An association between inflammation and cerebral venous thrombosis: A retrospective study

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Abstract

Background

Evidence is currently accumulating for the role of inflammation in cerebral venous thrombosis (CVT). Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), monocyte/high-density lipoprotein ratio (MHR), and systematic immune-inflammation index (SII) are easily obtainable indicators of systemic inflammations. However, there were few studies on the relationship between them and CVT. Therefore, we aimed to evaluate the connection between the occurrence of CVT and the inflammatory markers described.

Methods

The samples from 150 participants (including 90 CVT and 60 controls) with similar baseline characteristics were collected in this retrospective study. The NLR, PLR, MHR, SII and file records were employed to compare CVT patients with the control group.

Results

The levels of NLR (3.93 [2.27, 7.87] vs. 1.65 [1.31, 2.06], $P < 0.001$), PLR (149.52 [98.39, 198.82] vs. 107.34 [83.31, 129.47], $P < 0.001$), SII (382.45 [273.51, 520.92] vs. 896.84 [559.89, 1591.87], $P < 0.001$) and MHR (0.51 [0.40, 0.64] vs. 0.41 [0.29, 0.53], $P = 0.001$) were significantly higher in the CVT group. After multivariate logistic regression analysis, the SII degree (13.136, [5.675, 30.407], $P < 0.001$) and MHR degree (2.620, [1.123, 6.113], $P = 0.026$) were found as independent predictors of CVT.

Conclusions

NLR, PLR, SII, and MHR may be able to predict the onset of CVT which confirmed that inflammation played an important role in CVT.

Background

Cerebral venous thrombosis (CVT) is a little-known and rare cause (nearly 1%) of stroke that mainly affects the young, especially females [1]. As a report, increased cases of CVT were reported in recent years (12.3–15.7 cases per million people yearly), compared within 2011 (only 2–5 cases per million people) [1–4]. Risk factors can be divided into inflammatory factors (e.g., infection and nonspecific inflammation) and non-inflammatory factors (e.g., hypercoagulability, blood stasis, vascular wall injury, and intracranial hypotension) [5]. Recently, the association between inflammation and CVT has attracted growing attention [6–8].

The neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), monocyte/high-density lipoprotein (HDL) ratio (MHR) and systemic immune-inflammation index (SII = platelets * neutrophils/lymphocytes) were widely studied as inflammation indicators in recent years, considering their objectivity, low cost, effectiveness, and repeatability. So far, NLR, PLR, and SII were found to be prognostic factors for diseases such as different neurologic disorders, malignancies, and deep venous thrombosis (DVT) [9–17]. Besides, decreased HDL levels and increased monocyte counts were also found to be relevant to inflammation, thus MHR was potentially suggested to be a novel inflammatory biomarker [18, 19].

Despite these, the significance of inflammation indicators (NLR, PLR, MHR, and SII) in CVT was poorly investigated. Therefore, our study of NLR, PLR, SII, and MHR in CVT provided a new and cost-effective way of predicting CVT.

1. Methods

1.1 Study population

Ninety patients were newly diagnosed CVT by magnetic resonance venography (MRV), computed tomographic venography (CTV), or conventional digital subtraction angiography in three centers (Zhujiang Hospital of Southern Medical University (2012–2020), the third affiliated hospital of Sun Yat-Sen University (2013–2020) and Shenzhen Baoan People's Hospital (2017–2019)), from 2012 to 2020. Sixty cases of age- and sex-matched individuals admitted to Zhujiang Hospital of Southern Medical University Hospital (2017–2020) for headache and diagnosed with primary headaches were included in the control group. Medical history and medication use were determined. Patients underwent a detailed physical and neurological examination.

Patients and control individuals were excluded if they had the following conditions: arterial stroke, autoimmune disease, hematological diseases, hepatic failure, any inflammatory condition, malignancy, and use of anti-inflammatory medications, antiaggregant and anticoagulants drugs.

1.2 Data collection

Following data of patients with CVT were obtained at baseline in the study: demographics; dates of onset of symptoms and admission, the features of imaging; the National Institutes of Health Stroke Score (NIHSS) and blood test results (i.e. the level of direct bilirubin (DBil), HDL, white blood cell (WBC), red cell distribution width (RDW), mean platelet volume (MPV), monocytes, neutrophils, and lymphocytes. Demographics and blood test results were also collected in the control group.

