Inflammatory Biomarkers May Predict Poor Outcome in Patients with Chronic Cerebrospinal Venous Insufficiency.

Siying Song
Xuanwu Hospital
Duo Lan
Xuanwu Hospital
Xiao qin Wu
Xuanwu Hospital
Yu chuan Ding
Wayne State University
Xun ming Ji
Xuanwu Hospital
Ran Meng (victor65@126.com)
xuanwu hospital, capital medical university https://orcid.org/0000-0003-4505-4742

Research

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Abstract

Background and purpose Chronic cerebrospinal venous insufficiency (CCSVI) related inflammatory process is still unclear. This study aimed to evaluate peripheral inflammatory biomarkers in both intracranial CCSVI and the extracranial CCSVI group, as well as the relationship between the inflammatory state and prognosis of CCSVI.

Methods Patients with CCSVI were included from July 2017 to July 2019, divided into three groups by location of stenosis. The inflammatory biomarker assay included neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), red blood cell distribution width (RDW), C-reactive protein (CRP), interleukin- 6 (IL-6)) and neuron-specific enolase (NSE). The clinical outcome was assessed by the modified Rankin Scale (mRS) and Patient Global Impression of Change (PGIC) score. Univariate and multivariate regression analysis was performed to identify significant prognostic factors for poor outcome. Then a nomogram based on multivariate regression analysis was established.

Results *In total*, 248 consecutive patients were enrolled, 102 males and 146 females, with an average age of 57.85 ± 12.28 years. Patients with cerebral venous sinus stenosis (CVSS) were more likely to be younger age and present headaches and severe papilledema. Higher levels of NLR, RDW, and CRP were also observed in the CVSS group. In multivariate analysis, NLR, PLR, and IL-6 became the independent prognostic factors for predicting the poor outcome of CCSVI.

Conclusions The clinical presentations and the increased levels of NLR, PLR, and CRP may be more remarkable in the group with CVSS-related CCSVI than that with internal jugular venous stenosis (IJVS)-related CCSVI. The pro-inflammatory state may relate to CCSVI. An elevated level of NLR, PLR, and IL-6 played a negative role in the prognosis of CCSVI.

Introduction

Chronic cerebrospinal venous insufficiency (CCSVI) was first introduced as a chronic state of impaired cerebral or cervical venous drainage by Zamboni and colleagues in 2009.[1] Then, CCSVI was discussed on its probably close relationship with multiple sclerosis (MS), leukoaraiosis and vascular dementia in the last decade.[2] Although there is still a controversy over the relationship between CCSVI and neurological disorders, intriguingly, CCSVI was as well found in so-called “healthy people” and caused nonspecific symptoms, such as headache, tinnitus and head noises.[3–5] CCSVI may induce venous reflux and cerebral venous hypertension, resulting in brain-blood barrier (BBB) integrity disruption and peri-venous iron accumulation,[6, 7] decreased cerebral brain flow (CBF),[8, 9] which further led to chronic cerebral hypoxia, inflammatory cells infiltration into brain parenchyma and even local inflammatory process.[10, 11]

Our previous work demonstrated 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 (AIS). Furthermore, inflammation biomarkers, for instance, NLR, hypersensitive C-reactive protein (Hs-CRP),

interleukin- 6 (IL-6) was correlated with the severity and outcome of cerebral venous thrombosis (CVT).[14] We also discovered the coexistence of arterial stenosis and venous stenosis for the very first time.[15] Based on our findings,[16–19] we further aroused questions over whether CCSVI would relate to elevated peripheral inflammatory biomarkers [e.g., NLR, RDW, IL-6, CRP and neuron-specific enolase (NSE)]; whether extracranial (internal jugular vein stenosis, IJVS) and intracranial (cerebral venous sinus stenosis, CVSS) CCSVI would have difference concerning inflammatory state; and whether there is any correlation between inflammatory cells (e.g., neutrophils and lymphocytes) and inflammatory cytokines (e.g., IL-6, CRP, and NSE). We also aimed to explore the relationship between the inflammatory state and prognosis of CCSVI and build a prognostic model of CCSVI.

Methods

Population

We analyzed data from a single-center database on 248 consecutive patients with CCSVI having been admitted to the department of neurology, Xuanwu Hospital, Capital Medical University, from 2017 to 2019. This study was approved by the Ethics Committee of Xuanwu Hospital, Capital Medical University. All participants signed the consent form prior to entering this study.

Patients were enrolled according to the following criteria: (1) Patients with CCSVI, including IJVS, CVSS, or CVSS combined with IJVS, were confirmed by contrast-enhanced magnetic resonance venography (CE-MRV) or digital subtraction angiography (DSA); (2) No age and gender limitation. (3) No previous or current evidence of MS; (4) No remarkable parenchymal CCSVI-induced brain lesions; (5) Course of disease was at sub-acute or chronic stage, defined as the interval (from symptoms and signs onset to enrollment) of more than one month.

We excluded the patients with (1) definite acute or chronic infection; (2) use of anti-inflammatory medication within four weeks prior to blood collection; (3) during the menstrual period for female patients; (4) 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; (g) acute arterial stroke.

Clinical and Demographic Data

We recorded age, gender, course of CCSVI (from symptoms onset to admission), treatments, presumable risk factors known before hospitalization, or discovered during hospitalization. The risk factors included hypertension (use of antihypertensive medications or systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mm Hg before hospitalization), diabetes mellitus (use of anti-diabetic 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 12.5 g/dl=, HBV infection (anti-HBV agents usage or positive HBcAb/Ag or HBeAb/Ag), hyperhomocysteinemia (>

15 mmol/L), hyperuricemia (> 416 micromol/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, such as headache, tinnitus, head noises, papilledema, and IH. The severity of papilledema was evaluated by the Frisen papilledema grade criteria. Intracranial pressure (ICP) was detected by lumbar puncture, and IH was defined as ICP > 200 mmH_2O.

Inflammatory biomarkers assay

We defined the inflammatory biomarkers assay as NLR, platelet-to-lymphocyte ratio (PLR), IL-6, C-reactive protein (CRP), and neuron-specific enolase (NSE). Baseline values were measured on admission. NLR was computed using the absolute neutrophil count divided by the absolute lymphocyte count. PLR was calculated using the absolute platelet count divided by the absolute lymphocyte count. Baseline inflammatory markers were considered as continuous variables and in categories. The receiver operating characteristic (ROC) curve was constructed to assess the predictive value of inflammatory markers and define cutoff values. Optimal cutoffs were then used to find thresholds and transform the inflammatory markers into categorical variables.

Clinical outcome evaluation

Modified Rankin Scale (mRS) score was used to evaluate the functional outcome of the patients at discharge, and the Patient Global Impression of Change (PGIC) score was assessed to predict outcomes in outpatient telephone follow-up. PGIC is a semi-quantitated self-evaluation scale of the patients to their overall change of the symptoms using a 7-point scale (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 two groups: good outcome (PGIC $\leq$ 3) and poor outcome (PGIC > 3).

Statistical analysis

Bartlett's test for equal variances and the Shapiro-Wilk normality test for distribution were conducted for each continuous variable. We then used the Kruskal-Wallis test or Fisher exact test to compare continuous variables or categorical variables between patients with IJVS, CVSS, and CVSS combined with IJVS. Differences between baseline inflammatory markers values (NLR, PLR, and RDW) and that at discharge were tested by Wilcoxon signed-rank test.

