Original Article

Clinical characteristics, inflammation and coagulation status in patients with immunological disease-related chronic cerebrospinal venous insufficiency

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Background: Immunological disease-related chronic cerebrospinal venous insufficiency (CCSVI) is rarely reported. This study aimed to analyze clinical characteristics, inflammation, and coagulation status in patients with immunological disease-related CCSVI.

Methods: Patients with CCSVI were enrolled from 2017 to 2019 and divided into three cohorts based on their immunological disease backgrounds, including groups with confirmed autoimmune disease, with suspected/subclinical autoimmune disease, and with non-immunological etiology. Immunological, inflammatory, and thrombophilia biomarker assay in blood samples were obtained. Mann-Whitney U test or Fisher's exact test was used to compare continuous variables or categorical variables between the CCSVI patients with or without the immunological etiology. Spearman's correlation analysis was conducted among age, baseline neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), interleukin-6 (IL-6), C-reactive protein (CRP), and neuron-specific enolase (NSE) in the three groups.

Results: A total of 255 consecutive patients with CCSVI were enrolled, including three subgroups: CCSVI with confirmed autoimmune disease (n=41), CCSVI with suspected/subclinical autoimmune disease (n=116) and CCSVI with non-immunological etiology (n=98). In the first subgroup, a series of 41 cases was confirmed with eight different autoimmune diseases including antiphospholipid syndrome (n=18), Sjögren's syndrome (n=8), immunoglobulin G4-related disease (n=7), Behçet's disease (n=2), autoimmune hepatitis (n=2), Wegener's granulomatosis (n=2), systemic sclerosis (n=1) and AQP4 antibody-positive neuromyelitis optica spectrum disorder (n=1). Groups with immunological etiology did not show a higher incidence of thrombophilia or increased pro-inflammatory biomarkers (e.g., neutrophil, IL-6). However, patients with non-immunological etiology had a higher baseline level of CRP. Additionally, baseline PLR was moderately correlated to NLR and CRP in CCSVI patients with non-immunological etiology and suspected/subclinical autoimmune disease.

Conclusions: The formation of CCSVI may be based on the inflammatory process, facilitated by multiple risk factors, among which medical history of immunological diseases may play a significant role due to the intricate relationship between inflammation and coagulation. Moreover, CCSVI may also cause an independent inflammatory injury in venous walls, leading to focal stenosis or thrombus, without attacks from autoimmune antibodies.

Keywords: Chronic cerebrospinal venous insufficiency (CCSVI); cerebral venous sinus stenosis (CVSS); internal jugular vein stenosis (IJVS); inflammatory biomarkers; autoimmune disease

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Introduction

Chronic cerebrospinal venous insufficiency (CCSVI), as a state of impaired intracranial or extracranial venous drainage, has been heatedly discussed over its role in the pathogenesis of multiple sclerosis (MS) in the last decades (1-4). However, with the increasing evidence of CCSVI not unique to MS (5-7), the relationship between CCSVI and other autoimmune diseases has emerged. Given that autoimmune diseases are associated with hypercoagulation state due to elevated autoimmune antibodies, venous thromboembolism (VTE) is one of the most common complications. Nevertheless, studies on autoimmune disease-mediated cerebral venous sinus thrombosis (CVST) are rather rare. Only a few cohort studies of patients with systemic lupus erythematosus (SLE) (8-11) or Behçet's disease (BD) (12,13) were reported to have CCSVI as well. Moreover, several case series presented patients with the antiphospholipid-antibody syndrome (APS) (14,15), inflammatory bowel disease (IBD) (16), or Wegener's granulomatosis (17,18) with the coexistence of CVST.

The clinical features of autoimmune disease-mediated CCSVI are still unclear. Moreover, we also found a number of patients with CCSVI had positive tests of immunological biomarkers, such as decreased complement 3 (C3) or complement 4 (C4), increased erythrocyte sedimentation rate (ESR), immunoglobulin G (IgG), or immunoglobulin E (IgE), despite negative findings of antinuclear bodies or antineutrophil cytoplasmic antibodies. Thus, we aimed to enroll CCSVI patients with confirmed autoimmune disease or suspected/subclinical autoimmune disease and provided comprehensive clinical features of CCSVI with or without immunological etiology. Furthermore, thanks to the intricate relationship between coagulation, inflammation (adaptive immune system), and complement pathway (innate immune system), we evaluated relevant biomarkers in this study. The following article is presented in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-4201).

Methods

Population

A total of 255 consecutive patients with confirmed CCSVI were enrolled, with admission in the Department of Neurology, Xuanwu Hospital, Capital Medical University, from 2017 to 2019. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of Xuanwu Hospital, Capital Medical University (2019-006), and informed consent was taken from all individual participants.

Inclusion criteria were as follows: (I) patients with CCSVI, including internal jugular vein stenosis (IJVS), cerebral venous sinus stenosis (CVSS), or CVSS combined with IJVS were confirmed by contrast-enhanced magnetic resonance venography (CE-MRV) or digital subtraction angiography (DSA); (II) patients did not have parenchymal lesions due to CCSVI; (III) the course of the disease was at a subacute or chronic stage, defined as an interval of more than 4 weeks; (IV) patients with autoimmune diseases were confirmed by the Department of Rheumatology, Xuanwu Hospital, Capital Medical University.

We excluded patients with definite acute or chronic infection; use of anti-inflammatory medication within 4 weeks prior to blood collection; intracranial hypertension (IH) resulting from other reasons: (I) drug-induced IH; (II) cerebrospinal fluid shunt history; (III) intracranial mass occupation; (IV) arteriovenous malformations.

Clinical and demographic data

Age, gender, course of the disease (from onset to admission), treatments, and presumable risk factors known before hospitalization or discovered during hospitalization were recorded. The common risk factors included hypertension (use of antihypertensive medications or systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg before hospitalization diastolic blood pressure >90 mmHg before hospitalization), diabetes mellitus (use of antidiabetic therapies or fasting blood glucose >7 mmol/L on two occasions during hospitalization), hypercholesterolemia (use of lipid-lowering medications 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), hepatitis B virus (HBV) infection (use of anti-HBV therapies or positive hepatitis B core antibody/antigen or hepatitis B e antibody/antigen), hyperhomocysteinemia (>15 mmol/L), hyperuricemia (>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 signs, such as 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 more than 200 mmH_2O.

