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The Negative Prognostic Role of Inflammatory Biomarkers in Patients With Chronic Cerebrospinal Venous Insufficiency

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Background: The pathologic consequences of inflammatory responses in chronic cerebrospinal venous insufficiency (CCSVI) remains poorly understood. Hence, this study was aimed to evaluate the peripheral inflammatory biomarkers in patients with intracranial and extracranial CCSVI pathology. In addition, the relationship between inflammatory cytokine profile and CCSVI prognosis was also evaluated.

Methods: Patients diagnosed with CCSVI between July 2017 and July 2019 were included and subsequently divided into 3 groups based on the location of stenosis. The inflammatory biomarker assay included neutrophil-to-lymphocyte ratios (NLRs), platelet-to-lymphocyte ratios (PLRs), red blood cell distribution widths (RDW), C-reactive protein (CRP) levels, interleukin-6 (IL-6) levels, and neuron-specific enolase levels. Clinical outcomes were assessed using the modified Rankin Scale and Patient Global Impression of Change score. Univariate and multivariate regression analyses were performed to identify significant prognostic factors for poorer outcomes. Finally, we established a nomogram based on the multivariate regression analysis.

Results: We enrolled 248 patients in total, including 102 males and 146 females, with an average age of 57.85 ± 12.28 years. Compared with patients with internal jugular vein stenosis, cerebral venous sinus stenosis (CVSS) patients were mostly younger and had been suffering from headaches and severe papilledema. Higher levels of NLR, RDW, and CRP were also observed in the CVSS group. Multivariate analysis indicated that NLR, PLR, and IL-6 were the independent prognostic factors for poor CCSVI outcomes.

Conclusions: The clinical presentations and increases in NLR, PLR, IL-6, and CRP levels could be distinctly marked in patients with CVSS-related CCSVI than that in internal jugular vein stenosis–related CCSVI, indicating poor prognostic outcomes in these patients. A proinflammatory state might be associated with CCSVI pathology.

Key Words: chronic cerebrospinal venous insufficiency, cerebral venous sinus stenosis, internal jugular vein stenosis, inflammatory biomarkers, clinical outcome

(*The Neurologist* 2023;28:57–68)

Chronic cerebrospinal venous insufficiency (CCSVI) was first defined by Zamboni et al[1] as a chronic state of impaired cerebral or cervical venous drainage. The close relationship between CCSVI and multiple sclerosis (MS), leukoaraiosis, and vascular dementia has been discussed over the past decade.[2] Although there is still a controversy over the relationship between CCSVI and neurological disorders, CCSVI has been found in apparently "healthy people," and caused nonspecific symptoms, including headache, tinnitus, and head noises.[3–5] CCSVI may induce venous refluxes and cerebral venous hypertension, resulting in brain-blood barrier integrity disruption and perivenous iron accumulation,[6,7] and decreased cerebral brain flow (CBF),[8,9] which leads to chronic cerebral hypoxia, inflammatory cells infiltration into the brain parenchyma and even local inflammatory processes.[10,11]

Our previous work demonstrated that the neutrophil-to-lymphocyte ratio (NLR)[12] and red blood cell distribution width (RDW)[13] were negative diagnostic and prognostic markers for acute ischemic stroke. Furthermore, inflammatory biomarkers, such as NLR, hypersensitive C-reactive protein (CRP), and interleukin-6 (IL-6), were correlated with the severity and clinical outcomes of cerebral venous thrombosis.[14] We also discovered the coexistence of arterial stenosis and venous stenosis for the first time.[15] Based on these findings,[16–19] we were interested in determining if CCSVI would be related to elevations in peripheral inflammatory biomarkers [eg, NLR, RDW, IL-6, CRP, and neuron-specific enolase (NSE)], and whether there would be differences in inflammatory responses between the extracranial (internal jugular vein stenosis, IJVS) and intracranial (cerebral venous sinus stenosis, CVSS) forms of CCSVI. Furthermore, we were interested in investigating if there were any correlations between inflammatory cells (eg, neutrophils and lymphocytes) and inflammatory cytokines (eg, IL-6, CRP, and NSE). Besides, to establish the relationship

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This study was approved by the Institutional Review Board of Xuanwu Hospital. All informed consent was obtained from study participants in written form.

R.M.: helped in manuscript drafting and revision; and study concept and design. S.-y.S.: helped in manuscript drafting and revision; study conception and design; and data collection, assembly, and interpretation. R.M., S.-y.S., D.L., B.-l.J., and Y.-h.L.: helped in manuscript writing and final revision of the manuscript. R.M., X.-m.J., and Y.-c.D.: helped in manuscript drafting and revision.

This manuscript has been released as a preprint at Research Square, Si-ying Song et al, Inflammatory Biomarkers May Predict Poor Outcome in Patients with Chronic Cerebrospinal Venous Insufficiency; May 12, 2020, PREPRINT (Version 1) available at Research Square (https://doi.org/10.21203/rs.3.rs-27600/v1).

Supported by the National Natural Science Foundation under Grant (82171297), and the Beijing Natural Science Foundation (7212047).

The authors declare no conflict of interest.

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Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.theneurologist.org.

ISSN: 2331-2637/23/2802-0057
DOI: 10.1097/NRL.0000000000000443

between the hyperactivated inflammatory signaling and CCSVI prognosis, a prognostic model was established.

Thus, here, we specifically enrolled patients with CCSVI caused by the obstruction of internal jugular veins (IJVs) and/or cerebral venous sinuses (CVSs). We present this article in accordance with the STROBE reporting checklist (Supplementary Table 3, Supplemental Digital Content 1, http://links.lww.com/NRL/A87).

METHODS

Population

CCSVI is a hemodynamic condition in which cerebrospinal venous drainage is altered and inhibited. Outflow obstructions of the IJVs, vertebral veins (VVs), azygos vein, and/or CVS and their tributaries result in stasis or reflux of these outflow veins and redirection of flow through various circuits. Here, we specifically enrolled patients with CCSVI caused by the obstruction of IJVs and/or CVSs who were treated at the Department of Neurology, Xuanwu Hospital, at Capital Medical University, between 2017 and 2021. This study was approved by the Ethics Committee of Xuanwu Hospital at Capital Medical University. All procedures were carried out in accordance with relevant guidelines and regulations. All participants signed consent forms before the beginning of the study.

For enrollment in the study, patients were noninvasively screened using transcranial and extracranial echo-color Doppler ultrasounds based on venous hemodynamic criteria.[1] The 5 characteristic criteria of venous hemodynamic include: (1) reflux in the IJVs and/or VVs in sitting and supine postures; (2) reflux in the deep cerebral veins; (3) high-resolution B-mode evidence of IJVS; (4) non–Doppler-detectable flow in the IJVs and/or VVs; and (5) reverted postural control of the main cerebral venous outflow pathways. A subject was considered CCSVI-positive if >2 of these 5 characteristics were fulfilled.[20,21] Then, a confirmed CCSVI diagnosis was made using contrast-enhanced magnetic resonance venography or digital subtraction angiography.[22,23] There were no age and sex limitations. Patients had no previous or current evidence of MS, no remarkable parenchymal CCSVI-induced brain lesions, or a disease course at a subacute or chronic stage [defined as an interval (from symptoms and signs onset to enrollment) of >1 mo].

We excluded patients (1) with definite acute or chronic inflammatory diseases that could affect the levels of inflammatory biomarkers (eg, acute upper respiratory infection or gastrointestinal infection, asthma, chronic peptic ulcer, tuberculosis, rheumatoid arthritis, ulcerative colitis, and Crohn disease); (2) receiving anti-inflammatory medications within 4 weeks before blood collection; (3) who were on their menstrual periods; and (4) having intracranial hypertension (IH) induced by other reasons: (a) drug-induced IH; (b) cerebrospinal fluid shunt history; (c) intracranial mass occupation; (d) arteriovenous malformations; (f) traumatic brain injury, and (g) acute arterial stroke.