Correlation coefficients between inflammatory biomarkers were calculated with Spearman’s test. Kaplan-Meier was used to plot the distribution of time to poor outcomes among CCSVI subtypes (IJVS, CVSS, and CVSS combined with IJVS) and inflammatory biomarkers. Meanwhile, the log-rank test was used to compare the curves. We performed univariate and multivariate Cox proportional hazards model to examine the relationship between inflammatory markers and clinical outcomes. The groups with a lower

level of inflammatory biomarkers were used as references. In the univariate model, we included the most common symptoms (headache, sleep disturbances, head noise, tinnitus), risk factors (thrombophilia and overweight), and inflammatory markers. In multivariate analysis, we performed the following three models based on the results from the univariate model and our previous studies[20, 21] as well as clinical experience: Model 1 estimated the crude association with inflammatory markers; Model 2 then additionally adjusted for age and gender; Model 3 added several other potential confounders, including thrombophilia and anticoagulation. Furthermore, we generate a scoring system reflecting the individual prognosis according to Model 3. The performance of the model was assessed by discrimination (the C index) and calibration (internal validation by bootstrap resampling and calibration plot).[22, 23]

Values were presented as mean ± SD or percentage. Hazard ratio (HR) with 95% confidence intervals (CIs) was provided where appropriate. Differences were considered significant at a 2-sided p 0.05 level. Analyses were performed with Stata software (version 15.0 SE, Stata Corp, LP, Texas, USA) and R software [version 3.6.2 (2019-12-12)].

Results

1. Baseline clinical features

From July 2017 through July 2019, a total of 248 patients (102 males and 146 females) with CCSVI were enrolled in this real-world cohort study. The majority of patients (95.6%) were at a chronic stage and followed up with 18.00 ± 5.57 months. The top five common symptoms of CCSVI were sleep disturbances (61.5%), eye discomfort (58.9%), head noise (54.8%), tinnitus (52.0%), and headache (46.0%). Presumable risk factors, identified in 80%, were frequently multiple. Comorbidities of thrombophilia state, overweight, hyperlipidemia, hypertension, anemia followed by suspected thyroid disorders were common in CCSVI. Prevalence of protein S (PS) deficiency ranked the first among other prothrombotic abnormalities. Treatments for patients with CCSVI were antiplatelet drugs (59.9%), anticoagulants (32.4%), and endovascular therapy (12.1%). Most patients obtained good outcomes at discharge (mRS ≤ 2). Table 1 summarized the baseline data.

Table 1
Demographic and basic clinical features

Variables	All (n = 248)	IJVS (n = 171)	CVSS (n = 43)	CVSS combined with IJVS (n = 34)	P value
Personal data					
Age, mean ± SD, years	53.44 ± 14.94	57.85 ± 12.28	43.02 ± 16.20*	44.44 ± 15.30*	**0.001**
Gender (M: F)	102: 146	75: 96	11: 32	16: 18	0.067
Course of disease					**0.005**
Subacute (within 1 month)	11 (4.4%)	3 (2.1%)	4 (9.3%)	4 (8.8%)	
Chronic (more than 1 month)	237 (95.6%)	168 (98.2%)	39 (90.6%)	30 (88.2%)	
Follow-up time, months^	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	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**

#Compared with group of NLR tested on admission, statistically significant at $p < 0.05$.

*Compare with group of IJVS, statistically significant at $p < 0.05$.

^ Time from discharge to follow up, months.

&The number of patients who had complete blood count (CBC) Test at discharge (n = 36).

NLR = neutrophil to lymphocyte ratio; PLR = platelet to lymphocyte ratio; RDW = red blood cell distribution width; CRP = C-reactive protein; NSE = Neuron-specific enolase; IL-6 = interleukin-6; Protein C = PC; Protein S = PS; Antithrombin III = AT- III; Diabetes mellitus = DM; IS = ischemic stroke; ICH = intracranial hemorrhage; SS = Sjögren's syndrome; APS = antiphospholipid syndrome; CAD = coronary artery disease; HBV = hepatic type B virus; mRS = modified Rankin scale; IH = intracranial hypertension; ONSD = Optic nerve sheath decompression;

Variables	All (n = 248)	IJVS (n = 171)	CVSS (n = 43)	CVSS combined with IJVS (n = 34)	P value
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**

[#]Compared with group of NLR tested on admission, statistically significant at $p < 0.05$.

[*]Compare with group of IJVS, statistically significant at $p < 0.05$.

[^] Time from discharge to follow up, months.

[&]The number of patients who had complete blood count (CBC) Test at discharge (n = 36).

NLR = neutrophil to lymphocyte ratio; PLR = platelet to lymphocyte ratio; RDW = red blood cell distribution width; CRP = C-reactive protein; NSE = Neuron-specific enolase; IL-6 = interleukin-6; Protein C = PC; Protein S = PS; Antithrombin III = AT- III; Diabetes mellitus = DM; IS = ischemic stroke; ICH = intracranial hemorrhage; SS = Sjögren's syndrome; APS = antiphospholipid syndrome; CAD = coronary artery disease; HBV = hepatic type B virus; mRS = modified Rankin scale; IH = intracranial hypertension; ONSD = Optic nerve sheath decompression;

Variables	All (n = 248)	IJVS (n = 171)	CVSS (n = 43)	CVSS combined with IJVS (n = 34)	P value
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

[#]Compared with group of NLR tested on admission, statistically significant at $p < 0.05$.

[*]Compare with group of IJVS, statistically significant at $p < 0.05$.

[^] Time from discharge to follow up, months.

[&]The number of patients who had complete blood count (CBC) Test at discharge (n = 36).

NLR = neutrophil to lymphocyte ratio; PLR = platelet to lymphocyte ratio; RDW = red blood cell distribution width; CRP = C-reactive protein; NSE = Neuron-specific enolase; IL-6 = interleukin-6; Protein C = PC; Protein S = PS; Antithrombin III = AT- III; Diabetes mellitus = DM; IS = ischemic stroke; ICH = intracranial hemorrhage; SS = Sjögren's syndrome; APS = antiphospholipid syndrome; CAD = coronary artery disease; HBV = hepatic type B virus; mRS = modified Rankin scale; IH = intracranial hypertension; ONSD = Optic nerve sheath decompression;

Variables	All (n = 248)	IJVS (n = 171)	CVSS (n = 43)	CVSS combined with IJVS (n = 34)	P value
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					
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

[#]Compared with group of NLR tested on admission, statistically significant at $p < 0.05$.

*Compare with group of IJVS, statistically significant at $p < 0.05$.

^ Time from discharge to follow up, months.

[&]The number of patients who had complete blood count (CBC) Test at discharge (n = 36).

NLR = neutrophil to lymphocyte ratio; PLR = platelet to lymphocyte ratio; RDW = red blood cell distribution width; CRP = C-reactive protein; NSE = Neuron-specific enolase; IL-6 = interleukin-6; Protein C = PC; Protein S = PS; Antithrombin III = AT- III; Diabetes mellitus = DM; IS = ischemic stroke; ICH = intracranial hemorrhage; SS = Sjögren's syndrome; APS = antiphospholipid syndrome; CAD = coronary artery disease; HBV = hepatic type B virus; mRS = modified Rankin scale; IH = intracranial hypertension; ONSD = Optic nerve sheath decompression;

Variables	All (n = 248)	IJVS (n = 171)	CVSS (n = 43)	CVSS combined with IJVS (n = 34)	P value
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
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**

[#]Compared with group of NLR tested on admission, statistically significant at $p < 0.05$.

[*]Compare with group of IJVS, statistically significant at $p < 0.05$.

[^] Time from discharge to follow up, months.

[&]The number of patients who had complete blood count (CBC) Test at discharge (n = 36).