Subgroup analysis was conducted based on etiology. CCSVI patients with immunological etiology were defined as the coexistence of confirmed autoimmune disease or suspected/subclinical autoimmune disease, while CCSVI patients with non-immunological etiology included CVST-related CCSVI or bone/vessel/lymph node-compression-related CCSVI.

Immunological, inflammatory, and thrombophilia biomarkers assay in the blood sample

Immunological biomarker assay included autoimmune antibody tests in serum samples, including antinuclear antibodies (ANAs), anti-neutrophil cytoplasmic antibodies (ANCAs), and antiphospholipid antibodies (APLAs), as well as other immunological markers, such as C3, C4, IgG, IgE, ESR, and rheumatic factor (RF).

Inflammatory biomarker assay consisted of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in plasma EDTA samples, as well as interleukin-6 (IL-6), C-reactive protein (CRP), and neuron-specific enolase (NSE) in serum samples. Baseline levels 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.

Thrombophilia biomarker assay evaluated both antigens, including platelet, fibrinogen, d-dimer, antithrombin-III, protein C, and protein S, as well as activity, such as thrombin time, partial thromboplastin time (PTT) and activated PTT (aPTT) in plasma sodium-citrate sample without platelet depleted. Cutoff values were based on the referential interval in the Laboratory of Xuanwu Hospital, Capital Medical University.

All blood samples were collected in VACUETTE® Blood Collection Tubes (Greiner Bio-One, Kremsmünster, Austria). Detailed information on coagulation and inflammatory kits and instruments is presented in Table S1.

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 Mann-Whitney U test or Fisher's exact test to compare continuous variables or categorical variables between patients with immunological etiology CCSVI and non-immunological etiology CCSVI. Difference between levels of baseline inflammatory markers [NLR, PLR, and red blood cell distribution width (RDW)] and that at discharge was tested by Wilcoxon signed-rank test. Correlation coefficients were calculated with Spearman's test among age, baseline NLR, PLR, RDW, IL-6, CRP, and NSE. Quantitative variables with a normal distribution were specified as mean ± standard deviation, and those with abnormal distribution were expressed as median with interquartile range (IQR). Differences were considered significant at a two-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

Baseline clinical features

A total of 255 patients (104 males and 151 females) with CCSVI were enrolled in this retrospective study, of which more than 95% had a disease course over 1 month (chronic stage), and followed up with 18.13±5.58 months. Patients most likely presented with sleep disturbances (60.4%), eye discomfort (58.4%), head noise (53.7%), tinnitus (51.8%), headache (45.1%), and hearing loss (32.2%). Combined risk factors were commonly seen, for instance, thrombophilia state, overweight, hyperlipidemia, hypertension, anemia, and suspected thyroid disorders. Based on locations of CCSVI, IJVS, CVSS, and CVSS combined with IJVS were found in 68.2%, 16.9%, and 14.9% of enrolled patients, respectively. Treatments for CCSVI patients were antiplatelet drugs (60.0%), anticoagulants (32.2%), and endovascular therapy (12.5%). Details were displayed in *Table 1*.

Difference between CCSVI with or without immunological etiology

Immunological disease-related CCSVI was defined as confirmed autoimmune disease or suspected/subclinical autoimmune disease. The prevalence of autoimmune disease-related CCSVI was relatively low as 16.1% (n=41), while CCSVI was rather common in suspected/subclinical autoimmune disease (45.5%, n=116). A total of 41 cases

Table 1 Demographic and basic clinical features

Variables	All (n=255)	Immunological etiology (n=157)		Non-immunological etiology (n=98)	P value
		Confirmed autoimmune disease (n=41)	Suspected/subclinical autoimmune disease (n=116)		
Personal data					
Age, years	53.47±15.04	50.88±18.77	56.42±14.14*	51.05±13.81	0.017
Gender (M:F)	104:151	14:27	54:62	36:62	0.223
Course of disease					0.543
Subacute (within 1 month)	11 (4.3)	3 (7.3)	4 (3.4)	4 (4.1)	
Chronic (more than 1 month)	244 (95.7)	38 (92.7)	112 (96.6)	94 (95.9)	
Follow-up time, months^	18.13±5.58	18.27±5.52	18.46±5.31	17.69±5.94	0.656
mRS on admission	0.43±0.68	0.60±0.60	0.42±0.61	0.39±0.77	0.110
Symptoms and signs					
Sleep disturbances	154 (60.4)	22 (53.7)	79 (68.1)	53 (54.1)	0.078
Eye discomfort	149 (58.4)	23 (56.1)	71 (61.2)	55 (56.1)	0.716
Papilledema	49 (19.2)	16 (39.0)	17 (14.7)	16 (16.3)	0.004
Frisen scale	1.08±1.31	1.56±1.47	0.82±1.23	1.03±1.21	0.139
Head noises	137 (53.7)	18 (43.9)	72 (62.1)	47 (48.0)	0.045
Tinnitus	132 (51.8)	21 (51.2)	61 (52.6)	50 (51.0)	0.985
Headache	115 (45.1)	20 (48.8)	43 (37.1)	52 (53.1)	0.055
Neck discomfort	77 (30.2)	9 (22.0)	42 (36.2)	26 (26.5)	0.152
Hearing loss	82 (32.2)	11 (26.8)	39 (33.6)	32 (32.7)	0.738
Anxiety	45 (17.6)	4 (9.8)	20 (17.2)	21 (21.4)	0.266
Nausea/vomiting	47 (18.4)	4 (9.8)	19 (16.4)	24 (24.5)	0.097
Memory loss	21 (8.2)	0 (0.0)	11 (9.5)	10 (10.2)	0.078
IH	44 (17.3)	8 (19.5)	21 18.1)	15 (15.3)	0.368
Presumable risk factors					
Obesity	93 (36.5)	13 (31.7)	35 (30.2)	43 (43.9)	0.172
Type 2 diabetes mellitus	22 (8.6)	4 (9.8)	11 (9.5)	7 (7.1)	0.794
HBP	83 (32.5)	15 (36.6)	35 (30.2)	33 (33.7)	0.727
Hyperlipidemia	90 (35.3)	11 (26.8)	47 (40.5)	32 (32.7)	0.236
Anemia	57 (22.4)	13 (31.7)	26 (22.4)	18 (18.4)	0.234
Stroke	20 (7.8)	2 (4.9)	10 (8.6)	8 (8.2)	0.821
Hemorrhage	6 (2.4)	0 (0.0)	3 (2.6)	3 (3.1)	0.747
Hyperuricemia	18 (7.1)	5 (12.2)	4 (3.4)	9 (9.2)	0.075
Hyperhomocysteinemia	20 (7.8)	7 (17.1)	7 (6.0)	6 (6.1)	0.082
CAD	27 (10.6)	7 (17.1)	12 (10.3)	8 (8.2)	0.264
Previous otitis media/mastoiditis	7 (2.7)	3 (7.3)	2 (1.7)	2 (2.0)	0.175
Chronic rhinosinusitis	14 (5.5)	4 (9.8)	6 (5.2)	4 (4.1)	0.431