Clinical and Demographic Data

We recorded each patient's age, sex, course of CCSVI (from symptoms onset to admission), treatments, presumable risk factors known before hospitalization, and presumable risk factors discovered during hospitalization. The risk factors included hypertension (use of antihypertensive medications or systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg before hospitalization), diabetes mellitus (use of antidiabetic therapies or fasting blood glucose >7 mmol/L on 2 occasions during hospitalization), hypercholesterolemia (hypolipidemic agents usage or low-density lipoprotein cholesterol >1 g/L), a history of myocardial infarction or angina, overweight (body mass index >25 kg/m^2), anemia (hemoglobin count >12.5 g/dL), hepatitis B virus (HBV) infection (ie, use of anti-HBV agents or positive for hepatitis B core antibody/antigen or hepatitis B e antibody/antigen), hyperhomocysteinemia (serum homocysteine >15 mmol/L), hyperuricemia (serum uric acid >416 μmol/L), chronic rhinosinusitis, history of otitis media/mastoiditis, suspected thyroid disorders (including either abnormal thyroid ultrasound results or abnormal thyroid function results), autoimmune disease, thrombophilia (including protein S deficiency, protein C deficiency, antithrombin III deficiency, hyperfibrinogenemia, primary thrombocythemia, or increased D-dimer level), and history of ischemic or hemorrhagic stroke. We also collected clinical symptoms and signs, including instances of headache, tinnitus, head noises, papilledema, and IH. The severity of papilledema was evaluated by Frisen papilledema grading.[24] Intracranial pressure was detected with a lumbar puncture. IH was defined by the presentation of common IH symptoms (headache and blurry/double vision) and LP pressure >200 mm H_2O.[25]

Inflammatory Biomarkers Assay

The inflammatory biomarker assay included NLR, platelet-to-lymphocyte ratio (PLR), IL-6, CRP, and NSE measurement. Baseline values were measured on admission. NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. PLR was calculated as the absolute platelet count divided by the absolute lymphocyte count. Baseline inflammatory markers were considered both as continuous and categorical variables. We used receiver operating characteristic (ROC) curves to assess the predictive value of inflammatory markers and define cutoff values. We then used optimal cutoffs to find thresholds and change inflammatory markers into categorical variables.

Clinical Outcome Evaluation

The modified Rankin Scale (mRS) score was used to evaluate the functional outcomes of the patients at discharge, and the Patient Global Impression of Change (PGIC) score was used to predict outcomes during outpatient telephone follow-up. PGIC is a semiquantitated 7-point self-evaluation scale of the patients that reflects overall changes in symptoms (1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse). Based on PGIC scores, we divided the patients into 2 groups: those that had good outcomes (PGIC ≤ 3) and those that had poor outcomes (PGIC >3).

Statistical Analysis

The Bartlett test for equal variances and the Shapiro-Wilk test for normal distribution were conducted for each continuous variable. We then used either Kruskal-Wallis tests or Fisher exact tests to compare continuous and/or categorical variables between patients with IJVS, CVSS, and CVSS combined with IJVS. Finally, differences between baseline inflammatory marker values (NLR, PLR, and RDW) and values at discharge were tested using Wilcoxon signed-rank test.

Correlation coefficients were calculated between inflammatory biomarkers using the Spearman tests. The Kaplan-Meier score was used to plot the distribution of time and poor outcomes among CCSVI subtypes (IJVS, CVSS, and CVSS combined with IJVS) and inflammatory biomarkers. The log-rank test was also used to compare the curves. We performed univariate and multivariate Cox proportional hazards models to examine the relationship between inflammatory markers and clinical outcomes. Groups with lower levels of inflammatory biomarkers were used as references. We included the most common symptoms (headache, sleep disturbances, head noise, tinnitus), risk factors

