinks per week and 40 g alcohol per day for men and 20 g per day for women.

Fasting blood samples were collected from patients within 48 h of onset, and fasting laboratory tests were performed to examine WBC count, neutrophil count, lymphocyte count, homocysteine, C-reactive protein (CRP), D-Dimer, FBG, TC, triglyceride, low-density lipoprotein (LDL), cystatin, and other laboratory parameters. The NLR was calculated from the ratio of neutrophils to lymphocytes.

The severity of neurological impairment was assessed according to the National Institutes of Health Stroke Scale (NIHSS) [18]. According to the World Health Organization’s definition, an NIHSS score of >3 is classified as major stroke, while an NIHSS score of ≤3 is classified as minor stroke [19].

The modified Rankin scale (mRS) was used after 90 days of follow-up. An mRS score of 3-6 was defined as poor neurological function [20].

Statistical analysis

All statistics were analyzed using SPSS 23.0 software. Mean±standard deviation (x±SD) was used for data with a normal distribution. Continuous variables with a normal distribution were analyzed using the independent t test. Non-normally distributed continuous variables are expressed as median and quartenary, and differences among groups were evaluated using the Mann–Whitney U test. Categorical variables are expressed as frequency (percentage), and differences between groups were compared using the chi-squared test. Spearman’s correlation coefficient was used for correlation analysis. Multivariate logistic regression was used to analyze the risk factors for CSVD. Receiver operating characteristic (ROC) curves were used to evaluate the ability of NLR to identify CSVD. P value <0.05 was considered statistically significant.

Results

Comparison of Clinical Baseline Data

A total of 466 CSVD patients and 413 controls were enrolled. A previous history of hypertension, diabetes mellitus, coronary heart disease, hyperlipidemia, smoking, and drinking, as well as laboratory parameters, including NLR, systolic blood pressure, diastolic blood pressure, FBG, TC, LDL, CRP, D-dimer, and homocysteine, were significantly different between the 2 groups (P<0.05; Table 1). However, no significant differences in age, hyperuricemia history, serum uric acid, cystatin C, urea nitrogen, or fibrin were observed between the 2 groups (P>0.05; Table 1).

A multivariate logistic regression analysis showed that NLR was still an independent risk factor for CSVD after adjusting for smoking history, history of drinking, blood pressure, TC, LDL, and FBG (odds ratio [OR] 1.58, 95% confidence interval [CI] 1.015-1.322; P=0.029) (Table 2). Spearman’s correlation analysis was performed to assess the possible relationship between NLR and CSVD (r=0.259; P=0.001).

ROC curves were used to evaluate the value of NLR as a marker for predicting CSVD. The area under the ROC curve (AUC) was 0.774 (95% CI 0.742–0.806), and the optimal cut-off value of NLR for CSVD was 1.89, with a sensitivity of 74.7% and a specificity of 72.7%, P=0.000 (Figure 2A).

Relationship Between NLR and CSVD

NLR was higher in the major stroke group (P<0.004; Figure 2B) and in the high CSVD load score group (P=0.009) (Figure 3A). The trend was more pronounced in men (P=0.002) (Figure 3B) than in women (P=0.354) (Figure 3C).
A higher NLR was observed in the group more EPVSs ($P=0.017$) (Figure 4A). NLR was significantly higher in the high Fazakas score group, both in PWMHS groups ($P=0.028$) and DWMHS groups ($P=0.004$) (Figure 4B, 4C), but there was no significant difference in NLR among CMBs groups ($P=0.118$) (Figure 4D).

### Table 1. Baseline characteristics of the study population.

| Demographic characteristics | CSVD (466) | Control (413) | P value |
|-----------------------------|------------|---------------|---------|
| Age, years, mean (SD)       | 62.62 (11.77) | 63.17 (13.00) | 0.523   |
| Females, %                  | 181 (38.8%)  | 247 (59.8%)   | 0.370   |

| Vascular risk factors       |            |               |         |
|-----------------------------|------------|---------------|---------|
| Hypertension, %             | 316 (67.8%) | 228 (55.2%)   | 0.000*  |
| Diabetes, %                 | 142 (30.4%) | 77 (18.6%)    | 0.000*  |
| Coronary artery disease, %  | 38 (8.1%)   | 121 (29.2%)   | 0.000*  |
| Hyperlipidemia, %           | 30 (6.8%)   | 12 (2.9%)     | 0.022*  |
| Hyperuricemia, %            | 33 (7.0%)   | 16 (3.8%)     | 0.055   |
| Current smokers, %          | 153 (32.8%) | 62 (15.0%)    | 0.000*  |