Table 1 (*continued*)

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Variables	All (n=255)	Immunological etiology (n=157)		Non-immunological etiology (n=98)	P value
		Confirmed autoimmune disease (n=41)	Suspected/subclinical autoimmune disease (n=116)		
HBV infection	47 (18.4)	9 (22.0)	24 (20.7)	14 (14.3)	0.383
Suspected thyroid disorders					
Abnormal thyroid ultrasound	34 (13.3)	7 (17.1)	15 (12.9)	12 (12.2)	0.707
Abnormal thyroid function test	66 (25.9)	12 (29.3)	17 (14.7)	27 (27.6)	0.681
Pregnancy/postpartum	2 (0.8)	1 (2.4)	0 (0.0)	1 (1.0)	0.149
Thrombophilia					
Protein S deficiency	65 (25.5)	11 (26.8)	36 (31.0)	18 (18.4)	0.385
Protein C deficiency	25 (9.8)	5 (12.2)	11 (9.5)	9 (9.2)	0.191
Antithrombin III deficiency	27 (10.6)	8 (19.5)	13 (11.2)	6 (6.1)	0.213
Increased D-dimer level	22 (8.6)	7 (17.1)	7 (6.0)	8 (8.2)	0.192
Hyperfibrinogenemia	27 (10.6)	6 (14.6)	10 (8.7)	11 (11.2)	0.498
Primary thrombocythemia	25 (9.8)	5 (12.2)	11 (9.5)	9 (9.2)	0.100
Autoimmune disease					
APS	18 (7.1)	18 (43.9)	NA	NA	NA
Sjögren's syndrome	8 (3.1)	8 (19.5)	NA	NA	NA
IgG4-related disease	7 (2.7)	7 (17.1)	NA	NA	NA
Behcet's disease	2 (0.8)	2 (4.9)	NA	NA	NA
Autoimmune hepatitis	2 (0.8)	2 (4.9)	NA	NA	NA
Wegener's granulomatosis	2 (0.8)	2 (4.9)	NA	NA	NA
Others	2 (0.8)	2 (4.9)	NA	NA	NA
Suspected autoimmune disease					
Increased IgE	5 (2.0)	NA	5 (4.3)	NA	NA
Increased IgG	10 (3.9)	NA	10 (8.6)	NA	NA
Decreased C3	76 (29.8)	NA	76 (65.5)	NA	NA
Decreased C4	38 (14.9)	NA	38 (32.8)	NA	NA
Positive RF	4 (1.6)	NA	4 (3.4)	NA	NA
Increased ESR	21 (8.2)	NA	21 (18.1)	NA	NA
Inflammatory markers					
NLR on admission[&]	1.81±0.77	1.78±0.70	1.82±0.80	1.79±0.75	0.961
NLR at discharge	2.91±2.56[#]	2.16±1.09	2.53±1.29[#]	3.88±4.03	0.581
Delta-NLR	1.12±2.15	0.66±0.97	0.81±1.16	1.83±3.38	0.912
PLR on admission	124.13±46.94	120.31±41.89	122.47±41.78	127.54±54.31	0.878
PLR at discharge[&]	151.32±100.88	125.39±33.03	132.91±46.55	192.51±160.72	0.592
Delta-PLR	26.75±103.07	25.07±33.10	4.09±75.83	59.84±151.17	0.580
RDW on admission (%)	13.14±1.43	13.25±1.16	13.10±1.63	13.14±1.26	0.685

Table 1 (*continued*)

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Variables	All (n=255)	Immunological etiology (n=157)		Non-immunological etiology (n=98)	P value
		Confirmed autoimmune disease (n=41)	Suspected/subclinical autoimmune disease (n=116)		
RDW at discharge (%)[&]	13.49±2.28	12.77±0.43	13.52±2.37	13.92±2.84	0.637
Delta-RDW (%)	0.44±2.37	0.28±0.95	0.42±2.09	0.95±3.30	0.462
IL-6 (pg/mL)	4.70±5.71	6.36±7.51	4.65±5.91	4.12±4.48	0.391
CRP (mg/L)	2.80±3.69	2.44±1.07	2.38±1.89*	3.45±5.50	0.015
NSE (ng/mL)	12.95±2.72	13.56±3.33	12.82±2.26	12.88±2.95	0.734
Localization of CVSS/IJVS					0.026
CVSS	43 (16.9)	7 (17.1)	13 (11.2)	23 (23.5)	
SSS	15 (5.9)	2 (4.9)	5 (4.3)	8 (8.2)	0.523
LTS	34 (13.3)	7 (17.1)	9 (7.8)	21 (21.4)	0.013
RTS	36 (14.1)	10 (24.4)	11 (9.5)	15 (15.3)	0.063
SS	2 (0.8)	0 (0.0)	0 (0.0)	2 (2.0)	0.445
LSigS	22 (8.6)	6 (14.6)	5 (4.3)	11 (11.2)	0.058
RSigS	19 (7.5)	8 (19.5)	5 (4.3)	6 (6.1)	0.011
IJVS	174 (68.2)	24 (58.5)	90 (77.6)	60 (61.2)	
LIJV-J1 segment	16 (6.3)	5 (12.2)	7 (6.0)	4 (4.1)	0.218
RIJV-J1 segment	11 (4.3)	4 (9.8)	4 (3.4)	3 (3.1)	0.195
LIJV-J2 segment	26 (10.2)	5 (12.2)	13 (11.2)	8 (8.2)	0.667
RIJV-J2 segment	12 (4.7)	2 (4.9)	5 (4.3)	5 (5.1)	1.000
LIJV-J3 segment	144 (56.5)	21 (51.2)	71 (61.2)	52 (53.1)	0.530
RIJV-J3 segment	122 (47.8)	18 (43.9)	61 (52.6)	43 (43.9)	0.397
CVSS combined with IJVS	38 (14.9)	10 (24.4)	13 (11.2)	15 (15.3)	
Treatment					
Antiplatelet drugs	153 (60.0)	22 (53.7)	77 (66.4)	54 (55.1)	0.133
Anticoagulants	82 (32.2)	14 (34.1)	33 (28.4)	35 (35.7)	0.526
Endovascular therapies	32 (12.5)	8 (19.5)	10 (8.6)	14 (14.3)	0.138
Stenting	25 (9.8)	8 (19.5)	9 (7.8)	8 (8.2)	0.096
Balloon dilation	5 (2.0)	0 (0.0)	2 (1.7)	3 (3.1)	0.592
Intrasinus thrombolysis	4 (1.6)	0 (0.0)	0 (0.0)	4 (4.1)	0.035
ONSD	8 (3.1)	4 (9.8)	1 (0.9)	3 (3.1)	0.026