The severity of CVT on admission was divided into five grades according to NIHSS, with 0 to 1 as degree 1, 2 to 4 as degree 2, 5 to 15 as degree 3, 16 to 20 as degree 4, and over 20 as degree 5. The time from the onset of symptoms to admission was less than 30 days that were defined as an acute-subacute onset, while more than 30 days as a chronic onset.

1.3 Statistical analysis

All statistical analyses were performed by SPSS 20.0 for Windows (IBM, Armonk, N.Y., USA). Quantitative variables with a normal distribution were specified as mean $\pm$ standard deviation and with abnormal distribution were expressed as median with interquartile range (IQR). Categorical variables were specified with number and percentage (%) values. Student's t-test or Mann–Whitney test was used for continuous data, while the χ^2 test was used for categorical data. Student's t-test or Mann–Whitney test and univariate regression analysis were used to verify factors correlated with clinical outcomes. The receiver operating characteristic (ROC) curve was used to demonstrate the sensitivity and specificity of significant variables and the optimal cut-off values for predicting the onset. We obtained optimal cut-off values *via* calculating best Youden index. Factors with $P < 0.05$ in the univariate analysis were entered into a forward multivariable logistic regression analysis. The correlation between inflammation and the severity of CVT was evaluated by Spearman's correlation analysis. All statistical analyses were conducted using the statistical software package SPSS 20.0 for Windows. Two-tailed P -value ≤ 0.05 was considered to indicate a significant difference.

2. Results

2.1 Patients

A total of 90 CVT patients (mean age: 37.83 ± 15.92 years old, sex: 35 females and 55 males) and 60 controls (mean age: 39.17 ± 13.24 years old, sex: 21 females and 39 males) were included in the study. The demographic and clinical characteristics of the patients and controls were summarized in Table 1.

Table 1

Baseline characteristics and laboratory parameters of the study groups and manifestation of CVT

	CVT group n = 90	Control group n = 60	P value
Age, years	37.83 ± 15.92	39.17 ± 13.24	0.579
Female (%)	35 (38.9%)	21 (35%)	0.731
Hypertension (%)	7 (7.8%)	9 (15%)	0.184
Diabetes (%)	2 (2.2%)	3 (5%)	0.389
Alcohol consumption (%)	6 (6.7%)	3 (5%)	0.742
Smoking (%)	8 (8.9%)	8 (13.3%)	0.426
White cells (×10 ³ /μL)	9.92 ± 3.42	6.93 ± 1.88	< 0.001
Platelets (×10 ³ /μL)	242 ± 80	233 ± 58	0.458
Neutrophils (×10 ³ /μL)	6.66 (4.80, 9.51)	3.81 (3.07, 4.64)	< 0.001
Lymphocytes (×10 ³ /μL)	1.59 (1.12, 2.36)	2.27 (1.78, 2.71)	< 0.001
Monocytes (×10 ³ /μL)	0.65 ± 0.27	0.49 ± 0.14	< 0.001
DBil (μmol/L)	4.60 ± 2.33	4.79 ± 2.00	0.61
MPV (fL)	9.98 ± 1.09	10.50 ± 1.08	0.005
HDL (mmol/L)	1.22 ± 0.29	1.24 ± 0.33	0.666
PLR	149.52 (98.39, 198.82)	107.34 (83.31, 129.47)	< 0.001
NLR	3.93 (2.27, 7.87)	1.65 (1.31, 2.06)	< 0.001
MHR	0.55 ± 0.26	0.42 ± 0.17	0.001
SII	382.45 (273.51, 520.92)	896.84 (559.89, 1591.87)	< 0.001
Clinical manifestation (%)			
Headache	69 (76.7)		
Isolated headache	34 (37.8)		
Seizure	23 (25.6)		
Hemiparesis	25 (27.8)		

CVT cerebral venous thrombosis, PLR platelet/lymphocyte ratio, NLR neutrophil/lymphocyte ratio, SII systematic immune-inflammation index, MHR monocyte/high-density lipoprotein ratio.

	CVT group n = 90	Control group n = 60	P value
Aphasia	4 (4.4)		
Mental status disorder	12 (13.3)		
visual complaints	14 (15.6)		
CVT cerebral venous thrombosis, PLR platelet/lymphocyte ratio, NLR neutrophil/lymphocyte ratio, SII systematic immune-inflammation index, MHR monocyte/high-density lipoprotein ratio.			