NLR = neutrophil to lymphocyte ratio; PLR = platelet to lymphocyte ratio; RDW = red blood cell distribution width; CRP = C-reactive protein; NSE = Neuron-specific enolase; IL-6 = interleukin-6; Protein C = PC; Protein S = PS; Antithrombin III = AT- III; Diabetes mellitus = DM; IS = ischemic stroke; ICH = intracranial hemorrhage; SS = Sjögren's syndrome; APS = antiphospholipid syndrome; CAD = coronary artery disease; HBV = hepatic type B virus; mRS = modified Rankin scale; IH = intracranial hypertension; ONSD = Optic nerve sheath decompression;

Variables	All (n = 248)	IJVS (n = 171)	CVSS (n = 43)	CVSS combined with IJVS (n = 34)	P value
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 $p < 0.05$.

[*]Compare with group of IJVS, statistically significant at $p < 0.05$.

[^] Time from discharge to follow up, months.

[&]The number of patients who had complete blood count (CBC) Test at discharge (n = 36).

NLR = neutrophil to lymphocyte ratio; PLR = platelet to lymphocyte ratio; RDW = red blood cell distribution width; CRP = C-reactive protein; NSE = Neuron-specific enolase; IL-6 = interleukin-6; Protein C = PC; Protein S = PS; Antithrombin III = AT- III; Diabetes mellitus = DM; IS = ischemic stroke; ICH = intracranial hemorrhage; SS = Sjögren's syndrome; APS = antiphospholipid syndrome; CAD = coronary artery disease; HBV = hepatic type B virus; mRS = modified Rankin scale; IH = intracranial hypertension; ONSD = Optic nerve sheath decompression;

We then divided patients with CCSVI into three subgroups based on imaging finding: IJVS (n = 171), CVSS (n = 43), CVSS combined with IJVS (n = 34). Patients in the IJVS group were slightly older (mean age 57.85 ± 12.28 years) and complained more frequently of tinnitus, head noises, or sleep disturbances than that in the other two groups. Headache and severe papilledema were more common in CVSS than isolated IJVS, either isolated CVSS or CVSS combined with IJVS, which may result from higher ICP in these two groups. Optic nerve sheath decompression (ONSD) surgery was more likely to perform in patients with CVSS-related severe papilledema. CVSS was more related to protein C (PC) deficiency, primary thrombocythemia, overweight, and hyperhomocysteinemia. Figure 1 demonstrated the difference between subgroups in terms of symptoms and risk factors. The stenosis mainly involved transverse sinus (TS) and sigmoid sinus (SigS) as well as TS-SigS junction in almost all CVSS, and the common localization of IJVS was mainly involved in J3 segment **(Supplementary Table. 1).** Anticoagulants and endovascular therapies were more common in patients with cerebral venous sinus (CVS) involvement.

2. Inflammatory biomarkers in CCSVI

(1). Subgroups analysis of inflammatory biomarkers in CCSVI

Baseline NLR was significantly higher in groups with CVSS than that only with IJVS. The CVSS group also had increased baseline RDW and CRP. Besides, no significant difference in other inflammatory markers between CVSS and IJVS was found. To further evaluate dynamic changes of NLR/PLR/RDW during hospitalization, few patients underwent a complete blood count (CBC) test at discharge (n = 36). The mean hospital stay was 12.38 ± 5.27 days. The level of NLR at discharge was mildly higher than baseline, while the level of PLR and RDW at discharge did not show a significant difference compared with their baseline value.

(2). Correlations between inflammatory cells and inflammatory cytokines

A heat-map was constructed containing variables of inflammatory markers, age, and subgroups of CCSVI **(**Fig. 2**).** We presumed that patients with CVSS were more likely to be at a younger age and have a relatively higher level of inflammatory markers. Furthermore, correlation coefficients were calculated with Spearman's test among age, NLR, PLR, RDW, IL-6, CRP, and NSE (Fig. 3). As shown in **Supplementary Table 2**, baseline NLR was moderately correlated to PLR and IL-6. Moreover, IL-6 had a positive association with CRP. However, inflammatory biomarkers did not show any correlation with age.

(3). 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, PLR, IL-6, and CRP were found to have higher prognostic values in CCSVI while baseline RDW and NSE were proved non-significant in predicting outcomes in CCSVI. The optimal cutoff values of each variable were then defined based on the ROC curves (Table 2).

Table 2
ROC analysis of inflammatory markers for predicting poor outcomes

Variables	AUC	P value	Cut-off 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

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

3. Inflammatory biomarkers and clinical outcomes in CCSVI

(1) KM analysis in CCSVI

Clinical outcomes did not show any difference between subgroups of CCSVI (Fig. 5). However, in terms of different inflammatory biomarkers, the incidence of poor outcomes was significantly increased with higher baseline NLR, PLR, IL-6, and CRP values, while higher RDW and NSE levels were not associated with poor outcomes (Fig. 6).

(2) Univariate and multivariate cox regression analysis

We included age, gender, common symptoms (sleep disturbances, eye discomfort, head noise, tinnitus, and headache), common risk factors (thrombophilia state, overweight, DM, HP, hyperlipidemia, HBV infection, and suspected thyroid disorders), inflammatory biomarkers assay in the primary univariate analysis. However, only NLR, PLR, RDW, IL-6, and CRP were observed significant negative prognostic values in CCSVI (Fig. 7). Furthermore, we performed the multivariate analysis in three models (Table 3): In model 1, we only included the inflammatory biomarkers, and NSE was found not to be associated with poor prognosis (HR = 1.26, 95% CIs = 0.49–3.26); Then in model 2, groups with elevated NLR, PLR, IL-6, and CRP level had a greater risk of poor outcomes after the exclusion of NSE variable and adjustment of gender and age (as a continuous variable); In model 3, we added thrombophilia state and anticoagulation use as covariates. NLR, PLR, and IL-6 became the independent prognostic factors for negative outcomes.

Table 3
Multivariate cox regression analysis between inflammatory biomarkers and clinical outcomes

			Multivariate [#]		
Variable	**Category**	**Number**	**Model1**	**Model2**	**Model3**
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

NLR = neutrophil to lymphocyte ratio; PLR = platelet to lymphocyte ratio; RDW = red blood cell distribution width; CRP = C-reactive protein; NSE = Neuron-specific enolase; IL-6 = interleukin-6; NA = not applicable

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.

[#] Results were presented as Harzard ratio (95% CI).

* Statistically significant at $p < 0.05$.

(3). Nomogram for predicting CCVI clinical outcome

Based on model 3 and clinical experience, we constructed a nomogram with a weighted score for each variable (Fig. 8). One-year and two-year outcomes were the final output expressed in scores. A higher score of the nomogram, calculated from a sum of points from each variable, would be associated with unfavorable outcomes. This nomogram was proved a high overall predictive value by C-index test (C-index = 0.838). Furthermore, by using the bootstrap resampling method, calibration plots were constructed and indicated an adequate fit of the nomogram model in predicting clinical outcome in one-year and two-year (**Supplementary Fig. 1**).

Discussion

Our study, performed in a well-defined CCSVI population, showed that there was a significant difference among IJVS, CVSS, and CVSS combined with IJVS groups in terms of symptoms, risk factors, and inflammatory state (Table 1). CVSS group tended to have headaches and severe papilledema due to a higher prevalence of IH, presented at a younger age, and frequently combined with risk factors, such as PC deficiency, primary thrombocythemia, overweight, and hyperhomocysteinemia. Higher levels of NLR, RDW, and CRP were also observed in the CVSS group. Moreover, most patients with CCVSI, either intracranial cause or extracranial cause, acquired good clinical outcome during our follow-up (Fig. 5). NLR, PLR, and IL-6 were found to be the independent prognostic factors for outcomes (Table 3). We further constructed a reliable nomogram model for patients with CCSVI to predict long-term prognosis (Fig. 8).