Data were presented as mean ± standard deviation or n (%). *, compared with group of non-immunological etiology group, statistically significant at P<0.05; [&], the number of patients who had complete blood count (CBC) test at discharge (n=36); ^, time from discharge to follow-up (months); [#], compared with group of NLR tested on admission, statistically significant at P<0.05. P=0.001 in general groups (n=255), P=0.008 in group with suspected/subclinical autoimmune disease (n=116). mRS, modified Rankin scale; HBP, high blood pressure; CAD, coronary artery disease; HBV, hepatic type B virus; APS, antiphospholipid syndrome; C3, complement 3; C4, complement 4; RF, rheumatic factor; ESR, erythrocyte sedimentation rate; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; RDW, red blood cell distribution width; IL-6, interleukin-6; CRP, C-reactive protein; NSE, Neuron-specific enolase; CVSS, cerebral venous sinus stenosis; IJVS, internal jugular vein stenosis; SSS, superior sagittal sinus; TS, transverse sinus; LTS, left transverse sinus; RTS, right transverse sinus; SigS, sigmoid sinus; LSigS, left sigmoid sinus; RSigS, right sigmoid sinus; ONSD, optic nerve sheath decompression; NA, not applicable.

with confirmed autoimmune disease-related CCSVI (14 males and 27 females, mean age 50.88±18.77 years) were collected, among which, APS (n=18), Sjögren's syndrome (SS) (n=8), and IgG4-related disease (IgG4-RD) (n=7) were highly prevalent in our cohort. Apart from specific elevated autoantibodies, such as ANAs or ANCAs or APLAs, abnormal levels of nonspecific immunological markers were also coexisted within the CCSVI cohort of confirmed autoimmune disease, for instance, a decreased level of C3 (n=16) or C4 (n=9) as well as an increased level of ESR (n=9) or IgG (n=8). *Table 2* presented the case series of 41 cases with confirmed autoimmune disease-related CCSVI in detail.

There was a significant difference between CCSVI with or without immunological etiology in terms of symptoms and signs (*Table 1*). CCSVI patients with suspected/subclinical autoimmune disease presented at an older age on admission (P=0.017) and had a higher prevalence of head noises (P=0.045), while those with confirmed autoimmune disease were more prone to have papilledema (P=0.004). Intriguingly, the groups with immunological etiology did not show a higher incidence of thrombophilia or increased pro-inflammatory factors (e.g., neutrophil, IL-6) as we previously expected than the group with non-immunological etiology. However, patients with non-immunological etiology had a higher baseline level of CRP (P=0.015), which further predicted that an independent inflammatory process might involve in the pathogenesis of CCSVI.

Subgroup analysis in CCSVI with immunological etiology

We further conducted a subgroup analysis between CCSVI with confirmed autoimmune diseases and suspected/subclinical autoimmune diseases, particularly focusing on the difference of inflammatory biomarkers between these two subgroups (*Table 3*). CCSVI patients with APS and IgG4-RD had a relatively younger age than that with SS and a higher CRP level than that with decreased C3. The gender difference was also remarkable. The group of CCSVI with confirmed autoimmune diseases was female-dominated while that of CCSVI with suspected autoimmune diseases (e.g., group of increased ESR and IgG) was male-dominated.

Correlations between inflammatory cells and inflammatory cytokines

Correlation coefficients were calculated with Spearman's test among age, baseline NLR, PLR, RDW, IL-6, CRP, and NSE in groups with non-immunological etiology (*Figure 1A*), with suspected/subclinical autoimmune disease (*Figure 1B*), and with confirmed autoimmune disease (*Figure 1C*). As shown in *Table 4*, baseline PLR level was moderately correlated to NLR and CRP in the group of CCSVI patients with non-immunological etiology and suspected/subclinical autoimmune disease, indicating CCSVI itself may relate to the inflammatory process (*Table 4*, a and b). However, the level of IL-6 was only positively associated with CRP and age in the group of CCSVI patients with confirmed autoimmune disease (*Table 4*, c).

Discussion

To our knowledge, this is the first study evaluating the comprehensive clinical features of CCSVI with immunological disease background. In this study, a case series with 41 patients with confirmed autoimmune disease-related CCSVI was presented. Eight different immune-complex diseases, including APS, SS, IgG4-RD, BD, autoimmune hepatitis, Wegener's granulomatosis, systemic sclerosis, and AQP4-antibody (AQP4-IgG)-positive neuromyelitis optica spectrum disorder ($AQP4^+$ NMOSD) were analyzed. CCSVI cases combined with IgG4-RD, SS, and $AQP4^+$ NMOSD-related CCSVI were never reported before. Furthermore, we explored the inflammatory and coagulation status in CCSVI patients with immunological etiology.

Groups with immunological etiology (including CCSVI patients with confirmed autoimmune disease and suspected/subclinical autoimmune disease) did not show a higher incidence of thrombophilia or increased pro-inflammatory factors (e.g., neutrophil, IL-6). However, patients with non-immunological etiology had a higher baseline level of CRP. Besides, baseline PLR level was moderately correlated to NLR and CRP in CCSVI patients with non-immunological etiology and suspected/subclinical autoimmune disease. Due to these findings, we postulated that an independent inflammatory process might involve in the pathogenesis of CCSVI, facilitated by multiple risk factors, among which autoimmune disease background could play a major role. In the subgroup analysis of CCSVI patients with immunological etiology, patients with confirmed autoimmune disease had a higher prevalence of thyroid dysfunction and HBV infection. Apart from having elevated autoimmune antibodies, they were also correlated with decreased C3 or C4 and increased ESR or IgG. These

Table 2 Case series of autoimmune disease-related CCSVI (n=41)