TABLE 1. Demographic and Basic Clinical Features

Variables	All (N = 248)	IJVS (n = 171)	CVSS (n = 43)	CVSS Combined With IJVS (n = 34)	*P*
Personal data					
Age (mean ± SD) (y)	53.44 ± 14.94	57.85 ± 12.28	43.02 ± 16.20†	44.44 ± 15.30†	< 0.001
Sex (male:female)	102:146	75:96	11:32	16:18	0.067
Course of disease					0.005
Subacute (within 1 mo)	11 (4.4)	3 (2.1)	4 (9.3)	4 (8.8)	
Chronic (> 1 mo)	237 (95.6)	168 (98.2)	39 (90.6)	30 (88.2)	
Follow-up time (mean ± SD) (mo)‡	18.00 ± 5.57	18.79 ± 5.30	17.47 ± 6.36	17.00 ± 5.60	0.082
Symptoms and signs					
Sleep disturbances	152 (61.5)	125 (73.0)	11 (26.1)	16/34 (47.1)	< 0.001
Eye discomfort	146 (58.9)	97 (56.7)	29 (67.4)	20 (58.8)	0.441
Papilledema	46 (18.6)	15 (8.8)	17 (39.5)	14 (41.1)	< 0.001
Frisen scale (mean ± SD)	1.08 ± 1.31	0.50 ± 0.83	1.96 ± 1.49†	1.63 ± 1.30†	< 0.001
Head noises	136 (54.8)	112 (65.4)	11 (25.6)	13 (38.2)	0.001
Tinnitus	129 (52.0)	102 (60.0)	15 (34.9)	12 (35.2)	0.002
Headache	114 (46.0)	65 (38.0)	28 (65.1)†	21 (61.8)†	0.001
Neck discomfort	76 (30.7)	59 (34.5)	9 (20.9)	8 (23.5)	0.146
Hearing loss	82 (33.1)	67 (39.1)	9 (20.9)	6/34 (17.6)	0.009
Anxiety	44 (17.7)	35 (20.5)	7 (16.3)	2 (5.9)	0.114
Nausea/vomiting	47 (19.0)	28 (16.3)	10 (23.3)	9 (26.7)	0.266
Memory loss	21 (8.5)	17 (9.9)	2 (4.7)	2 (5.9)	0.566
IH	42/84 (50.0)	23/49 (46.9)	13/15 (86.7)	6/20 (30.0)	0.003
Presumable risk factors					
Thrombophilia					
PS deficiency	65/227 (28.6)	42/163 (25.9)	11/32 (34.3)	12/32 (37.5)	0.109
PC deficiency	25/227 (11.0)	11/163 (6.7)	7/32 (21.9)	7/32 (21.9)	0.002
AT-III deficiency	26/227 (11.5)	21/158 (13.3)	5/39 (12.8)	0 (0)	0.006
Increased D-dimer level	22/206 (10.7)	10/136 (7.4)	7/38 (18.4)	5/32 (15.6)	0.075
Hyperfibrinogenemia	26/247 (10.5)	16/170 (9.4)	6 (14.0)	4 (11.8)	0.592
Primary thrombocythemia	9/246 (3.7)	2/170 (1.2)	5/42 (11.9)	2 (5.9)	0.021
Overweight (BMI > 25)	89/240 (37.1)	52/165 (31.5)	24/41 (58.3)	13/34 (38.2)	0.006
Hyperlipidemia	86 (34.7)	64 (37.4)	10 (23.2)	12 (35.3)	0.219
HBP	79 (31.9)	61 (35.7)	10 (23.2)	8 (23.5)	0.181
Anemia	56/246 (22.8)	37/170 (21.8)	12/42 (28.6)	7 (20.6)	0.617
HBV infection	46 (18.6)	34/170 (20.0)	6 (14.0)	6 (17.6)	0.745
Suspected thyroid disorders					
Abnormal thyroid ultrasound	31 (12.5)	25 (14.6)	2 (4.7)	4 (11.8)	0.230
Abnormal thyroid function test	64 (25.9)	42 (24.6)	9 (20.9)	13 (38.2)	0.166
CAD	25 (10.1)	21 (12.2)	1 (2.3)	3 (8.8)	0.156
Type 2 DM	20 (8.1)	17 (9.9)	1 (2.3)	2 (5.9)	0.261
IS history	20 (8.1)	16 (9.4)	2 (4.7)	2 (5.9)	0.717
Hyperhomocysteinemia	19 (7.7)	9 (5.3)	7 (16.3)	3 (8.8)	0.046
Hyperuricemia	18 (7.3)	12/170 (7.1)	3/42 (7.1)	3 (8.8)	0.929
Chronic rhinosinusitis	13 (5.2)	12 (7.0)	1 (2.3)	0 (0)	0.266
Previous otitis media/mastoiditis	6 (2.4)	5 (2.9)	0 (0)	1 (2.9)	0.672
ICH history	6 (2.4)	3 (1.8)	3 (7.0)	0 (0)	0.126
Pregnancy/postpartum	1 (0.4)	0 (0)	1 (2.3)	0 (0)	0.310
Autoimmune disease					
SS	6 (2.4)	4 (2.3)	0 (0)	2 (5.9)	0.189
APS	3 (1.2)	3 (1.8)	0 (0)	0 (0)	1.000
Behcet disease	2 (0.8)	1 (0.6)	1 (2.3)	0 (0)	0.525
IgG4-related disease	4 (1.6)	2 (1.2)	1 (2.3)	1 (2.9)	0.367
Increased IgE	2 (0.8)	1 (0.6)	0 (0)	1 (2.9)	0.285
Others	4 (1.6)	3 (1.8)	1 (2.3)	0 (0)	1.000
Inflammatory markers (mean ± SD)					
NLR on admission§	1.81 ± 0.77	1.71 ± 0.67	1.97 ± 0.76†	2.10 ± 1.09†	0.026
NLR at discharge*	2.91 ± 2.56*	2.71 ± 1.60*	3.55 ± 4.48	2.49 ± 1.63	0.183
Delta-NLR	1.12 ± 2.15	1.07 ± 1.66	1.29 ± 3.41	0.98 ± 1.39	0.641
PLR on admission	124.13 ± 46.93	118.69 ± 36.70	133.82 ± 49.19	139.78 ± 76.95	0.183
PLR at discharge§	151.32 ± 100.88	147.72 ± 112.74	158.15 ± 69.93	165.46 ± 104.12	0.779
Delta-PLR	26.75 ± 103.07	31.58 ± 113.15	6.66 ± 81.94	56.83 ± 69.44	0.746
RDW on admission (%)	13.14 ± 1.43	12.97 ± 1.15	13.72 ± 1.96†	13.29 ± 1.78	0.013
RDW at discharge (%)§	13.49 ± 2.28	13.43 ± 2.23	13.76 ± 2.77	13.05 ± 0.49	0.837
Delta-RDW (%)	0.44 ± 2.37	0.57 ± 2.27	0.06 ± 2.95	0.70 ± 1.26	0.315
IL-6 (pg/mL)	4.70 ± 5.71	4.60 ± 5.65	4.97 ± 6.97	5.05 ± 4.68	0.621
CRP (mg/L)	2.80 ± 3.69	2.42 ± 1.70	4.78 ± 8.68†	2.69 ± 1.53	0.017
NSE (ng/mL)	12.93 ± 2.71	12.80 ± 2.48	12.99 ± 3.08	13.55 ± 3.33	0.861

TABLE 1. (*continued*)

Variables	All (N = 248)	IJVS (n = 171)	CVSS (n = 43)	CVSS Combined With IJVS (n = 34)	*P*
Treatment					
Antiplatelet drugs	148 (59.9)	118/170 (69.4)	18 (41.9)	12 (5.9)	<0.001
Anticoagulants	80 (32.4)	26/170 (15.3)	30 (69.7)	24 (70.6)	<0.001
Endovascular therapies	30 (12.1)	10 (5.8)	14 (32.6)	6 (17.6)	<0.001
Stenting	23 (9.3)	9 (5.3)	9 (20.3)	5 (14.7)	0.003
Balloon dilation	5 (2.0)	1 (0.6)	3 (7.0)	1 (2.9)	0.022
Intrasinus thrombolysis	4 (1.6)	0 (0)	2 (4.7)	1 (2.9)	0.090
ONSD	7 (2.8)	1 (0.6)	2 (4.7)	4 (11.8)	0.002
Outcomes at discharge					0.062
mRS <3	246 (99.1)	171 (100)	41 (95.3)	34 (100)	
mRS ≥3	2 (0.9)	0 (0)	2 (4.7)	0 (0)	

*Compared with group of NLR tested on admission, statistically significant at $P < 0.05$.
†Compared with group of IJVS, statistically significant at $P < 0.05$.
‡Time from discharge to follow-up (mo).
§The number of patients who had complete blood count test at discharge (n = 36).
APS indicates antiphospholipid syndrome; AT-III, antithrombin III; BMI, body mass index; CAD, coronary artery disease; CRP, C-reactive protein; CVSS, cerebral venous sinus stenosis; DM, diabetes mellitus; HBP, high blood pressure; HBV, hepatic type B virus; ICH, intracranial hemorrhage; Ig, immunoglobulin; IH, intracranial hypertension; IJVS, internal jugular vein stenosis; IL-6, interleukin-6; IS, ischemic stroke; mRS, modified Rankin Scale; NLR, neutrophil-to-lymphocyte ratio; NSE, neuron-specific enolase; ONSD, optic nerve sheath decompression; PLR, platelet to lymphocyte ratio; PC, protein C; PS, protein S; RDW, red blood cell distribution width; SS, Sjögren syndrome.

(thrombophilia and overweight), and inflammatory markers in the univariate model. For the multivariate analysis, we used the following 3 models based on the results from the univariate model and our previous studies[26,27] as well as clinical experiences: model 1 estimated the crude association with inflammatory markers; model 2 also adjusted for age and sex; and model 3 added several other potential confounders, including thrombophilia and anticoagulation. We also generated a scoring