2.2 Inflammation between patients with CVT and controls

Compared with the controls, the CVT patients had higher NLR (3.93 [2.27, 7.87] vs. 1.65 [1.31, 2.06], $P < 0.001$), PLR (149.52 [98.39, 198.82] vs. 107.34 [83.31, 129.47], $P < 0.001$), SII (382.45 [273.51, 520.92] vs. 896.84 [559.89, 1591.87], $P < 0.001$), MHR (0.51 [0.40, 0.64] vs. 0.41 [0.29, 0.53], $P = 0.001$) and lower MPV (9.98 ± 1.09 vs. 10.50 ± 1.08 , $P = 0.005$) (Table 1).

2.3 Inflammation indicators and the onset of CVT

The ROC curves were applied to investigate whether NLR, PLR, SII, and MHR could be used to predict the onset of CVT (Fig. 1). The results showed that the predicting power of baseline serum NLR, PLR, SII, and MHR on the onset with an area under the curve value of 0.826, 0.702, 0.827, 0.657 (all $P < 0.05$), respectively (Table 2). The optimal cutoff of NLR, PLR, SII and MHR is 2.14 (sensitivity 0.789, specificity 0.800), 147.11 (sensitivity 0.533, specificity 0.867), 496.07 (sensitivity 0.844, specificity 0.75), and 0.42 (sensitivity 0.711, specificity 0.600), respectively. To further estimate the baseline inflammation status on predicting the onset of CVT, the level of SII and MHR was divided into two degrees (SII < 496 and ≥ 496 ; MHR < 0.42 and ≥ 0.42) according to the optimal cutoff value of those indicators. The multivariate logistics analysis found that degree of SII and MHR were significantly associated with the onset of CVT (SII degree, adjusted OR 13.136, 95% CI 5.675–30.407, $P < 0.001$; MHR degree, adjusted OR 2.620, 95% CI 1.123–6.113, $P = 0.026$) (Table 3). The ROC curve revealed the predicting power of the model with an area under the curve value of 0.847 ($P < 0.001$, 95% CI 0.779–0.916) (Fig. 2).

Table 2
The predicting power of inflammation indicators in CVT.

	Cut off	Sensitivity	Specificity	AUC	95% CI(AUC)	P value
PLR	147.11	0.544	0.867	0.702	0.617–0.786	< 0.001
NLR	2.14	0.789	0.800	0.826	0.757–0.896	< 0.001
MHR	0.42	0.689	0.6	0.657	0.570–0.745	0.001
SII	496.07	0.844	0.75	0.827	0.758–0.896	< 0.001

Table 3
Multivariate regression analysis of CVT and inflammation indicators

	Univariate regression analysis		Multivariable regression analysis	
	OR (95% CI)	Pvalue	OR (95% CI)	Pvalue
MPV	0.645 (0.468, 0.889)	0.007	-	-
SII degree	16.286 (7.199, 36.841)	< 0.001	13.136 (5.675, 30.407)	< 0.001
MHR degree	3.100 (1.570, 6.120)	0.001	2.620 (1.123, 6.113)	0.026

2.4 Inflammation indicators and the severity of CVT

All 90 patients were divided into five groups based on NHISS on admission. Correlation analysis demonstrated that the level of NLR ($r = 0.369$, $P < 0.001$), PLR ($r = 0.242$, $P = 0.022$) and SII ($r = 0.329$, $P < 0.001$) were positively associated with baseline NHISS. Correlation analysis did not reflect the correlation between the number of segments involved and the level of NLR, PLR, SII or MHR (Fig. 3).

2.5 Inflammation indicators and stages of CVT

The levels of NLR, PLR and SII in the acute-subacute stage were higher compared with those in the chronic stage (NLR, 4.6 [2.88, 8.46] vs. 2.25 [1.61, 3.61], $P < 0.001$; PLR, 157.61 [98.64, 225.81] vs. 147.95 [113.20, 180.28], $P = 0.362$; SII, 1113.45 [587.32, 1824.46] vs. 610.98 [386.02, 988.48], $P = 0.004$) (Fig. 4).

3. Discussion

In recent years, CVT has attracted more attention to the morbidity increasing [1]. It presents various neurological signs and symptoms, and its common clinical presentations (e.g., headache, seizures, focal neurological deficits, altered consciousness, and papilledema) can present in isolation or association with other symptoms [20]. Headache, the most common symptom in CVT, was present in nearly 90% of patients in the International Study on Cerebral Vein and Dural Sinus Thrombosis [21]. Similar headache frequency was reported in our study and 37.8% CVT patients presented isolated headache (Table 1). For this reason, patients with primary headaches were selected as the control group.