Variables	Number	Age (years)/ gender	Symptoms and signs	Course of disease	Presumable risk factors	Localization of CCSVI	Abnormal lab test	Treatment
APS (n=18)	Case 1	55/M	Eye discomfort, anxiety and sleep disorder	7 months	Obesity, hyperlipidemia, hyperuricemia and previous HBV infection, and AT-III deficiency	LIJV-J3	AT-III, C3, C4↓; anti-β2GP1 Ab↑ (113 RU/mL)	Anti-PLT
	Case 2	75/F	Hearing loss, Head noises, tinnitus, papilledema [1]*, neck discomfort, anxiety and sleep disorder	30 years	Type 2 DM, HBP, and anemia	RIJV-J3	IgE↑, C3↓; anti-β2GP1 Ab↑ (47 RU/mL)	None
	Case 3	29/M	Headache, papilledema [1]*, head noises and sleep disorder	2 months	Current HBV infection, and anemia	LIJV-J3, RIJV-J1/J3	C4, C3↓; anti-β2GP1 Ab↑ (40 RU/mL)	Anti-PLT
	Case 4	30/F	Hearing loss, tinnitus, headache, neck discomfort, papilledema [3]* and IH	1.5 years	Obesity, hyperhomocysteinemia, and anemia	RTS, RSigS	DD, ESR↑; anti-β2GP1 Ab↑ (50 RU/mL)	Anti-PLT, anti-coagulation, ONSD
	Case 5	33/M	Headache and papilledema [5]*	3 months	Obesity and current HBV infection	RTS	Anti-β2GP1 Ab↑ (60 RU/mL)	Anti-PLT, anti-coagulation, stenting, ONSD
	Case 6	75/F	Dizziness and tinnitus	2 years	Obesity, hyperlipidemia, HBP, Hashimoto's thyroiditis, and previous otitis media	Bilateral IJV-J1	Anti-β2GP1 Ab↑ (65 RU/mL)	Anti-PLT
	Case 7	62/F	Head noises, neck discomfort, blurry vision and sleep disorder	2 months	Obesity, type 2 DM, hyperlipidemia, HBP, and CAD	LIJV-J1	aCL↑ (40 RU/mL)	Anti-PLT
	Case 8	32/F	Fever, headache, papilledema [3]* and IH	1 month	Postpartum, anemia	Bilateral TS, SigS, RIJV-J2/J3, LIJV-J3	WBC, hs-CRP, IL-6, PLT↑; anti-β2GP1 Ab↑ (61 RU/mL)	Corticosteroids
	Case 9	54/F	Tinnitus, eye discomfort and sleep disorder	4 years	Obesity, hyperlipidemia, Hashimoto's thyroiditis, and CAD	RTS, LIJV-J3, RIJV-J3	ESR↑; anti-β2GP1 Ab↑ (151 RU/mL)	Anti-PLT, anti-coagulation and stenting
	Case 10	63/F	Headache and head noises	2 years	HBP	RTS, LIJV-J3	DD↑; anti-β2GP1 Ab↑ (59 RU/mL)	Anti-PLT, anti-coagulation and stenting
	Case 11	33/F	Headache, nausea/vomiting, neck discomfort, sleep disorder, and papilledema [4]*	2 weeks	Hashimoto's thyroiditis	RTS, RSigS, LIJV-J3	DD↑; IgG ↑; C4, C3↓; anti-β2GP1 Ab↑ (50 RU/mL)	Anti-coagulation and stenting
	Case 12	56/F	Tinnitus, hearing loss and sleep disorder	5 months	HBP, CAD	RIJV-J3	aCL↑ (42 RU/mL)	Anti-PLT
	Case 13	19/M	Headache, nausea/vomiting, and eye discomfort	3 weeks	Obesity	LIJV-J3, RIJV-J3	AT-III↓; anti-β2GP1 Ab↑ (108 RU/mL)	None
	Case 14	60/M	Tinnitus, and hearing loss	1.5 years	None	LIJV-J3	PS, PC, C3↓; anti-β2GP1 Ab↑ (43.4 RU/mL)	Anti-coagulation and stenting
	Case 15	69/F	Tinnitus, head noises, eye discomfort and sleep disorder	15 years	Hyperuricemia, CAD, and Hashimoto's thyroiditis	LIJV-J2/J3	DD↑; anti-β2GP1 Ab↑ (135 RU/mL)	Anti-PLT