Our study is the first evaluating the possible association between inflammation and CCSVI. In the last decade, a number of studies were carried out to explain the underlying mechanism of CCSVI (Fig. 9**)**,[2, 24, 25] however, the majority of previous studies are exclusively enrolled MS population to explore the causative relationship between CCSVI and MS, instead of regarding CCSVI as an independent disease entity. Besides, few case-control studies observed CCSVI was also highly prevalent in the non-MS population, and not unique to MS,[3, 4, 26] then leading to a lively discussion on whether CCSVI was anatomical variants of a complex vascular system or pathological process.[27–30]

Intriguingly, our enrolled patients, without any previous or current evidence of MS, had elevated NLR, PLR, RDW, IL-6, and CRP, which may be attributed to CCSVI itself rather than MS. Thus, we assumed CCSVI as an independent disease entity, which closely related to the chronic inflammatory process. Firstly, CCSVI may cause the mechanical effect of engorgement and reflux on the brain tissue,[10, 31] which would increase cerebral venous pressure (CVP), decrease transmural pressure (TP), and then lead to perivenous edema and disruption of BBB integrity.[2] CVP could also cause decreased cerebral blood flow (CBF), cerebral blood volume (CBV) and elevated mean transit time (MTT).[8, 24, 32, 33] Secondly, the suboptimal drainage could result in iron deposition within the brain parenchyma with the potential of initiating local

inflammatory responses.[6, 34, 35] Furthermore, CCSVI was also associated with the autonomic neurological system (ANS) dysfunction.[25, 36]

As reviewed by Sternberg, 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 demands of cerebral cortical activity resulting in decreased CBF and chronic hypoxia, trigger for venous remodeling,[37–39] but also regulate the immune system to activate cellular inflammation, adhesion and migration.[36] Besides, the role of the hyper-coagulation state in inflammatory process should not be overlooked.[7] We found hyper-coagulation state (e.g., PC deficiency, primary thrombocythemia, overweight) and increased inflammatory biomarkers (e.g., NLR, PLR, CRP) were more likely in CVSS group. Last but not least, we thought CCSVI-induced inflammation was a well-balanced state of pro-inflammatory and anti-inflammatory factors. Our correlation analysis between inflammatory cells and inflammatory cytokines indicated that NLR and PLR were positively associated with IL-6. Patients with higher NLR, PLR, IL-6, or CRP had poorer clinical outcomes. Thus, we postulated that when CCSVI-induced inflammatory state tilted toward the pro-inflammatory side, patients would suffer more severe symptoms and poor prognosis.

There are several limitations in our study. There is no established diagnostic criteria and imaging modality, either non-invasive or invasive, that can serve as the “gold standard” for the detection of CCSVI.[40, 41] The 'Zamboni criteria' only focused on evaluating the major venous drainage pathway, such as IJV, vertebral vein (VV), CVS, and deep cerebral vein,[1] while overlooked the presumable risk factors,[20] degrees of collateral circulation compensation and inflammatory biomarkers.[7] We suggested that future studies could combine clinical and imaging features to define CCSVI. Additionally, we established a nomogram prognostic scoring model with high predictive value. A higher score of the nomogram, calculated from a sum of points from each variable, would be associated with unfavorable outcomes. However, this nomogram was only tested by internal validation by bootstrap resampling and calibration plot. Further external validation was needed in the future.

Conclusion

CCSVI may be an independent disease entity in the Chinese population despite its non-specific symptoms. Patients with CVSS-related CCSVI, more likely presented in a younger population, had more severe clinical features, such as papilledema and IH, and a higher level of NLR, PLR, and CRP, than that with IJVS-related CCSVI. NLR and PLR were positively associated with IL-6, indicating the pro-inflammatory state may relate to the development of CCSVI. An elevated level of NLR, PLR, and IL-6 in peripheral blood may be independent prognostic factors for predicting the unfavorable outcome of CCSVI.

Abbreviations

CCSVI
Chronic cerebrospinal venous insufficiency
NLR
neutrophil-to-lymphocyte ratio
PLR
platelet-to-lymphocyte ratio
RDW
red blood cell distribution width
CRP
C-reactive protein
IL-6
interleukin-6
NSE
neuron-specific enolase
mRS
modified Rankin Scale
PGIC
Patient Global Impression of Change
CVSS
Cerebral venous sinus stenosis
MS
Multiple sclerosis
BBB
brain-blood barrier
CBF
cerebral brain flow
CBV
cerebral blood volume
MTT
mean transit time
Hs-CRP
hypersensitive C-reactive protein
ANS
autonomic neurological system
CVT
cerebral venous thrombosis
CE-MRV
contrast-enhanced magnetic resonance venography
DSA
digital subtraction angiography

IJVS
internal jugular venous stenosis
TS
transverse sinus
SigS
sigmoid sinus
CBC
complete blood count
ONSD
Optic nerve sheath decompression

Declarations

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Authors' contributions

MR: manuscript drafting and revision, and study concept and design. S-SY: manuscript drafting and revision, study concept and design, collection, assembly, and interpretation of the data. MR, S-SY, DL, WXQ: manuscript writing, and final approval of the manuscript. MR, JXM, DYC: Manuscript drafting and revision.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Xuanwu Hospital.

Availability of supporting data

Not applicable

Consent for Publication

The authors agree to publish.

Acknowledgements

Not applicable

Competing interests

All authors report no conflicts of interest.