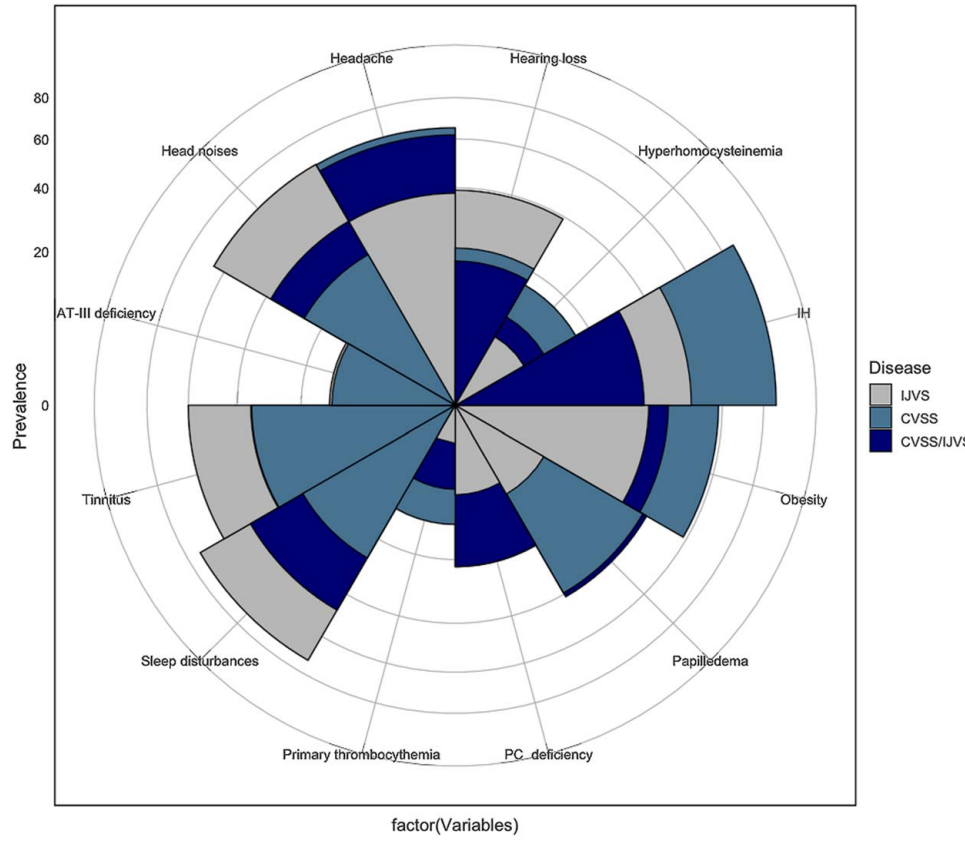

FIGURE 1. Significant differences in symptoms and risk factors among subgroups of chronic cerebrospinal venous insufficiency. AT-II indicates antithrombin III; CVSS, cerebral venous sinus stenosis; IH, intracranial hypertension; IJVS, internal jugular vein stenosis; PC, protein C.

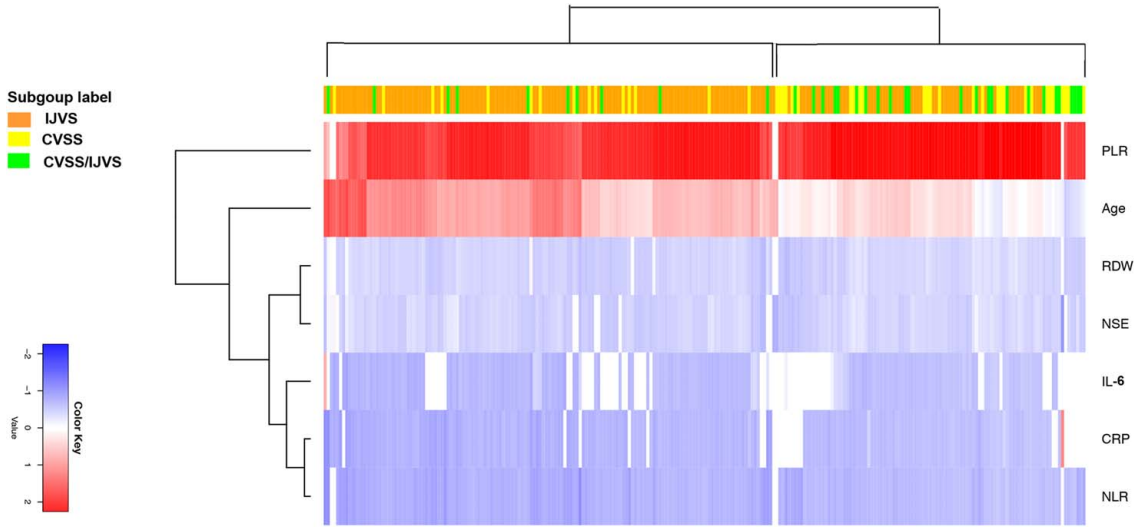

FIGURE 2. Heatmap analysis of age, inflammatory biomarkers, and subgroups of chronic cerebrospinal venous insufficiency. CRP indicates C-reactive protein; CVSS, cerebral venous sinus stenosis; IJVS, internal jugular vein stenosis; IL-6, interleukin-6; NLR, neutrophil-to-lymphocyte ratio; NSE, neuron-specific enolase; PLR, platelet to lymphocyte ratio; RDW, red blood cell distribution width.

system reflecting individual prognoses according to model 3. Model performance was assessed using discrimination (the *C*-index) and calibration (internal validation by bootstrap resampling and calibration plots).[28,29]

Values were presented as mean ± SD or percentages. Hazard ratios (HRs) with 95% confidence intervals (CIs) were provided where appropriate. Differences were considered significant at a 2-sided *P*-value <0.05 level. Analyses were

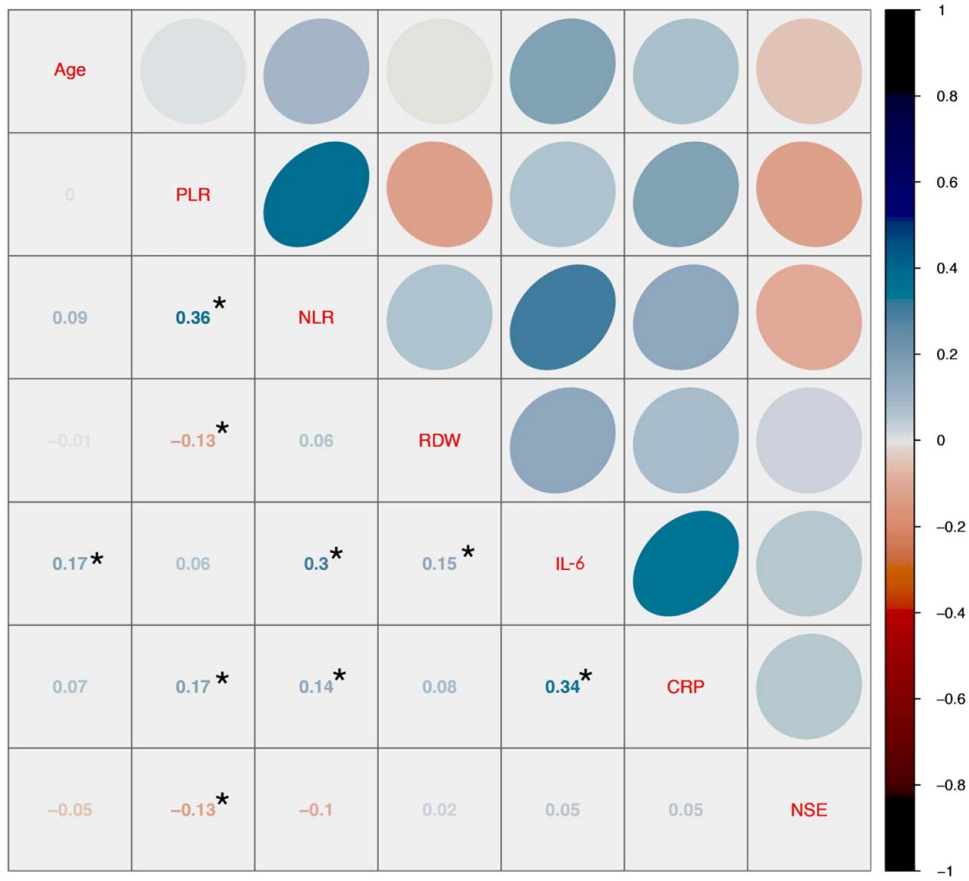

FIGURE 3. Spearman correlations between age and inflammatory biomarkers. *$P < 0.05$. CRP indicates C-reactive protein; IL-6, interleukin-6; NLR, neutrophil-to-lymphocyte ratio; NSE, neuron-specific enolase; PLR, platelet to lymphocyte ratio; RDW, red blood cell distribution width.