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Number	Age (years)/ gender	Symptoms and signs	Course of disease	Presumable risk factors	Localization of CCSVI	Abnormal lab test	Treatment
	Case 16	39/F	Headache	20 years	Hashimoto's thyroiditis	RIJV-J2/J3	Anti-β2GP1 Ab↑ (53 RU/mL)	None
	Case 17	62/M	Tinnitus, head noises, neck discomfort, hearing loss, and sleep disorder	20 years	Hyperuricemia and anemia	LIJV-J3	PS, PC, C3↓; anti-β2GP1 Ab↑ (81 RU/mL)	Anti-PLT
	Case 18	61/F	Headache, tinnitus, and sleep disorder	4 months	Anemia and Hashimoto's thyroiditis	LTS, LIJV-J3, RIJV-J3	Fig↑, C3↓, ESR↑; anti-β2GP1 Ab↑ (52 RU/mL)	None
SS (n=8)	Case 19	74/M	Headache, head noises, tinnitus, and papilledema [1]*	3 years	Anemia, Hashimoto's thyroiditis, and previous ischemic stroke	RIJV-J1	PS↓; anti-Ro-52 (+++), anti-CENP-B (+++)	Anti-PLT
	Case 20	63/F	Headache, head noises, sleep disorder and papilledema [1]*	2 years	HBP and Hashimoto's thyroiditis	LTS, LIJV-J3, RIJV-J3	C3, C4↓, RF↑; anti-SS-A (+++), anti-Ro-52 (+++)	Anti-coagulation
	Case 21	61/F	Headache, head noises, tinnitus and hearing loss	4 months	HBP, CAD, anemia, and previous HBV infection	RTS, RSigS, LIJV-J2/J3, RIJV-J3	Fig, IgG ↑, PS↓; anti-SS-A (+++), anti-SS-B (+), anti-Ro-52 (+++)	Anti-PLT
	Case 22	72/M	Head noises, sleep disorder and IH	3.5 months	Type 2 DM, hyperlipidemia, HBP, CAD, and previous HBV infection	LIJV-J3, RIJV-J3	PS, C3↓; anti-SS-A (++), anti-Ro-70 (++)	Anti-PLT
	Case 23	68/M	Tinnitus, hearing loss, and sleep disorder	10 years	Obesity, hyperhomocysteinemia, previous ischemic stroke, Hashimoto's thyroiditis	LIJV-J1/J3	AT-III, PS, PC↓; anti-SS-A, anti-Ro-52, anti-β2GP1 Ab↑ (40 RU/mL)	None
	Case 24	56/F	Head noises and eye discomfort	2 years	Hyperlipidemia, HBP, and anemia	RIJV-J3	IgG, ESR, DD↑; anti-SS-A (+++), anti-SS-B (+), anti-Ro-52 (+++),	Anti-coagulation
	Case 25	44/F	Headache, papilledema [3]* and IH	10 years	Obesity and anemia	Bilateral TS, SigS	Anti-SS-A (++), anti-Ro-70 (++)	Optic nerve decompression surgery
	Case 26	56/F	Eye discomfort, neck discomfort, and sleep disorder	1 month	Hyperlipidemia, HBP, and previous HBV infection	LSigS	Fig, DD↑, AT-III↑; C3, C4↓, RF, IgG↑; anti-SS-A (++), anti-Ro-52 (++)	Anti-coagulation
IgG4-related disease (n=7)	Case 27	53/F	Tinnitus, head noises, hearing loss, sleep disorder and IH	4 years	HBP and Hashimoto's thyroiditis	LIJV-J3	C3, C4↓, RF↑; anti-PNMA2 (CSF) (+)	Anti-PLT
	Case 28	15/F	Headache, nausea/vomiting, and papilledema [2]*	1.5 months	Obesity, hyperhomocysteinemia, and hyperuricemia	RTS, SSS	Fig↑, PS, PC↓, IgE↑; IgG4 (serum) ↑ (1,760 mg/L)	Anti-coagulation and ONSD
	Case 29	23/F	Headache, tinnitus, head noises, nausea/vomiting, sleep disorder, papilledema [3]* and IH	4 months	Hashimoto's thyroiditis	RTS, RSigS	TBil, DBil, IBILI, ALP↑; IL-6, C3↓; IgG4 (serum)↑ (1,660 mg/L);	Anti-coagulation and ONSD
	Case 30	78/F	Headache, tinnitus, head noises, hearing loss, sleep disorder, anxiety and IH	4 years	HBP	LIJV-J3, RIJV-J3	DD↑, AT-III↓; C3, C4↓; anti-RNP/Sm (+)	Anti-PLT

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Number	Age (years)/ gender	Symptoms and signs	Course of disease	Presumable risk factors	Localization of CCSVI	Abnormal lab test	Treatment
	Case 31	25/M	Headache, neck discomfort, sleep disorder, papilledema [2]*, and IH	2 years	Hyperlipidemia, hyperhomocysteinemia, and previous mastoiditis	SSS, LTS, LSigS, LIJV-J1, RIJV-J2/J3	IgG4 (CSF) (2,020 mg/L)	Anti-coagulation
	Case 32	36/F	Tinnitus, papilledema [3], and IH	1.5 years	None	Bilateral TS, LIJVS-J1	C3↓; IgG (serum) ↑(1,180 mg/L); IgG4 (serum) ↑ (363 mg/L)	Anti-PLT, anti-coagulation, stenting and ONSD
	Case 33	32/M	Dizziness, eye discomfort, papilledema [2]*, and IH	12 years	Chronic nasal sinusitis, Hashimoto's thyroiditis	Bilateral TS, SigS	ESR↑, IgG4 (serum) (2,550 mg/L)	Anti-PLT, anti-coagulation, stenting
Behcet's disease (n=2)	Case 34	28/M	Headache, head noises, eye discomfort and sleep disorder	20 years	Hyperhomocysteinemia, and anemia	LIJV	PS, PC, C3, C4↓; IgE↑	Anti-PLT
	Case 35	23/F	Headache, tinnitus, papilledema [2]* and IH	3 years	Anemia and Hashimoto's thyroiditis	Bilateral TS, SigS	PS, C4↓	Immunomodulatory drugs (corticosteroids+ mycophenolate mofetil) and anticoagulation
Autoimmune hepatitis (n=2)	Case 36	74/F	Head noises, tinnitus, eye discomfort, and sleep disorder	5 years	Hyperlipidemia, chronic nasal sinusitis, Hashimoto's thyroiditis and previous HBV infection	LIJV-J3	ALT, AST, LDH, ALP↑; Fig, DD↑, AT-III, PS↓, IgG, IgM, CRP, Hs-CRP, RF, ESR↑; anti-Ro-52(+++), anti-CENP (+++)	Anti-PLT
	Case 37	51/M	Tinnitus and eye discomfort	2 months	Obesity, hyperlipidemia, HBP, CAD, and previous HBV infection	RIJV-J1	C3↓; TBil, DBil, IBILI, ALP↑; IgG (CSF), IgG (serum)↑	Anti-PLT
Wegener's granulomatosis (n=2)	Case 38	67/F	Headache, tinnitus, head noises, hearing loss, eye discomfort, and sleep disorder	20 years	Obesity, chronic nasal sinusitis, previous mastoiditis, Hashimoto's thyroiditis, and previous HBV infection	RIJV-J3	AT-III, C3↓; anti-PR3↑	Anti-PLT
	Case 39	55/M	Tinnitus, head noises, and neck discomfort	5 years	Obesity	LIJV-J3, RIJV-J3	C3, C4↓; anti-PR3 (120 RU/mL)	None
Systemic sclerosis (n=1)	Case 40	83/M	Headache	2 months	Obesity, HBP, type 2 DM, Hashimoto's thyroiditis	RTS, RSigS, LIJV-J1, RIJV-J2	Anti-CENP-B (+++)	Anti-PLT and stenting
AQP4$^+$ NMOSD (n=1)	Case 41	42/M	Progressive blurry vision, vision defect, papilledema [2]*, hyposmia	1 year	Chronic nasal sinusitis, splenomegaly	LTS, LSigS, LIJV-J2/ J3	WBC (CSF) ↑, AQP4 (serum) (+)	Corticosteroids