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Figures

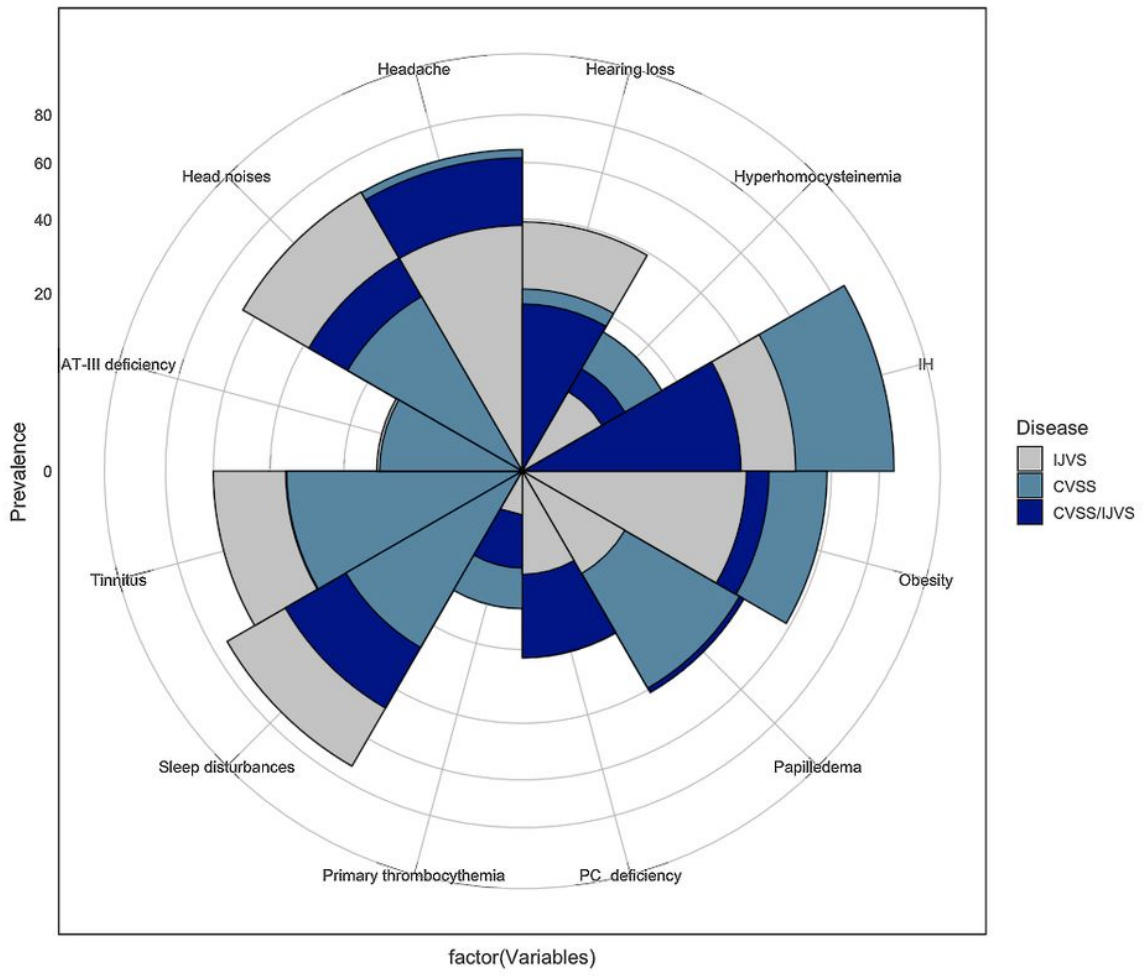

Figure 1

Significant differences in symptoms and risk factors among subgroups of CCSVI.

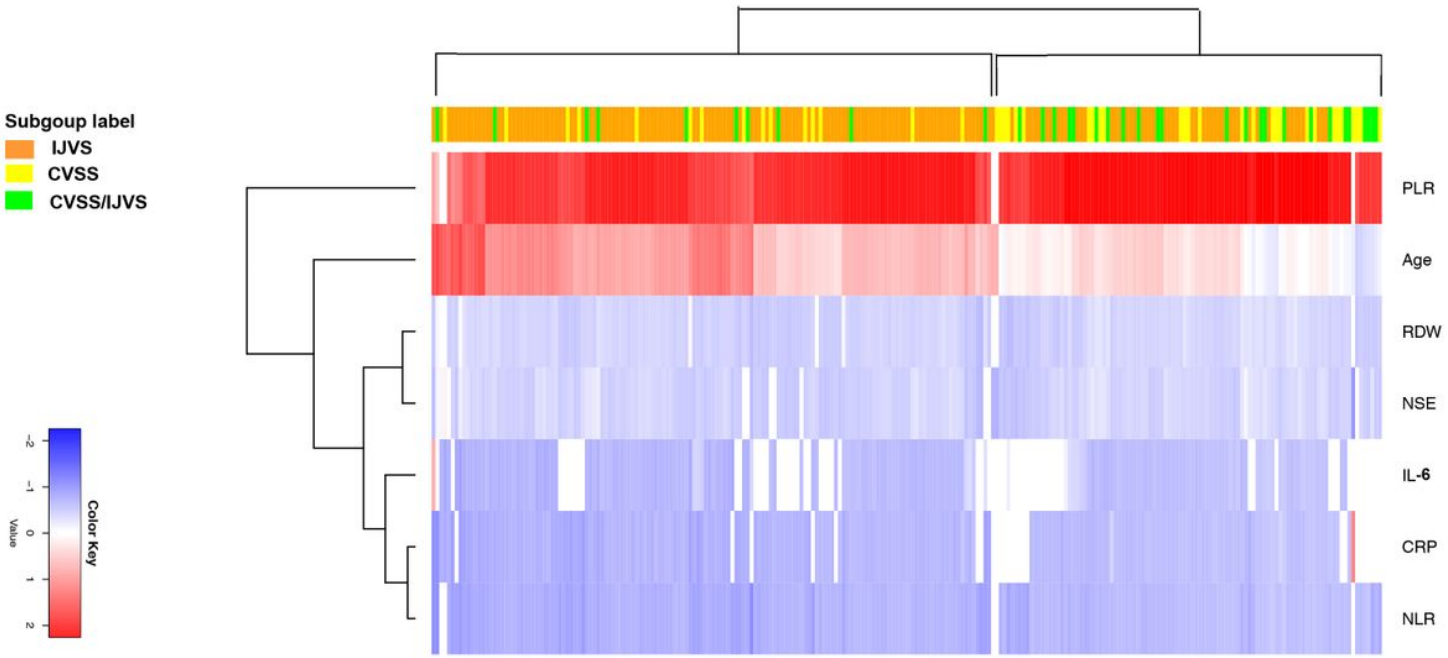

Figure 2

Heatmap analysis of age, inflammatory biomarkers, and subgroups of CCSVI.

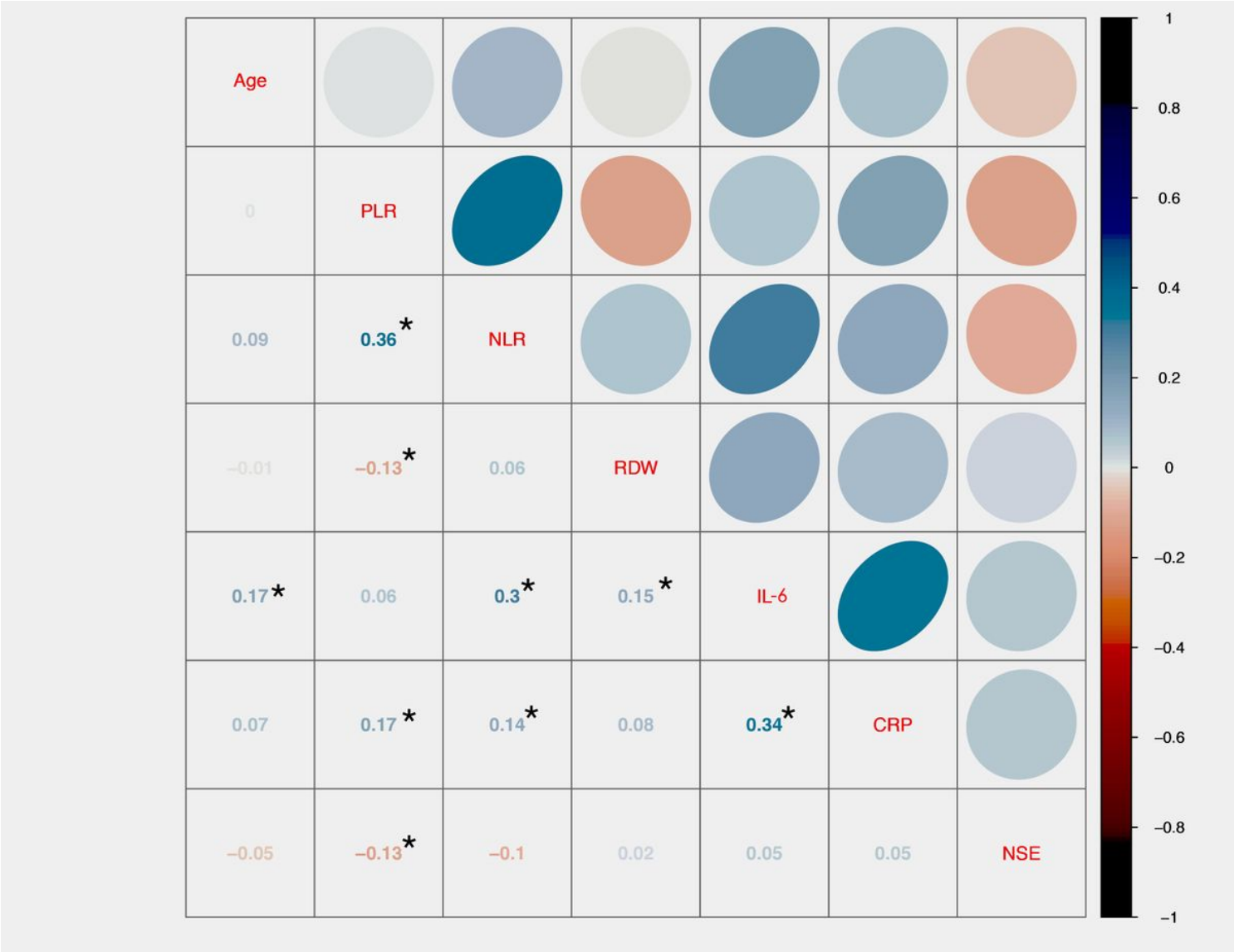

Figure 3

Spearman's correlations between age and inflammatory biomarkers.