Due to complex and nonspecific clinical findings of CVT, delay in diagnosis and misdiagnosis frequently occurred. It's reported that an initial misdiagnosis of CVT could occur in 73% of patients [22] and delays in diagnosis for over 10 days could happen in 40% of patients admitted to the hospital [23]. A median delay of 7 days (mean $\pm$ SD, 18.3 $\pm$ 59.4 days) was reported [24]. Even though they received standard anticoagulation, the deterioration of neurological function was hard to be reversed or stopped [25]. Over 50% of the discharged patients complained about headache and 20–30% complained about depression, concentration problems, linguistic difficulties, or cognitive impairment, which had an impact on their psychosocial functioning and employment status [26–28]. Therefore, finding an accurate and accessible

indicator to achieve prompt diagnosis is essential and important since it might reduce the incidence of death and long-term sequelae [29].

Up to now, D-dimer is the only recognized blood index related to CVT. However, there are some shortages. First, it was considered to help excluding CVT for its low positive predictive value [1]. Second, CVT patients with less clot burden may be particularly at risk of false-negative results [30]. Furthermore, a number of different D-dimer assays are available with variable test performance characteristics [1]. Therefore, it is expected to access a better index from routine blood work.

A close link between inflammation and thrombosis has been detected in previous studies [31, 32]. Although the pathophysiology of CVT has not been defined yet, the evidence is currently accumulating for the role of inflammation in CVT. Gu et al. [7] have demonstrated that recombinant human soluble thrombomodulin reduced infarct volume in a model of CVT, *via* inhibiting inflammation by blocking high mobility group box 1 (HMGB1) binding to a receptor for advanced glycation end-products. Rashad and Nagai et al. [6, 33] found intense inflammatory cell infiltration on the infarct area and high level in several inflammation indicators in the early stage of CVT. Also, previous clinical studies have found inflammation indicators (e.g., MPV, RDW, CRP, ESR, and bilirubin) increasing in patients with CVT [8, 34, 35], potentially hinting the correlation between inflammation and the severity and outcome of CVT. Consistent with the previous results, the high levels of WBC, monocyte, neutrophils, and platelets were found in CVT patients compared with the control group. Incompatibly, the MPV value was found within the normal range with a lower value in the CVT group. Several studies believed that MPV is not able to reflect inflammation properly, and that could decrease in the acute stage [36]. Based on the results of this study, it is hard to define whether a lower MPV level resulted from a low number of participants or the pathophysiological properties of CVT. All of these pathologic processes, well-known risk factors, and laboratory findings of CVT were associated with an inflammatory state. Regardless of the direction of the relationship, it was believed to have a significant correlation between inflammation and CVT.

With the growing understanding of inflammation, NLR, PLR, SII, and MHR have been widely investigated in malignancies, inflammatory diseases, cardiovascular and cerebrovascular diseases. These indicators are more stable than individual blood parameters, which may be altered by several variables (e.g., dehydration, overhydration, and blood specimen handling) [37]. Indicating the balance of the neutrophils (the active component of the inflammation) with the lymphocytes (the regulatory and protective component), NLR was found to be a good prognostic factor in functional outcomes and mortality in patients with severe traumatic brain injury [38]. Zeng et al. [17] demonstrated that both NLR and PLR can be used to predict the diagnosis and prognosis of nasopharyngeal carcinoma [17]. Many studies revealed that DVT improves the levels of NLR and PLR [11, 39]. As for SII, considering together neutrophil, platelet, and lymphocyte, it suggested the balance between host systemic inflammation and coagulation status comprehensively, thus it was used in predicting outcomes of malignancies and ischemic stroke [15–17, 40, 41]. Monocytes were reported to involve in inflammatory and pro-thrombotic pathways, while HDL interferes with the pro-inflammatory effects of monocytes by inhibiting the migration of macrophages [42–45]. Therefore, it assumed that MHR was a reliable and more comprehensive indicator of

inflammation. Indeed, it has been reported that higher MHR was associated with poor outcome of cardiovascular diseases and renal dysfunction [18, 19, 45]. For this reason, we hypothesized the association between SII, NLR, PLR, and MHR with the onset of CVT. Our study confirmed that the levels of NLR, PLR, SII, and MHR were significantly higher in CVT patients. ROC curves were analyzed and showed a satisfying result. The area under the ROC curve (AUC) of NLR, PLR, SII, and MHR was 0.826, 0.702, 0.827, and 0.657, respectively, suggesting the power of SII, NLR, and PLR in predicting CVT. NLR and SII yielded a sensitivity of 0.780 and 0.844 and a specificity of 0.800 and 0.750, respectively. Basing on the multivariable regression analysis, the degrees of SII and MHR remained as independent indicators of CVT that the AUC was 0.847 representing a good predicting power. Therefore, NLR, PLR, SII, and MHR could help clinicians to suspect CVT, especially among the patients with unexplained headache and a normal plain CT, then decide which patients require MRI/MRV immediately for confirmation of the diagnosis. These would help to shorten the time from the onset of symptoms to diagnosis and reduce misdiagnosis.