*, the severity of papilledema was evaluated by Frisen scale, presented as papilledema [Frisen scale]. DM, diabetes mellitus; CCSVI, chronic cerebrospinal venous insufficiency; APS, antiphospholipid syndrome; AT-III, anti-thrombin III; RIJV, right internal jugular vein; LIJV, left internal jugular vein; C3, complement 3; C4, complement 4; PLT, platelet; anti-β2GP1 Ab, anti-beta-2 glycoproteins antibodies; HBV, hepatic type B virus; IH, intracranial hypertension; TS, transverse sinus; LTS, left transverse sinus; RTS, right transverse sinus; LSigS, left sigmoid sinus; RSigS, right sigmoid sinus; DD, di-dimer; ESR, erythrocyte sedimentation rate; ONSD, optic nerve sheath decompression; HBP, high blood pressure; DM, diabetes mellitus; CAD, coronary artery disease; WBC, white blood cell; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; aCL, anti-cardiolipin antibodies; SigS, sigmoid sinus; PS, protein S; PC, protein C; anti-Ro-52, anti-Ro52 antibodies; anti-Ro-70, anti-Ro70 antibodies; anti-CENP-B, anti-centromere protein B antibodies; Fig, fibrinogen; anti-SS-A, anti-Sjögren's-syndrome-related antigen A; anti-SS-B, anti-Sjögren's-syndrome-related antigen B; RF, rheumatic factor; SSS, superior sagittal sinus; CSF, cerebrospinal fluid; TBil, total bilirubin; DBil, direct bilirubin; IBILI, indirect bilirubin; ALP, alkaline phosphatase; anti-PR3, anti-proteinase 3 antibodies; anti-PLT, antiplatelet drugs; AQP, aquaporin-4; AQP4 antibody-positive neuromyelitis optica spectrum disorder.

Table 3 Inflammatory biomarkers in subgroup analysis of autoimmune diseases and suspected autoimmune diseases-related CCSVI

Variables	APS (n=18)	SS (n=8)	IgG4-related disease (n=7)	Decreased C3 (n=76)	Decreased C4 (n=38)	Increased ESR (n=21)	Increased IgG (n=10)	Increased IgE (n=5)	Positive RF (n=4)	P value
Age	49.61±3.75^	61.75±3.48	43.00±9.73^	57.17±1.49#^	53.71±2.75^	58.61±2.65^	58.90±5.62	47.00±6.17^	70.75±1.75	0.009
Gender (M:F)	8:10	3:5	1:6	40:36	23:15	4:17	2:8	4:1	2:2	0.021
NLR on admission[&]	1.81±0.16	2.20±0.36	1.48±0.12	1.80±0.09	1.76±0.12	1.97±0.24	1.74±0.17	1.81±0.45	1.70±0.16	0.865
NLR at discharge	NR	1.98±0.79	1.90±0.45	2.59±0.49	2.76±0.49	2.41±0.38	NR	NR	NR	0.350
PLR on admission	112.13±9.27	148.78±16.02	104.96±13.76	121.59±5.36	117.43± 7.57	123.45±6.41	108.23±8.73	139.56±25.72	116.68±8.80	0.472
PLR at discharge[&]	NR	143.48±21.89	99.46±4.44	126.27±16.43	151.60±12.82	121.41±29.79	NR	NR	NR	0.695
RDW on admission (%)	13.15±0.34	13.2±0.23	12.83±0.14	13.06±0.17	13.0±0.17	13.35±0.53	15.3±1.44	13.2±0.14	13.08±0.33	0.513
RDW at discharge (%)[&]	NR	12.77±0.27	12.90±0.29	12.69±0.13	12.62±0.12	15.52±1.72	NR	NR	NR	0.373
IL-6 (pg/mL)	4.66±1.26	8.72±5.42	5.80±2.13	4.82±0.90	4.99±1.67	4.75±1.02	5.30±1.29	2.66±0.66	3.57±0.81	0.291
CRP (mg/L)	2.44±0.22[§]	2.29±0.43	2.46±0.65[§]	1.78±0.10	1.89±0.16	4.39±0.76	3.30±0.85[§]	2.66±0.69	2.08±0.33	<0.001
NSE (ng/mL)	12.70±0.47	14.75±1.58	14.97±2.35	12.57±0.79	11.58±0.61	12.82±0.37	11.58±0.61	12.57±0.79	13.39±1.01	0.536

[&], the number of patients who had complete blood count (CBC) test at discharge (n=36); #, compared with group of APS, statistically significant at P<0.05; ^, compared with group of SS, statistically significant at P<0.05; [§], compared with group of decreased C3, statistically significant at P<0.05. CCSVI, chronic cerebrospinal venous insufficiency; APS, antiphospholipid syndrome; SS, Sjögren's syndrome; C3, complement 3; C4, complement 4; ESR, erythrocyte sedimentation rate; RF, rheumatic factor; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; RDW, red blood cell distribution width; IL-6, interleukin-6; CRP, C-reactive protein; NSE, neuron-specific enolase.

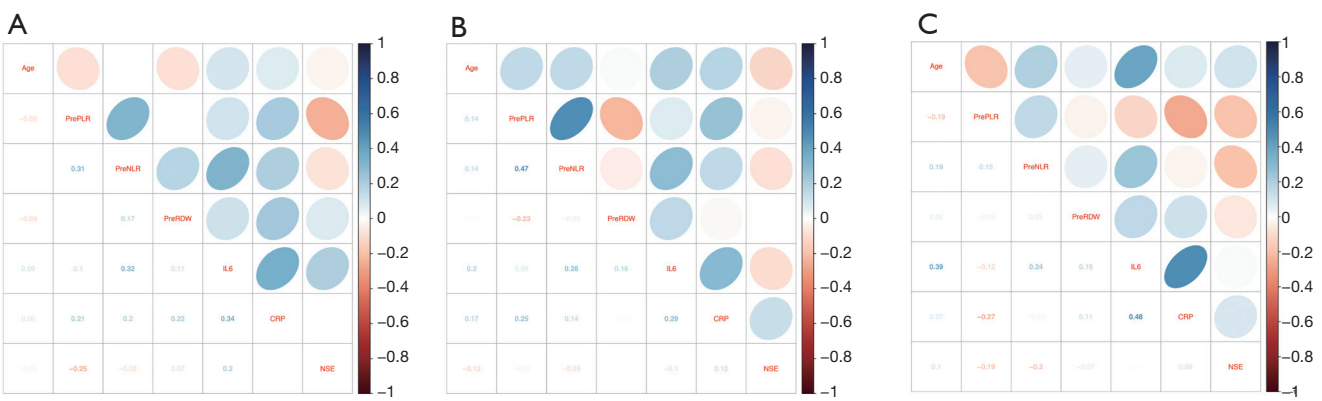

Figure 1 Spearman's correlations between age and inflammatory biomarkers in CCSVI with non-immunological etiology (A), with suspected/subclinical autoimmune disease (B), and with confirmed autoimmune disease (C). CCSVI, chronic cerebrospinal venous insufficiency.

results were consistent with former clinical studies (19-21). Moreover, groups with APS and IgG4-RD presented in a relatively younger population than that with SS and had a higher CRP level than that with decreased C3.