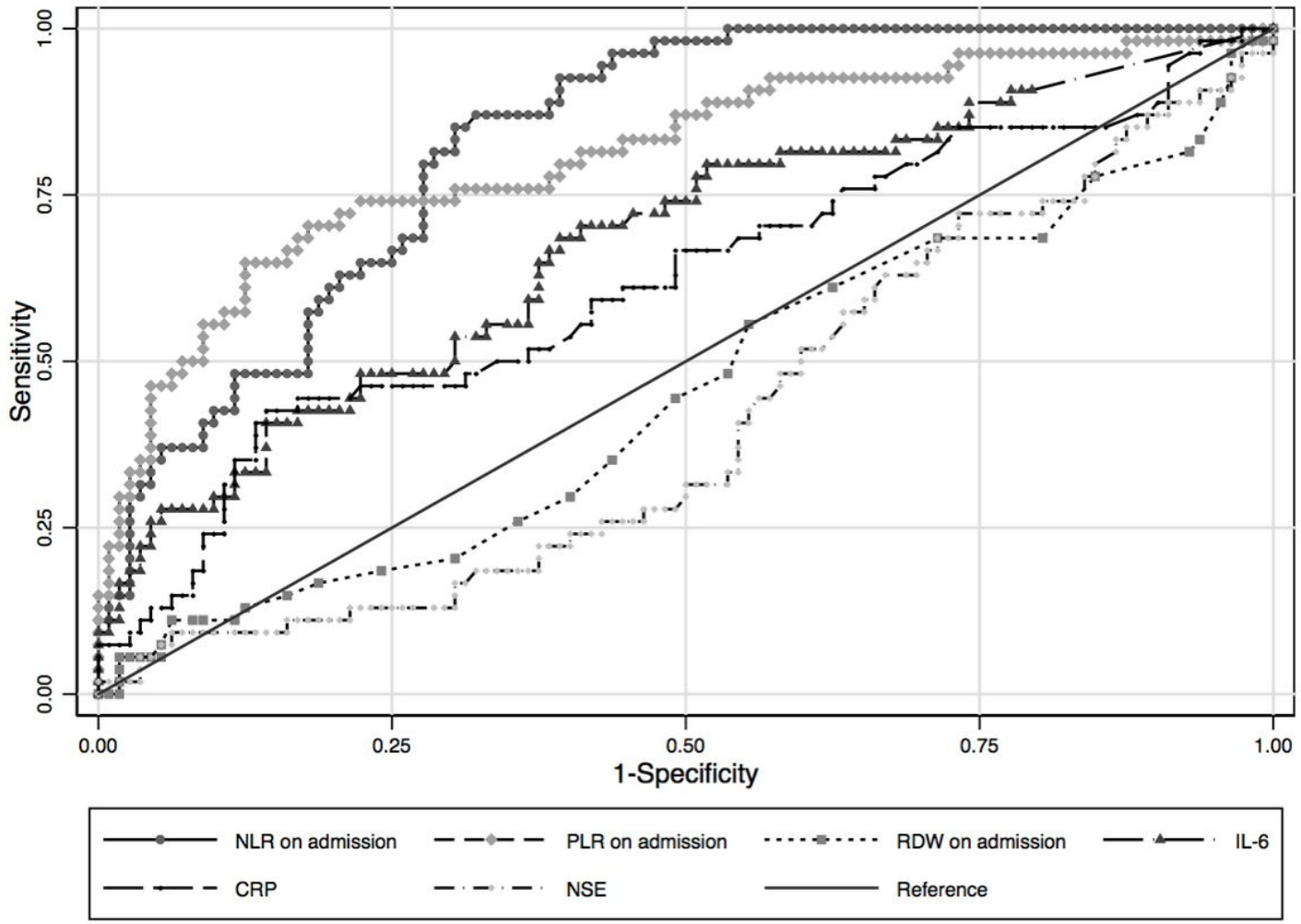

Figure 4

ROC curves for inflammatory biomarkers.

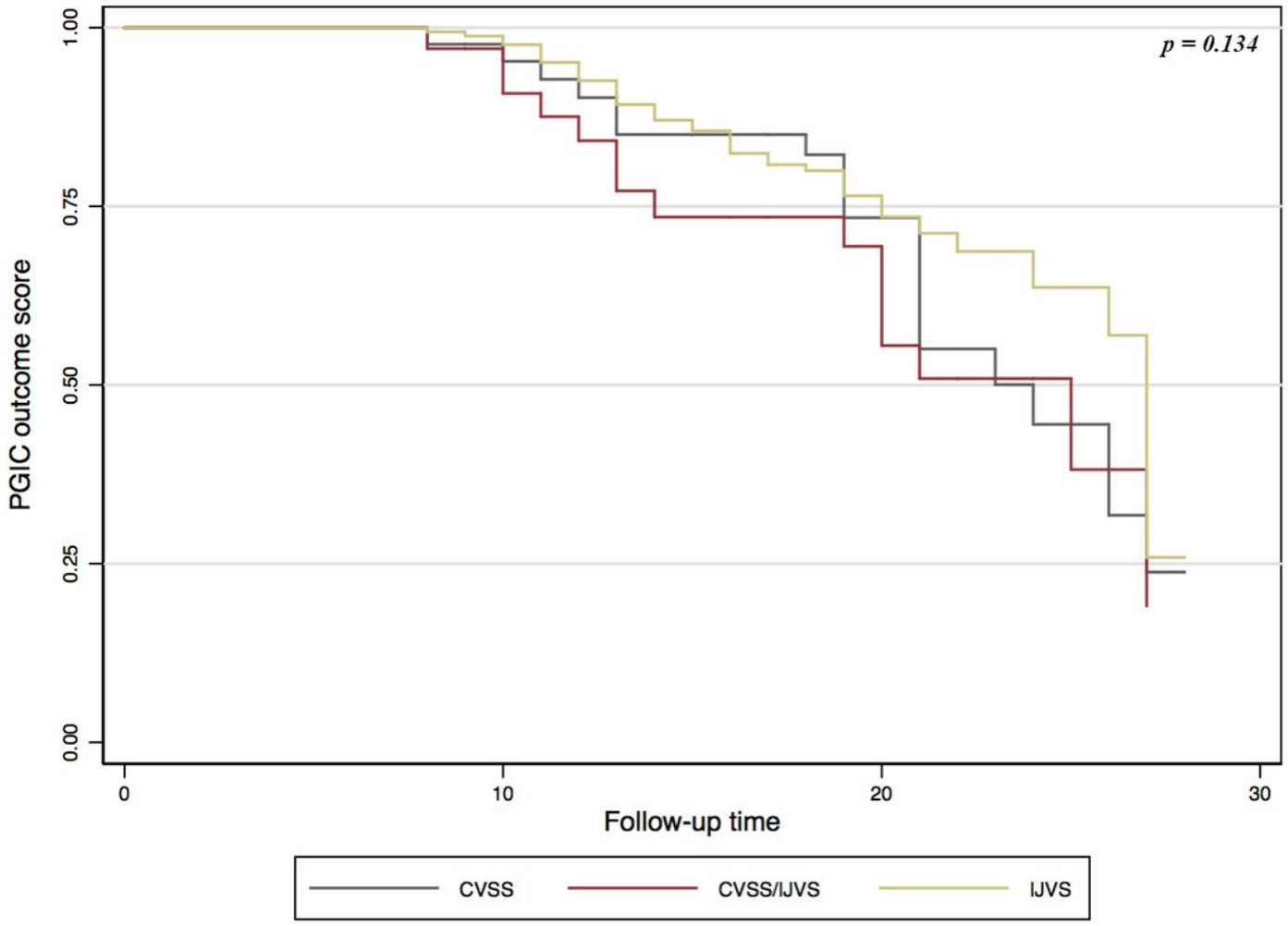

Figure 5

Kaplan - Meier estimation for the clinical outcomes in subgroups of CCSVI.