| The history of drinking, %  | 111 (23.8%) | 46 (11.1%)    | 0.000*  |

| Clinical characteristics at admission | CSVD (466) | Control (413) | P value |
|--------------------------------------|------------|---------------|---------|
| SBP, mmHg, mean (SD)                 | 150.61 (22.92) | 138.41 (21.63) | 0.000*  |
| DBP, mmHg, mean (SD)                 | 84.50 (14.41)  | 78.44 (12.28)  | 0.000*  |
| glucose, mmol/L, median (SD)         | 6.29 (2.50)   | 5.79 (2.01)   | 0.001*  |
| TG, mmol/L, median (SD)              | 1.47 (0.86)   | 1.80 (4.61)   | 0.123   |
| TC, mmol/L, median (SD)              | 4.38 (1.61)   | 4.69 (1.09)   | 0.001*  |
| LDL, mmol/L, median (SD)             | 2.59 (0.86)   | 2.90 (0.87)   | 0.000*  |
| BUN, mmol/L, median (SD)             | 5.21 (1.77)   | 5.27 (1.96)   | 0.633   |
| Ccr, mmol/L, median (SD)             | 87.48 (21.31) | 71.86 (27.59) | 0.000*  |
| CRP, mg/L, median (SD)               | 8.59 (20.56)  | 4.33 (13.40)  | 0.007*  |
| Uric acid, umol/L, median (SD)       | 307.35 (87.61) | 311.07 (89.83) | 0.542  |
| The elf inhibition, mg/L, median (SD)| 0.98 (0.40)   | 3.50 (30.44)  | 0.08    |
| Homocysteine, umol/L, median (SD)    | 13.32 (8.29)  | 12.16 (7.9)   | 0.045*  |
| White blood cell count, $\times10^9$/L, median (SD) | 6.42 (2.11) | 8.96 (50.21) | 0.277   |
| Neutrophil count, $\times10^9$/L, median (SD) | 3.89 (1.82) | 3.73 (2.28) | 0.093   |
| INR, mean (SD)                      | 0.92 (0.09)   | 1.22 (4.60)   | 0.180   |
| D-dimer, ng/mL, median (SD)         | 346.49 (621.59) | 107.62 (418.32) | 0.000*  |
| NLR, median (IQR)                   | 1.97 (1.48, 2.68) | 1.51 (1.08, 2.02) | 0.000*  |

SBP – systolic blood pressure; DBP – diastolic blood pressure; TG – triglycerides; TC – total cholesterol; LDL – low density lipoprotein; BUN – blood urea nitrogen; Ccr – creatinine; INR – International Normalized Ratio; NLR – neutrophil-to-lymphocyte ratio; IQR – interquartile range; SD – standard deviation. * $P<0.05$.

### Relationship Between NLR and CSVD Outcome

After 90 days of follow-up, there was a significant difference in NLR between the poor neurological function group and good neurological function group ($P=0.000$) (Figure 5A). Spearman's
correlation analysis was performed between NLR and mRS \( (r=0.213; \ P=0.000) \). The ROC curve was plotted to assess the value of NLR in predicting CSVD prognosis. The AUC was 0.732 (95% CI 0.684~0.779), and the optimal cut-off value for predicting a poor CSVD outcome was 2.413, with a sensitivity of 73.0% and a specificity of 72.8% \( (P=0.000) \) (Figure 5B).

**Discussion**

In this study, we found that NLR was a risk factor for CSVD and was positively correlated with CSVD. Previous studies confirmed that NLR could predict AIS \([21-23]\). The possible mechanism was that brain tissues were hypoxic and ischemic in AIS, and infiltration of WBCs lead to necrosis of neurons and generation of reactive oxygen free radicals, which induced inflammatory cells and promote release of inflammatory mediators into the blood, triggering a series of inflammatory cascade reactions, thus leading to systemic inflammation \([24]\). These processes increase the number of WBCs and neutrophils. Neutrophils accumulated in cerebral vessels several hours after AIS \([25]\), which can cause release of inflammatory mediators into the damaged area, aggravating neuronal damage. Previous studies found that the inflammatory response can be involved in

| B     | S.E. | Wald  | df  | P value | Exp(B) | 95% EXP(B) | The lower limit | The upper limit |
|-------|------|-------|-----|---------|--------|-----------|----------------|----------------|
| SBP   | .022 | .005  | 19.470 | 1       | .000   | 1.022     | 1.012          | 1.032          |
| DBP   | .016 | .008  | 3.943 | 1       | .047   | 1.016     | 1.000          | 1.032          |
| TC    | .059 | .114  | .262 | 1       | .609   | 1.060     | .847           | 1.327          |
| LDL   | -.341| .164  | 10.922| 1       | .001   | .582      | .422           | .802           |
| Glu   | .156 | .043  | 12.894| 1       | .000   | 1.169     | 1.074          | 1.273          |
| NLR   | .147 | .067  | 4.754 | 1       | .029   | 1.580     | 1.015          | 1.322          |
| Current smokers | .854 | .255  | 11.197| 1       | .001   | 2.350     | 1.425          | 3.876          |
| The history of drinking | .248 | .287  | .748 | 1       | .387   | 1.281     | .731           | 2.247          |

SBP – systolic blood pressure; DBP – diastolic blood pressure; TC – total cholesterol; LDL – low density lipoprotein white; NLR – neutrophil-to-lymphocyte ratio.