The intricate relationship between inflammation (adaptive immune system) and complement pathway (innate immune system) and hemostasis (coagulation and thrombolysis) in immune-complex-mediated autoimmune

Table 4 Spearman correlations among inflammatory markers and age

Variables	Age	PrePLR	PreNLR	PreRDW	IL-6	CRP
(a) CCSVI with non-immunological etiology (n=98)						
PrePLR	−0.094					
PreNLR	−0.008	0.306*				
PreRDW	−0.091	−0.005	0.175			
IL-6	0.090	0.105	0.324*	0.107		
CRP	0.062	0.213*	0.196	0.224*	0.339*	
NSE	−0.028	−0.245*	−0.084	0.070	0.201	0.004
(b) CCSVI with suspected/subclinical autoimmune disease (n=116)						
PrePLR	0.139					
PreNLR	0.137	0.465*				
PreRDW	0.008	−0.231*	−0.045			
IL-6	0.202	0.061	0.275*	0.161		
CRP	0.166	0.249*	0.144	−0.019	0.291*	
NSE	−0.124	−0.029	−0.090	−0.002	−0.101	0.118
(c) CCSVI with confirmed autoimmune disease (n=41)						
PrePLR	−0.194					
PreNLR	0.188	0.148				
PreRDW	0.049	−0.045	0.055			
IL-6	0.388*	−0.117	0.241	0.163		
CRP	0.069	−0.268	−0.031	0.108	0.477*	
NSE	0.095	−0.188	−0.197	−0.065	0.005	0.083

*, statistically significant at $P<0.05$. PreNLR, neutrophil to lymphocyte ratio on admission; PrePLR, platelet to lymphocyte ratio on admission; PreRDW, red blood cell distribution width on admission; CRP, C-reactive protein; NSE, neuron-specific enolase; IL-6, interleukin-6.

diseases was reviewed in several studies (22-24). Based on their common points, we preferred to explain the mechanism from two perspectives: on a physiological level, the coexistence of hemostatic and inflammatory mediators is served as the first line to protect the body from self-antigens and non-self antigens, also termed as "immunothrombosis" or "thromboinflammation" in recent years (22,24). The common structural characteristic of consisting serine proteinases with trypsin-like activity contributes to the precise interplay between the complement system, the coagulation, and fibrinolytic cascade (25). Certain coagulation factors (FXa, thrombin, plasmin) have C3 and C5 convertase activity, contributing to an additional pathway of complement activation (21,26). Complement-derived inflammatory mediators (anaphylatoxin), such as C3a, C4a, and C5a, could increase vascular permeability, activate neutrophils, promote the release of tumor necrosis factor (TNF) from monocyte, upregulate tissue factor (TF), then initiating extrinsic coagulation pathway (27). Platelet can also be activated by the deposition of C4d split fragments, resulting in the facilitation of the coagulation process (20). While on the pathological level, hypocomplementemia is frequently prevalent in patients with APS and SLE, which predominantly relates to the chronic inflammatory process with the basis of the pathophysiology of immune complex-mediated diseases. The overly activated immune system causes the production of self-antigens with unbalanced consumption of complements. With the inverse relationship between complements and their derivatives, anaphylatoxin

(C3a, C4a, and C5a) would further cause hypercoagulation state and even thrombotic events. Meanwhile, complement regulatory factors also decrease due to either attack from autoimmune antibodies, or increased consumption or lower expression of relevant genes (28,29). For example, during the pathogenesis of APS, beta-2 glycoprotein-I (β2-GPI) undergoes a conformational change from a circular form to an elongated form that can bind C3; then, C3 exposes its binding sites, which is more susceptible to degradation by complement factor H (CFH) and factor I (30). Moreover, β2-GPI shares structural similarity to CFH so that antibodies could also combine with CFH (31). With the growing appreciation of complement activation and thrombosis in immune-complex-mediated autoimmune diseases, novel therapies would be fostered, including antiplatelet, anticoagulants as immunomodulators, and targeted molecular therapy toward complements (25,26).

There are several limitations in our study. This is a real-world case-control study of patients with well-defined CCSVI. Patients with a history of autoimmune diseases usually underwent long-term standardized immunomodulation treatment prior to their enrollment, so that the inflammatory biomarker assay tended to be normal despite positive findings of autoimmune antibodies. Therefore, further studies on acute thrombotic events of autoimmune disease are needed. Moreover, our findings indicated the difference in the inflammatory activity among immunological diseases. Based on the complementary relationship between inflammation and thrombosis, we further raised a question on whether the severity of immunological diseases was correlated with increased inflammatory activity and elevated risk of thrombotic events.

Conclusions

Groups with immunological etiology did not show a higher incidence of thrombophilia or increased pro-inflammatory biomarkers. However, patients with non-immunological etiology had a higher baseline level of CRP. Besides, baseline PLR was moderately correlated to NLR and CRP in CCSVI patients with non-immunological etiology and suspected/subclinical autoimmune disease. Therefore, an independent inflammatory process may involve in the pathogenesis of CCSVI. For those with immunological etiology, autoimmune antibodies-mediated vessel wall damage and hypercoagulation state may also play a major role.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of Xuanwu Hospital, Capital Medical University (2019-006), and informed consent was taken from all individual participants.

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Supplementary

Table S1 Detailed information on coagulation and inflammatory kits and instruments

Product name	Company name
CRP (Human) ELISA Kit	R&D Systems
IL-6 ELISA	R&D Systems
Human Enolase 2/Neuron-specific Enolase Quantikine ELISA Kit	R&D Systems
Antinuclear antibodies (ANAs), anti-neutrophil cytoplasmic antibodies (ANCAs), and antiphospholipid antibodies (APLAs) ELISA Kit	R&D Systems
C3, C4 ELISA Kit	R&D Systems
Human fibrinogen ELISA Kit	R&D Systems
REAADS Monoclonal Free Protein S	REAADS
REAADS Protein C Antigen	REAADS
Technozym® D-Dimer ELISA	Technozym
Antithrombin-III ELISA Kit	R&D Systems

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