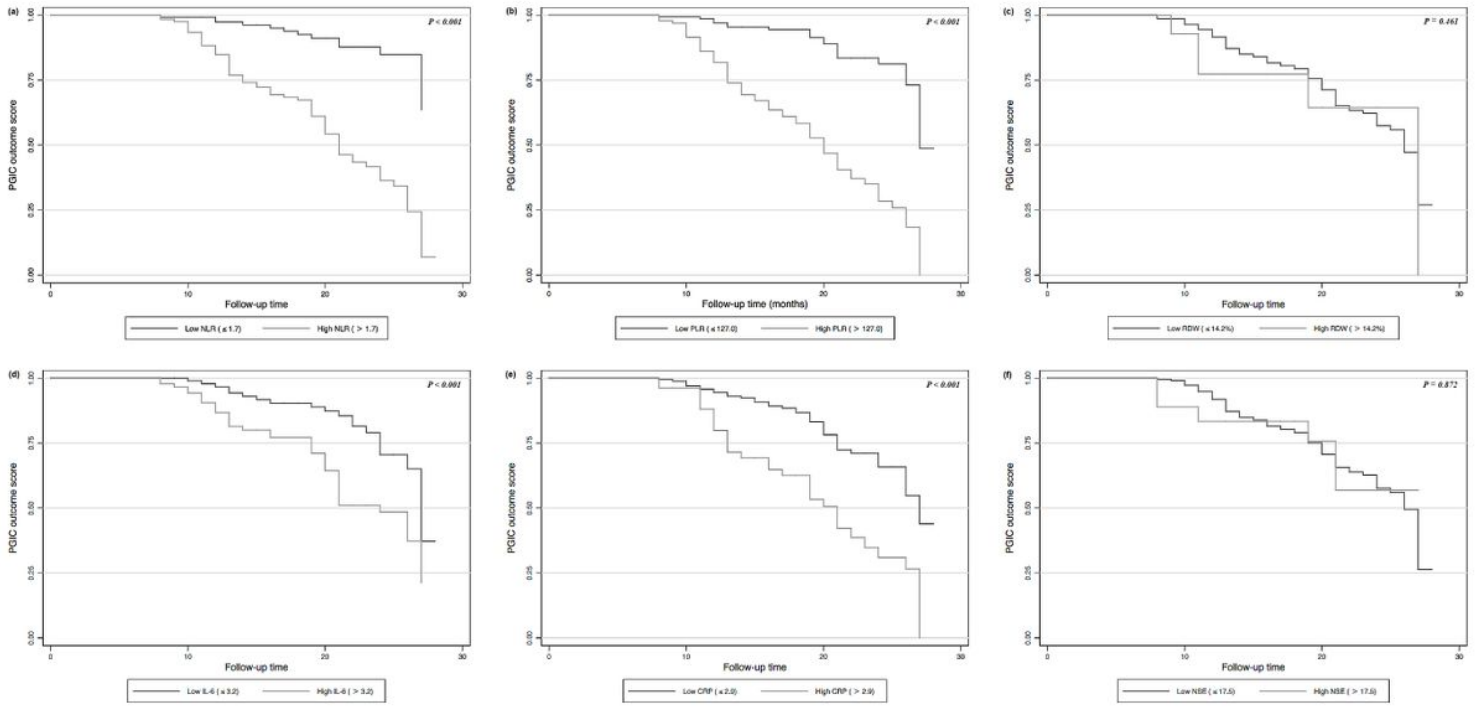

Figure 6

Kaplan - Meier estimation for the clinical outcomes in subgroups of inflammatory biomarkers. (a) NLR subgroup (b) PLR subgroup (c) RDW subgroup (d) IL-6 subgroup (e) CRP subgroup (f) NSE subgroup.

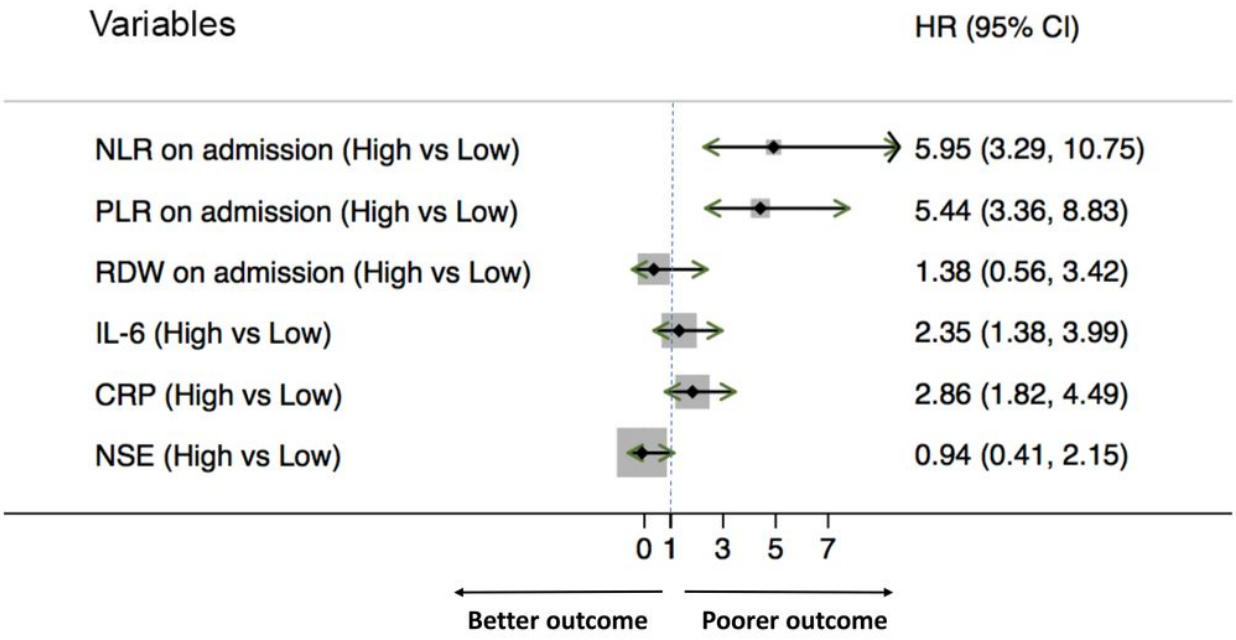

Figure 7

Forest plot of univariate cox proportional hazards model of inflammatory biomarkers associated with clinical outcome.