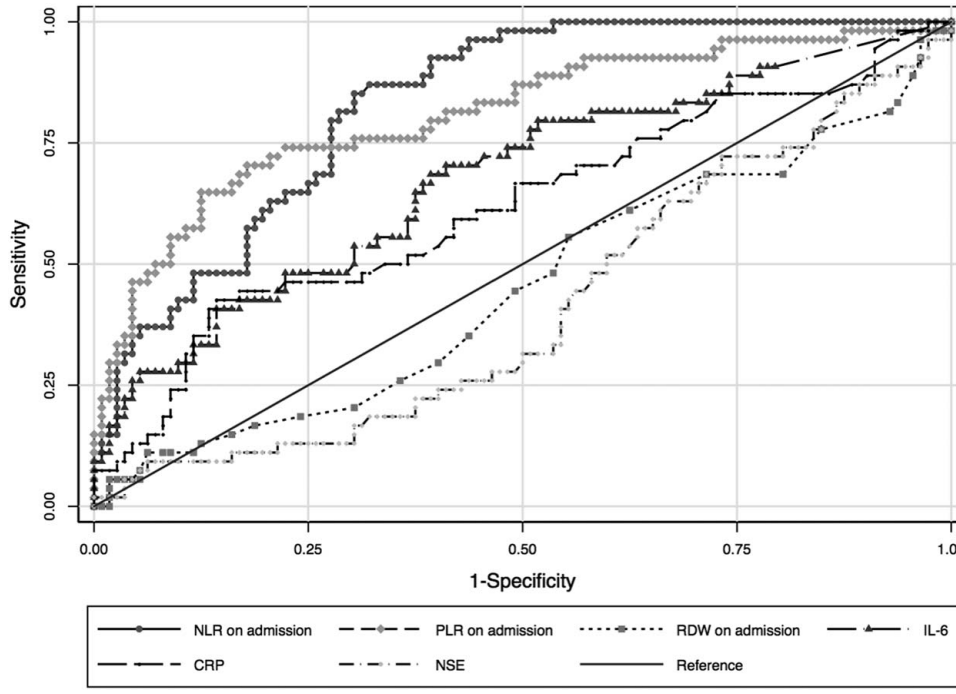

FIGURE 4. Receiver operating characteristic curves for inflammatory biomarkers. CRP indicates C-reactive protein; IL-6, interleukin-6; NLR, neutrophil-to-lymphocyte ratio; NSE, neuron-specific enolase; PLR, platelet to lymphocyte ratio; RDW, red blood cell distribution width.

performed using Stata software (version 15.0 SE; Stata Corp, LP, TX) and R software [version 3.6.2 (2019-12-12)].

RESULTS

Baseline Clinical Features

A total of 248 patients (102 males and 146 females) with CCSVI were enrolled in this study. The majority of patients (95.6%) were at a chronic stage of disease and were followed for an average of 18.00 ± 5.57 months. The top 5 CCSVI symptoms were sleep disturbances (61.5%), eye discomfort (including dry or itchy feeling, eye pain, or irritation) (58.9%), head noise (54.8%), tinnitus (52.0%), and headache (46.0%). Common presumable risk factors identified in $>80\%$ of patients were: comorbid thrombophilia (69.8%), overweight (body mass index >25) (37.1%), hyperlipidemia (34.7%), hypertension (31.9%), and anemia (22.8%), followed by suspected thyroid disorders (38.4%). Protein S deficiency was the most common prothrombotic abnormality (28.6%). Common treatments for patients with CCSVI included antiplatelet drugs (59.9%), anticoagulants (32.4%), and endovascular therapy (12.1%). Most patients had good outcomes at the time of discharge (mRS ≤ 2). Table 1 summarizes baseline clinical data.

We next divided patients with CCSVI into 3 subgroups based on imaging findings: those with IJVS (n = 171), those with CVSS (n = 43), and those with CVSS combined with IJVS (n = 34). Patients in the IJVS group were slightly older (mean age: 57.85 ± 12.28 y, $P < 0.001$) and complained more frequently of tinnitus (60.0%, $P = 0.002$), head noises (64.5%, $P = 0.001$), and/or sleep disturbances (73.0%, $P < 0.001$) than those in the other 2 groups. Headache ($P = 0.001$) and severe papilledema ($P < 0.001$) were more common in CVSS (either isolated CVSS or CVSS combined with IJVS) than in isolated IJVS patients, which might have resulted from the higher intracranial pressure levels in these 2 groups. Optic nerve sheath decompression surgery was more likely to be performed in patients with CVSS-related severe papilledema ($P = 0.002$). CVSS was more commonly related to protein C deficiencies (21.9%, $P = 0.002$), primary thrombocythemia (11.9%, $P = 0.021$), being overweight (58.3%, $P = 0.006$), and hyperhomocysteinemia (16.3%, $P = 0.046$). Figure 1 demonstrates the differences in symptoms and risk factors between the subgroups. Stenoses mainly involved transverse sinus and sigmoid sinus as well as transverse sinus-sigmoid sinus junctions in almost all CVSS cases, and the common localization of IJVS was typically the J3 segment (Supplementary Table 1, Supplemental Digital Content 2, http://links.lww.com/NRL/A88). Anticoagulants (69.7%, $P < 0.001$) and endovascular therapies (32.6%, $P < 0.001$) were more common in patients with CVS involvement.

TABLE 2. Receiver Operating Characteristic Analysis of Inflammatory Markers for Predicting Poor Outcomes

Variables	AUC	*P*	Cutoff Value
NLR on admission	0.830 (0.770, 0.890)	< 0.001	1.7
PLR on admission	0.809 (0.735, 0.883)	< 0.001	127.0
RDW on admission (%)	0.451 (0.356, 0.547)	0.310	14.2
IL-6 (pg/mL)	0.676 (0.587, 0.765)	0.013	3.2
CRP (mg/L)	0.619 (0.524, 0.715)	< 0.001	2.9
NSE (ng/mL)	0.413 (0.321, 0.504)	0.068	17.5

AUC indicates area under the curve; CRP, C-reactive protein; IL-6, interleukin-6; NLR, neutrophil-to-lymphocyte ratio; NSE, neuron-specific enolase; PLR, platelet to lymphocyte ratio; RDW, red blood cell distribution width.