**Table 2.** Multivariate logistic regression of risk factors for CSVD.

**Figure 2.** (A) ROC curve analysis of difference in NLR between the CSVD group and the control group. The AUC was 0.774 (95% CI 0.742~0.806, \( P=0.000 \)); (B). Relationship between NLR and NIHSS, \( P=0.004 \).
Figure 3. Relationship between NLR and the total load score of CSVD. (A) Comparison of NLR among CSVD load score groups, $P=0.009$; (B) Comparison of NLR among load score groups in males, $P=0.002$; (C) Comparison of NLR among load score groups in females, $P=0.354$. 
Figure 4. (A) Comparison of NLR among EPVS grading groups, \( P = 0.017 \); (B) Comparison of NLR among groups with PWMHs, \( P = 0.028 \); (C) Comparison of NLR among groups with DWMHS, \( P = 0.004 \). (D) Comparison of NLR among CMB grading groups, \( P = 0.118 \).

Figure 5. Relationship between NLR and CSVD outcome. (A) Comparison of NLR between different mRS groups, \( P = 0.000 \); (B) NLR ROC curve for evaluating prognosis of CSVD. The AUC of NLR was 0.732 (95% CI 0.684–0.779, \( P = 0.000 \)).
CSVD pathogenesis [6,7]. At present, there have been few and controversial studies on NLR and CSVD. In healthy populations, a higher NLR was associated with a greater WMH volume [12], but a previous study found no link between them [13,14]. Our study also found that NLR was an independent risk factor for CSVD and was positively correlated with CSVD. Our results further support the inflammatory mechanisms of CSVD.

Then, we investigated the relationship between NLR and CSVD. NIHSS score is the most commonly used tool to assess the severity of stroke [26]. There was a strong linear correlation between NLR and NIHSS score in patients with AIS [23]. We observed similar results in patients with CSVD, suggesting that NLR is closely related to CSVD severity. The total burden score of CSVD can reflect CSVD severity [15,16]. We found that the total burden score of CSVD increased as the NLR increased, which indicated that NLR can reflect the severity of CSVD to a certain extent, and the trend was more pronounced in men. The possible mechanism of this trend was that neutrophil infiltration activates the androgen receptor-c-Myc signaling pathway [27], leading to cerebral ischemia [28].

We further investigated the relationship between NLR and WMHs, EPVS, and CMBs. NLR was related to WMHs. We found that the Fazekas score increased as the NLR increased, which is consistent with previous research [12]. NLR was positively correlated with Fazekas scores in PWMHS groups and DWMHS groups. Previous studies [29,30] found that inflammatory factors were associated with DWMHs or PWMHs in neurodegenerative diseases. Our results suggest that the inflammatory response is involved in WMHs. The possible mechanisms are neutrophil aggregation, cytokine release, and microglia and astrocyte activation and proliferation in patients with chronic ischemia, resulting in proinflammatory factor injury, white matter injury, oligodendrocyte reduction, and diffuse demyelination and axonal injury [31,32]. Rouhi et al [33] found that the inflammatory response may be involved in EPVS, and EPVS in the basal ganglia relates to CSVD severity [34]. To the best of our knowledge, the present study is the first to report that NLR is closely related to the numbers of EPVS and suggests that the inflammatory reaction participates in EPVs. Inflammatory cells enter the diseased perivascular space in patients with multiple sclerosis and drive ongoing inflammatory pathological activity [35]. However, no correlation was found between NLR and CMBs. The etiology of CMBs is complex, and its pathogenesis remains unclear. A recent study had found that endothelial cell dysfunction and the inflammatory response may also play an important role in the pathogenesis of CMBs [36]. No studies have yet examined the relationship between NLR and CMBs. Our results showed that NLR was not related to CMBs, which required further study with larger sample sizes.

After 90-day follow-up, NLR was shown to be positively correlated with mRS in CSVD. Previous studies found that an elevated NLR could predict the outcome of AIS [11,37,38]. However, there are no relevant studies on the relationship between NLR and CSVD prognosis. We found that NLR was closely related to CSVD outcome. CSVD patients with an NLR of 2.413 or greater are more likely to have a poor outcome. This may be because an elevated NLR leads to persistence of the inflammatory response, which determines CSVD outcome.

This study has several limitations. First, all patients in this study were Han people in northern China, so the results cannot be generalized to other ethnic groups. Second, the pathogenesis of CSVD is diverse and complex and different subtypes may have different mechanisms. Thus, a larger sample size is needed in future studies.

Conclusions

NLR has potential diagnostic value for CSVD. It is positively correlated with the severity of CSVD and it can predict short-term outcomes. NLR may be a useful biomarker to predict CSVD and its outcome.

Declaration of Figures’ Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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