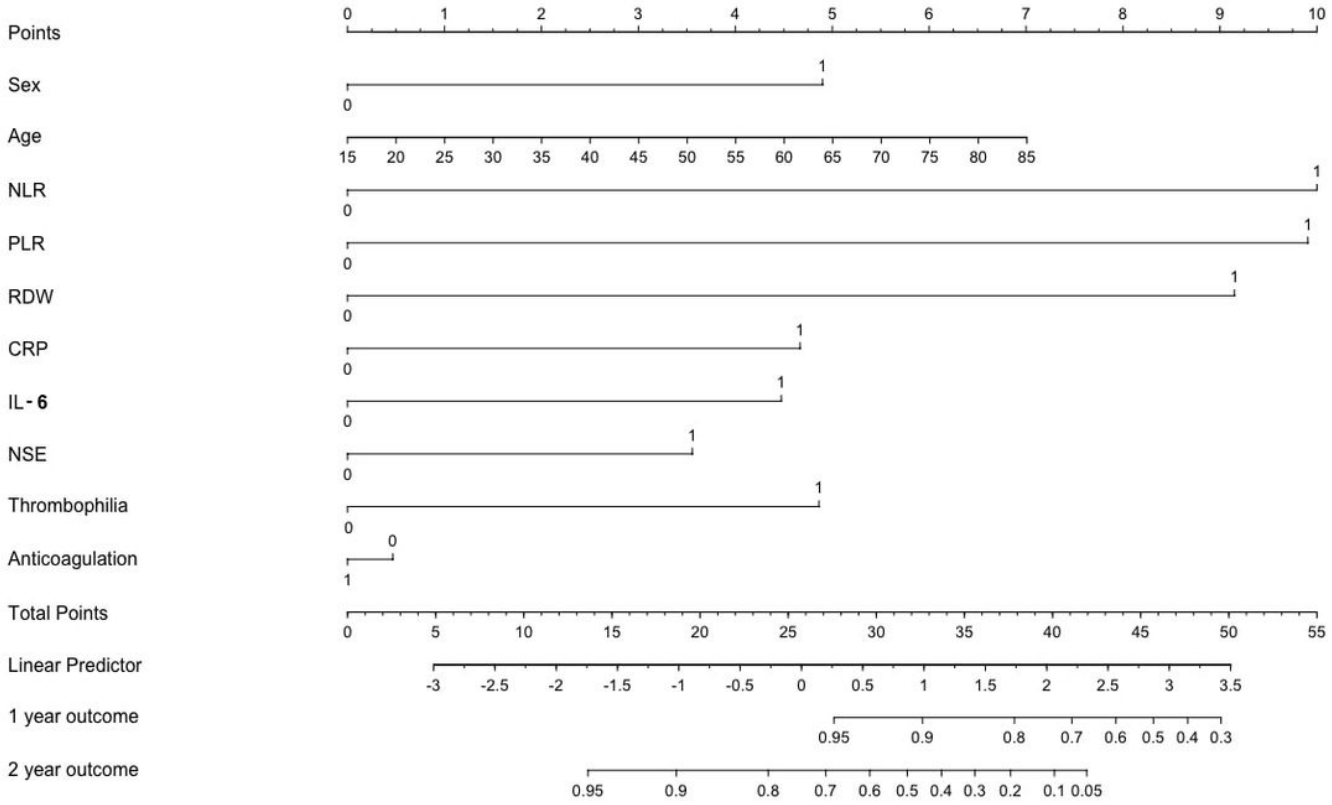

Figure 8

Nomogram for predicting CCSVI clinical outcome.

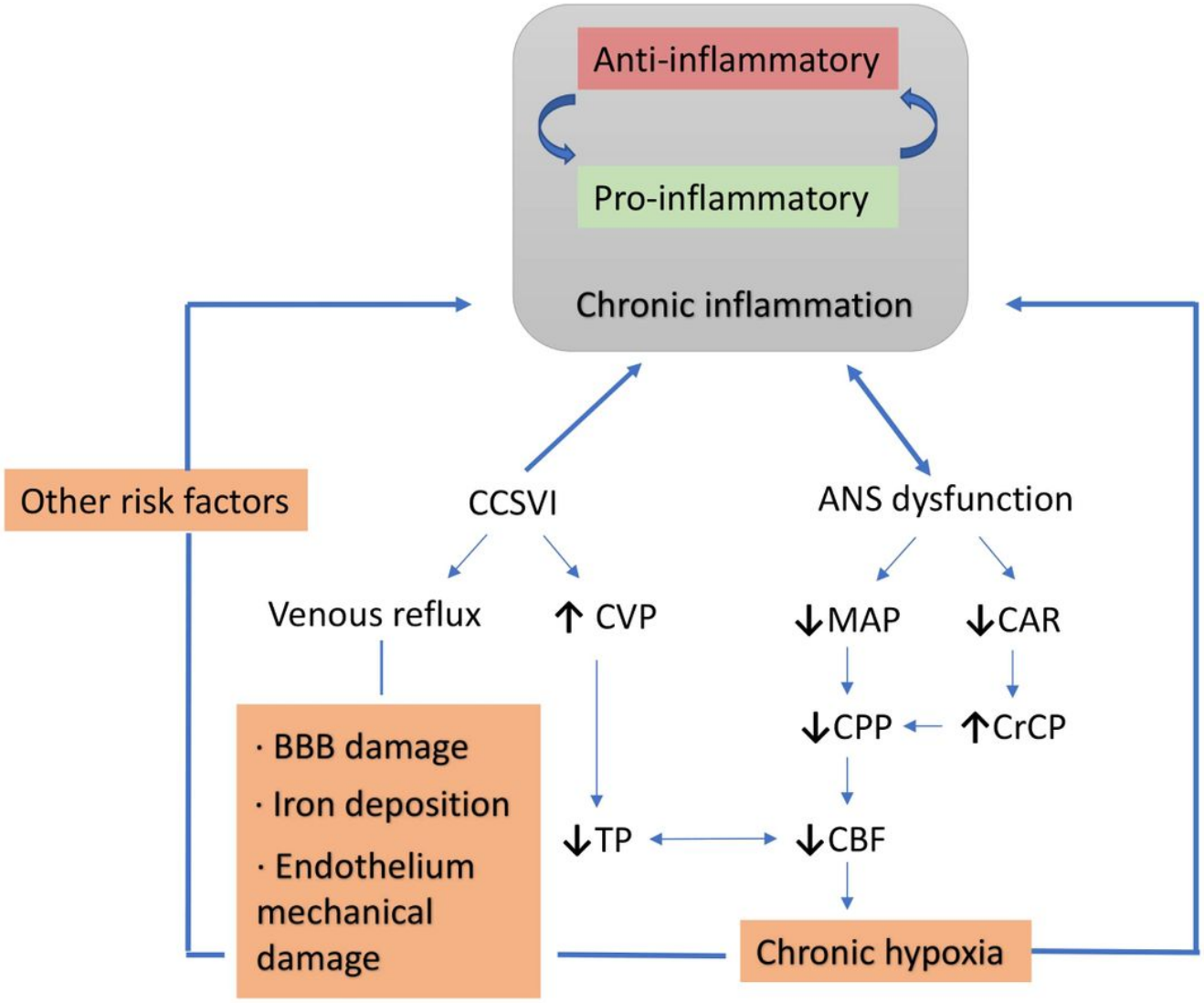

Figure 9

The mechanism of CCSVI-induced inflammation. CBV = cerebral blood volume, CVP = cerebral venous pressure, MAP = Mean arterial pressure, CBF = cerebral blood flow, CrCP = critical closure pressure, CPP = cerebral perfusion pressure, CAR = cererbal auto-regulation, TP = transmural pressure, BBB = blood brain barrier, ANS = Autonomic neurological system

Supplementary Files

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