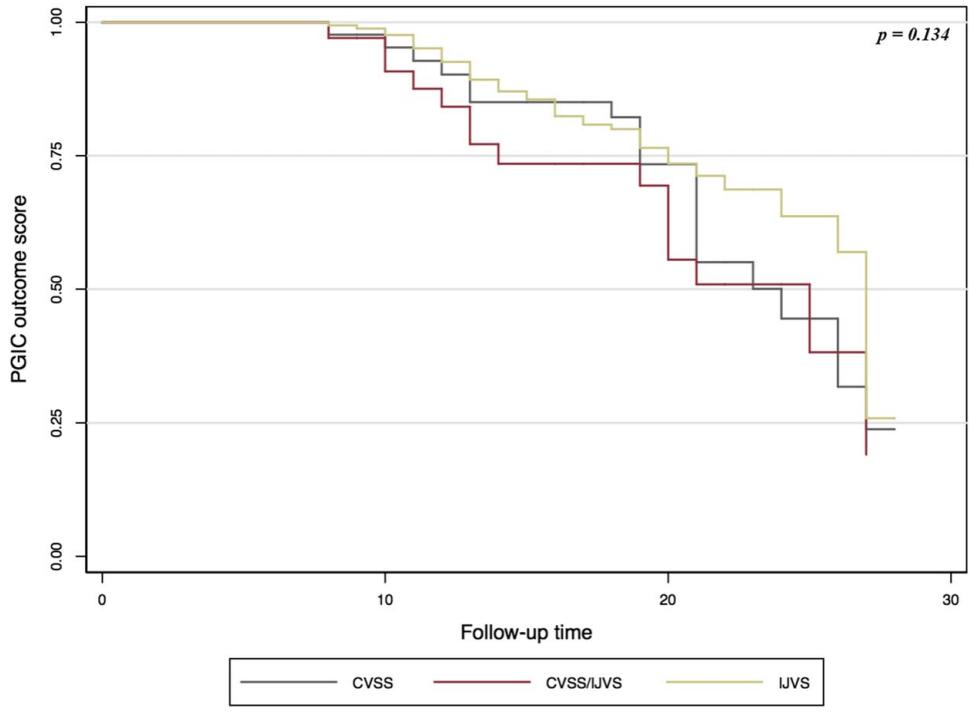

FIGURE 5. Kaplan-Meier estimation for the clinical outcomes in subgroups of chronic cerebrospinal venous insufficiency. CVSS indicates cerebral venous sinus stenosis; IJVS, internal jugular vein stenosis; PGIC, Patient Global Impression of Change.

Inflammatory Biomarkers in CCSVI

Subgroups Analysis of Inflammatory Biomarkers in CCSVI

Baseline NLR was significantly higher in groups with CVSS than in those with IJVS only ($P = 0.026$). The CVSS group also had increased baseline RDW ($P = 0.013$) and CRP ($P = 0.017$) levels. In addition, there were no other significant differences in other inflammatory markers between the CVSS and IJVS groups. To further evaluate the dynamic changes of NLR/PLR/RDW during the hospitalization, a few patients underwent a complete blood count test at discharge (n = 36). The mean hospital stay was 12.38 ± 5.27 days. The level of NLR at discharge was slightly higher than the baseline ($P = 0.001$), while levels of PLR and RDW at discharge did not show any significant differences compared with their baseline values.

Correlations Between Inflammatory Cells and Inflammatory Cytokines

A heat map was constructed containing variables of inflammatory markers, age, and CCSVI subgroups (Fig. 2). We assumed that patients with CVSS would more likely be younger and had relatively higher levels of inflammatory markers. Furthermore, we calculated correlation coefficients for NLR, PLR, RDW, IL-6, CRP, and NSE using Spearman tests (Fig. 3). As shown in Supplementary Table 2 (Supplemental Digital Content 3, http://links.lww.com/NRL/A89), the baseline NLR was moderately correlated with PLR ($\rho = 0.358$) and IL-6 ($\rho = 0.297$) levels. In addition, IL-6 had a positive association with CRP ($\rho = 0.340$). However, inflammatory biomarkers did not show any correlation with age.

ROC Analysis of Inflammatory Biomarkers in CCSVI

We constructed ROC curves to evaluate the sensitivity and specificity of inflammatory biomarkers for predicting clinical outcomes of CCSVI (Fig. 4). Baseline NLR ($P < 0.001$), PLR ($P < 0.001$), IL-6 ($P = 0.013$), and CRP ($P < 0.001$) levels had higher prognostic values in CCSVI, while baseline RDW and NSE values proved to be nonsignificant for predicting CCSVI outcomes. The optimal cutoff value for each variable was then defined based on the respective ROC curve (Table 2).

Inflammatory Biomarkers and Clinical Outcomes in CCSVI

KM Analysis in CCSVI

There were no differences in clinical outcomes between CCSVI subgroups ($P = 0.134$) (Fig. 5). However, the chance of poor outcomes was significantly increased with higher baseline NLR, PLR, IL-6, and CRP values ($P < 0.001$), while higher RDW ($P = 0.461$) and NSE ($P = 0.872$) levels were not associated with poorer outcomes (Fig. 6).

Univariate and Multivariate Cox Regression Analysis

We included age, sex, common symptoms (sleep disturbances, eye discomfort, head noise, tinnitus, and headache), common risk factors (thrombophilia state, overweight, diabetes mellitus, high blood pressure, hyperlipidemia, HBV infection, and suspected thyroid disorders), and the results of the inflammatory biomarker assay in the primary univariate analysis. However, only NLR, PLR, RDW, IL-6, and CRP had significant negative prognostic values in CCSVI (Fig. 7). In addition, we performed the multivariate analysis in 3 models (Table 3). In model 1, we only included the inflammatory biomarkers, and NSE was not associated with poor prognosis (HR = 1.26, 95% CI = 0.49-3.26). In model 2, groups with elevated NLR, PLR, IL-6, and CRP levels had a greater risk of poorer outcomes after the exclusion of NSE variables and adjustments for sex and age (as a continuous variable). In model 3, we added thrombophilia and anticoagulation as covariates. NLR (HR = 4.14, 95%