Moreover, the results of this study found that the levels of SII, NLR, and PLR were positively correlated with the baseline NHISS degree, indicating the vital role of inflammation in the progression of CVT. However, there was no difference in inflammation indicators among patients with different numbers of cerebral venous sinus involved. In another word, SII, NLR, and PLR levels were not correlated with the anatomic extent of thrombosed sinuses, which enable them to better identify patients with lighting clot burden than D-dimer [30].

Furthermore, the NLR and SII levels were distinctly higher in the acute-subacute stage of CVT, which was consistent with the results of another study [34]. Wang et al. [34] demonstrated that inflammation may develop soon after CVT and gradually decrease during the course. Inflammation may affect mainly during the early stage. The previous study on DVT mouse model found that neutropenic mice developed no or significantly smaller thrombi compared with controls [32], but it needed further research to confirm whether an early intervention of inflammation is benefited for CVT patients.

The results of this study focused on the differences between CVT patients and primary headache patients, which might help more in clinical practice since CVT patients presenting isolated headache were more likely to be at risk of delay in diagnosis and misdiagnosis. However, there were still some limitations. First, there was not enough study population because of the low morbidity of CVT. Second, as a retrospective study, there was some missing data and only baseline values were analyzed rather than the temporal trend. Third, it cannot explain whether the milieu of increased inflammation was present before the onset of disease and caused the thrombus or it was a response to the thrombus.

4. Conclusion

NLR, PLR, SII, and MHR levels were remarkably higher in CVT patients, which can be utilized to predict the onset. Inflammation exerts a critical role in CVT and may be a promising therapeutic target for CVT. Further prospective randomized controlled study and animal experiments are needed to verify our findings and define the underlying mechanism of inflammation acting on CVT.

Abbreviations

AUC	area under the ROC curve
CVT	cerebral venous thrombosis
DBil	direct bilirubin
ESR	erythrocyte sedimentation rate
HMGB1	high mobility group box 1
HDL	high-density lipoprotein
MHR	monocyte/high-density lipoprotein ratio
MPV	mean platelet volume
NLR	neutrophil/lymphocyte ratio
PLR	platelet/lymphocyte ratio
RDW	red cell distribution width
ROC	receiver operating characteristic
SII	systematic immune-inflammation index
WBC	white blood cell

Declarations

Ethics approval and consent to participate

This study was approved both by the Ethics Committee of Zhujiang Hospital and the Ethics Committee of the Third Affiliated Hospital of Sun Yat-Sen University. All patients verbally consented to the scientific use of their clinical data.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Not applicable.

Authors' contributions

WQ planned the experiment and enabled the realization of the whole project. ZX and DR analyzed the data, including statistical tests, figures, and table production. LY, LH and HQ helped with selecting the samples. OW contributed to the sample measurements. TY corrected the draft of the manuscript. ZX and DR wrote the manuscript. All authors read and approved the final manuscript.

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Figures

Diagonal segments are produced by ties.

Figure 1

Comparison of ROC curves of NLR, PLR, SII, and MHR values for predicting the presence of CVST. PLR, platelet/lymphocyte ratio; NLR, neutrophil/lymphocyte ratio; SII systematic immune-inflammation index; MHR monocyte/high-density lipoprotein ratio.

Figure 2

ROC curve for the regression model on predicting the onset of CVT. CVT, cerebral venous thrombosis; AUC, area under the curve; CI, confidence interval.

Figure 3

The correlation between inflammation indicators and the severity of CVT. PLR, platelet/lymphocyte ratio; NLR, neutrophil/lymphocyte ratio; SII, systematic immune-inflammation index; MHR, monocyte/high-density lipoprotein ratio.

Figure 4

The correlation between inflammation indicators and CVT stage. PLR, platelet/lymphocyte ratio; NLR, neutrophil/lymphocyte ratio; SII, systematic immune-inflammation index; MHR, monocyte/high-density lipoprotein ratio.