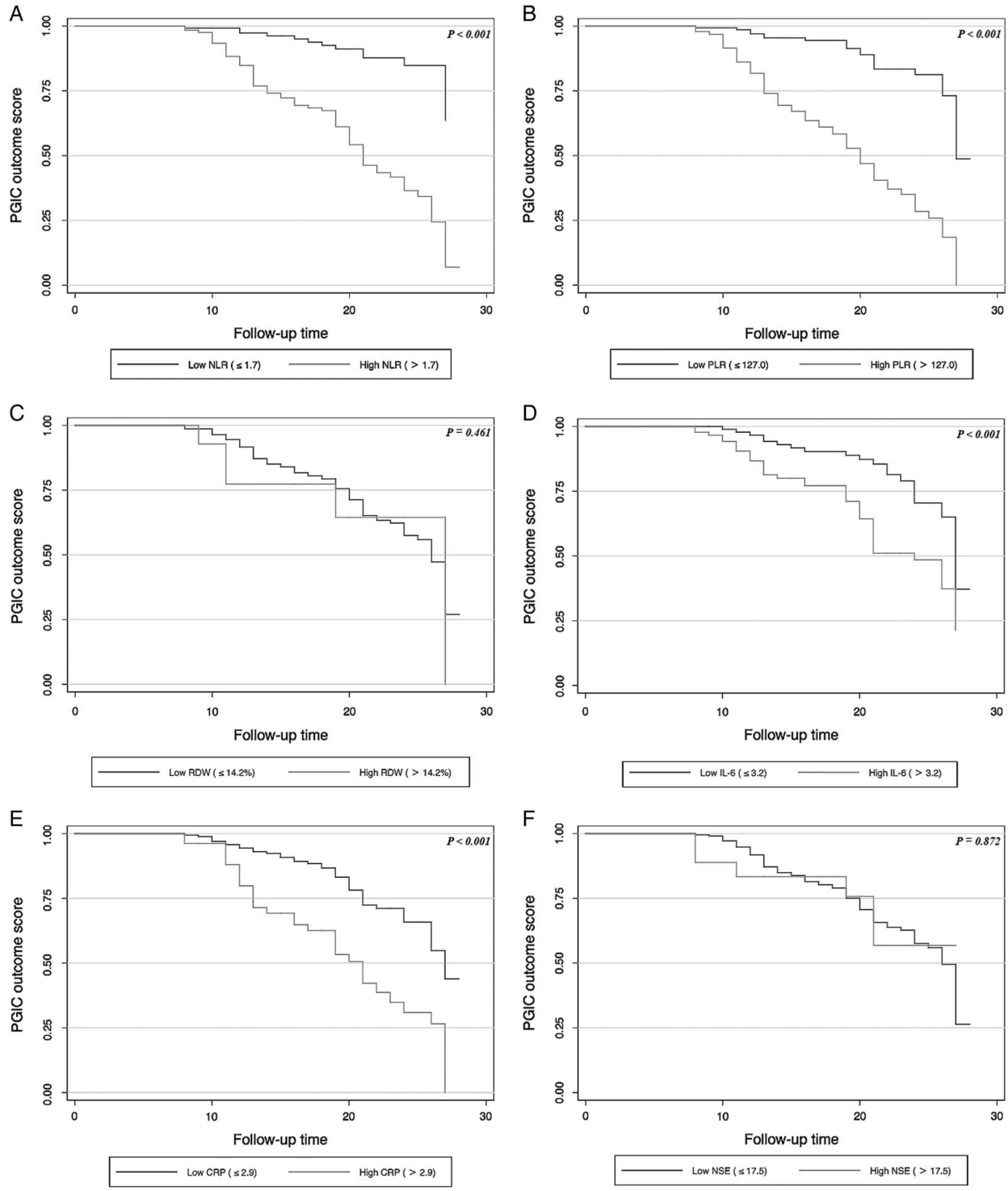

FIGURE 6. Kaplan-Meier estimation for the clinical outcomes in subgroups of inflammatory biomarkers. NLR subgroup (A), PLR subgroup (B), RDW subgroup (C), IL-6 subgroup (D), CRP subgroup (E), NSE subgroup (F). CRP indicates C-reactive protein; IL-6, interleukin-6; NLR, neutrophil-to-lymphocyte ratio; NSE, neuron-specific enolase; PGIC, Patient Global Impression of Change; PLR, platelet to lymphocyte ratio; RDW, red blood cell distribution width.

CI = 1.91-9.00), PLR (HR = 4.48, 95% CI = 2.38-8.44), and IL-6 (HR = 1.97, 95% CI = 1.09-3.56) became the independent prognostic factors for negative outcomes.

Nomogram for Predicting CCVI Clinical Outcome

Based on model 3 and clinical experiences, we constructed a nomogram with a weighted score for each variable

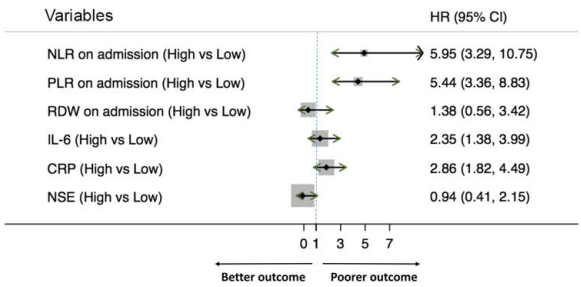

FIGURE 7. Forest plot of univariate Cox proportional hazards model of inflammatory biomarkers associated with clinical outcome. CI indicates confidence interval; CRP, C-reactive protein; HR, hazard ratio; IL-6, interleukin-6; NLR, neutrophil-to-lymphocyte ratio; NSE, neuron-specific enolase; PLR, platelet to lymphocyte ratio; RDW, red blood cell distribution width.

(Fig. 8). One- and 2-year outcomes were the final output expressed in scores. A higher score on the nomogram, calculated using a sum of points from each variable, was associated with unfavorable outcomes. However, this nomogram was shown to have a high overall predictive value using *C*-index tests (*C*-index = 0.838). We also constructed calibration plots using the bootstrap resampling method, and these plots showed an adequate fit for predicting clinical outcomes at 1- and 2-year time points (Supplementary Fig. 1, Supplemental Digital Content 4, http://links.lww.com/NRL/A90).

DISCUSSION

Our study, performed in a well-defined CCSVI population, showed that there were significant differences in symptoms, risk factors, and inflammatory states between IJVS, CVSS, and CVSS combined with IJVS groups (Table 1). The CVSS group tended to have headaches and severe papilledema due to a higher prevalence of IH. They also had symptom onset at younger ages and were frequently affected by risk factors like PC deficiency, primary thrombocythemia, being overweight, and hyperhomocysteinemia. Higher NLR, RDW, and CRP levels were also observed in the CVSS group. In addition, most patients with CCVSI, either from intracranial or extracranial causes, had good clinical outcomes during the follow-up phase (Fig. 5). NLR, PLR, and IL-6 were the independent prognostic factors mostly tied to outcomes (Table 3). We then constructed a reliable nomogram model for patients with CCSVI that could predict long-term prognosis (Fig. 8).

Our study was the first to evaluate the possible association between inflammation and CCSVI pathology. In the last decade, a number of studies were conducted to reveal the underlying mechanism of CCSVI (Fig. 9),[2,30,31] but the majority of them enrolled MS populations to explore the causative relationship between the CCSVI and MS, instead of considering CCSVI to be an independent disease entity. Moreover, few case-control studies observed that CCSVI was also highly prevalent in the non-MS population and was not unique to MS,[3,4,32] which led to a lively discussion on whether CCSVI was an anatomic variant of a complex vascular system or a pathologic process.[33–36]

Intriguingly, our enrolled patients, none of whom showed any previous or current MS symptoms, had elevated NLR, PLR, RDW, IL-6, and CRP levels, which may be attributed to the CCSVI itself rather than MS. Thus, we assumed CCSVI to be an independent disease entity that was also closely related to chronic inflammatory processes. CCSVI may first cause the mechanical effect of engorgement and reflux on the brain tissue,[10,37] which would increase cerebral venous pressure, decrease transmural pressure, and then lead to perivenous edema and disruption of brain-blood barrier integrity.[2] Cerebral venous pressure could also cause reduced decreased CBF, cerebral blood volume, and elevated mean transit time.[8,30,38,39] This suboptimal drainage could then result in iron deposition within the brain parenchyma with the potential of initiating local inflammatory responses.[6,40,41] CCSVI was found to be associated with autonomic neurological system (ANS) dysfunction.[31,42]

As reviewed by Sternberg, the sympathetic ANS has widespread α- and β-adrenergic receptors on endothelial cells and inflammatory cells. ANS dysfunction could not only weaken the modulation of the cardiovascular system to adapt to the demands of cerebral cortical activity, resulting in decreased CBF and chronic hypoxia, a trigger for venous remodeling,[43–45] but also could regulate the immune system to activate cellular inflammation, adhesion, and migration.[42] The role of the

TABLE 3. Multivariate Cox Regression Analysis Between Inflammatory Biomarkers and Clinical Outcomes

			Multivariate [Hazard Ratio (95% CI)]		
Variables	**Category**	**N**	**Model 1**	**Model 2**	**Model 3**
NLR on admission	≤ 1.7	122	1.00	1.00	1.00
	> 1.7	121	3.83 (1.68-8.70)*	3.58 (1.59-8.09)*	4.14 (1.91-9.00)*
PLR on admission	≤ 127.0	148	1.00	1.00	1.00
	> 127.0	95	3.18 (1.70-5.94)*	3.42 (1.83-6.39)*	4.48 (2.38-8.44)*
RDW on admission	≤ 14.2%	228	1.00	NA	NA
	> 14.2%	14	2.09 (0.72-6.06)	NA	NA
IL-6 on admission	≤ 3.2 pg/mL	95	1.00	1.00	1.00
	> 3.2 pg/mL	89	1.90 (1.04-3.45)*	1.94 (1.08-3.48)*	1.97 (1.09-3.56)*
CRP on admission	≤ 2.9 mg/L	169	1.00	1.00	NA
	> 2.9 mg/L	53	1.74 (1.00-3.04)*	1.61 (0.91-2.84)*	NA
NSE on admission	≤ 17.5 ng/mL	221	1.00	NA	NA
	> 17.5 ng/mL	18	1.26 (0.49-3.26)	NA	NA

Model 1 factors: NLR, PLR, RDW, IL-6, CRP, and NSE.
Model 2 factors: NLR, PLR, IL-6, CRP, age, and sex.
Model 3 factors: NLR, PLR, IL-6, age, sex, thrombophilia state, and anticoagulants use.
*Statistically significant at $P < 0.05$.
CRP indicates C-reactive protein; IL-6, interleukin-6; NA, not applicable; NLR, neutrophil-to-lymphocyte ratio; NSE, neuron-specific enolase; PLR, platelet to lymphocyte ratio; RDW, red blood cell distribution width.

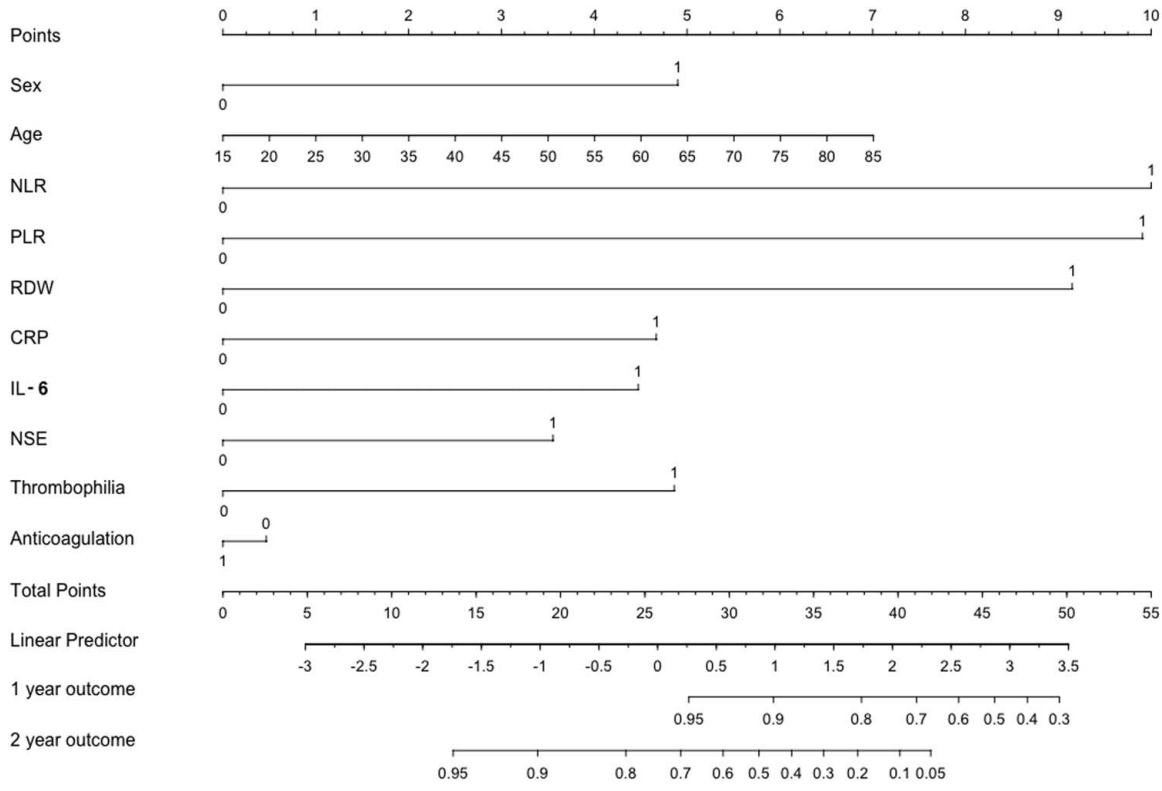

FIGURE 8. Nomogram for predicting chronic cerebrospinal venous insufficiency clinical outcome. CRP indicates C-reactive protein; IL-6, interleukin-6; NLR, neutrophil-to-lymphocyte ratio; NSE, neuron-specific enolase; PLR, platelet to lymphocyte ratio; RDW, red blood cell distribution width.

hypercoagulation state in inflammatory processes should also not be overlooked.[7] We found that a state of hypercoagulation (eg, PC deficiency, primary thrombocythemia, overweight) and increased inflammatory biomarkers (eg, NLR, PLR, CRP) were more likely in the CVSS group. Finally, we also assumed that

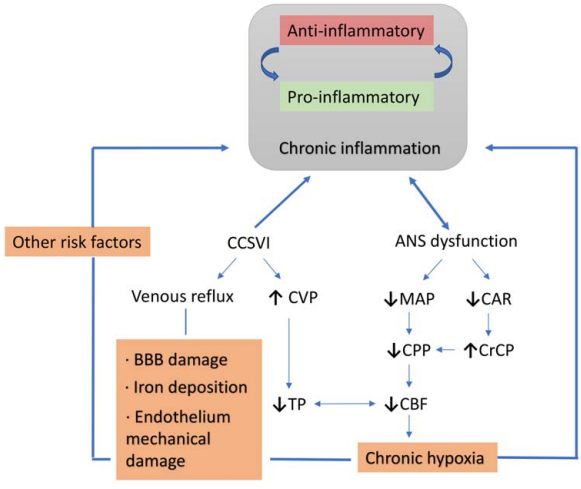

FIGURE 9. The mechanism of CCSVI-induced inflammation. ANS indicates autonomic neurological system; BBB, blood-brain barrier; CAR, cererbal autoregulation; CBF, cerebral blood flow; CCSVI, chronic cerebrospinal venous insufficiency; CPP, cerebral perfusion pressure; CrCP, critical closure pressure; CVP, cerebral venous pressure; MAP, mean arterial pressure; TP, transmural pressure.

CCSVI-induced inflammation was a well-balanced state of proinflammatory and anti-inflammatory factors. A correlation analysis between inflammatory cells and inflammatory cytokines indicated that NLR and PLR were positively associated with the IL-6 levels. Patients with higher NLR, PLR, IL-6, or CRP levels had poorer clinical outcomes. Thus, we postulate that patients would suffer from more severe symptoms and poorer prognoses when the CCSVI-induced inflammatory state tilted toward the proinflammatory side.

There were several limitations in our study. There were no established diagnostic criteria and imaging modalities, neither in the form of noninvasive nor invasive. The imaging examination is considered the "gold standard" for the detection of CCSVI.[46,47] The "Zamboni criteria" only focuses on evaluating the major venous drainage pathway, including the IJV, VV, CVS, and deep cerebral veins,[1] while overlooking presumed risk factors,[26] degrees of collateral circulation compensation and inflammatory biomarkers.[7] We suggested that future studies should combine clinical and imaging features to define CCSVI. In addition, we established a nomogram prognostic scoring model with a high predictive value. A higher score on the nomogram, calculated from a sum of points from each variable, was associated with unfavorable outcomes. However, this nomogram was only tested with internal validation by bootstrap resampling and a calibration plot. Further external validation is needed in the future.

CONCLUSIONS

CCSVI may be an independent disease entity in the Chinese population despite its nonspecific symptoms. Patients

with CVSS-related CCSVI were mostly likely to be younger, had more severe clinical features (including papilledema and IH), and had higher NLR, PLR, and CRP levels, than those with IJVS-related CCSVI. NLR and PLR levels were positively associated with IL-6 levels, indicating that the proinflammatory state could be related to the development of CCSVI. Elevated NLR, PLR, and IL-6 levels in peripheral blood may be independent prognostic factors for unfavorable outcomes in CCSVI.

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