Inflammatory biomarkers are correlated with thrombus burden in cerebral venous sinus thrombosis

Biomarcadores inflamatórios estão relacionados à carga trombótica na trombose venosa cerebral

Aslı Yaman Kula[1] Ahmet Volkan Kurtoğlu[1] Vildan Güzel[1] Serdar Balsak[2] Ayşegül Yabacı Tak[3] Talip Asil[4]

[1] Bezmialem Foundation University, Faculty of Medicine, Department of Neurology, Istanbul, Turkey.
[2] Bezmialem Foundation University, Faculty of Medicine, Department of Radiology, Istanbul, Turkey.
[3] Bezmialem Foundation University, Faculty of Medicine, Department of Biostatistics, Istanbul, Turkey.
[4] Memorial Hizmet Hospital, Department of Neurology, Istanbul, Turkey.

Address for correspondence Aslı Yaman Kula (email: dr.asliyaman@gmail.com)

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Abstract

Background Increasing evidence suggests that inflammatory biomarkers play a significant role in cerebral venous sinus thrombosis (CVST). The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) are related to thrombotic conditions and indicators of systemic inflammation.

Objective To analyze the correlation between inflammatory biomarkers and the extent of thrombus, determined by the CVST-Score.

Methods A total of 40 patients with CVST (24 female subjects; 60%) and 40 age- and sex-matched healthy controls were retrospectively evaluated. Inflammatory biomarkers, including C-reactive protein (CRP), PLR, NLR, MLR, and the CVST-Score, were recorded to assess the relationship between biomarkers and thrombus burden. The patients were grouped according to symptom duration (group 1: 0–3 days; group 2: 4–7 days; and group 3: 8–30 days) to compare biomarker levels.

Results The CRP, NLR, and PLR were significantly higher in the CVST group ($p < 0.001$; $p = 0.003$; $p = 0.014$ respectively). The NLR and PLR presented a significant positive correlation with the CVST-Score ($p = 0.003$, $r = 0.464$; $p = 0.040$, $r = 0.326$ respectively). The NLR was significantly higher in group 1 compared with groups 2 and 3 ($p = 0.016$ and $p = 0.014$ respectively). In group 1, there was a stronger positive correlation between the CVST-Score and the NLR ($p = 0.026$, $r = 0.591$) and the PLR ($p = 0.012$, $r = 0.648$). The multiple linear regression analysis revealed that the NLR is a key factor in predicting the CVST-Score ($p = 0.019$).

Keywords
- Sinus Thrombosis, Intracranial
- Biomarkers
- Inflammation

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Conclusion The NLR and PLR are associated with thrombus burden in CVST, especially in patients admitted to the hospital in the early stages. The NLR is an independent factor to predict the thrombus burden in CVST.

Resumo

Antecedentes Há evidências crescentes de que biomarcadores inflamatórios desempenham um papel importante na trombose venosa cerebral (TVC). A razão neutrófilo-linfócito (NLR), a razão plaqueta-linfócito (PLR) e a razão monócito-linfócito (MLR) estão relacionadas a condições trombóticas e são indicadores de inflamação sistêmica.

Objetivo Analisar a correlação entre NLR, PLR, MLR e a extensão do trombo, determinada pelo escore de TVC.

Métodos Avaliamos retrospectivamente 40 pacientes com TVC (24 mulheres; 60%) e 40 controles pareados por idade e sexo. Biomarcadores inflamatórios, incluindo proteína C reativa (PCR), PLR, NLR, MLR e escore de TVC, foram registrados para avaliar a relação entre biomarcadores e carga trombótica. Os pacientes foram agrupados de acordo com a duração dos sintomas (grupo 1: 0–3 dias; grupo 2: 4–7 dias; e grupo 3: 8–30 dias) para a comparação dos níveis de biomarcadores.

Resultados A PCR, a NLR e a PLR foram significativamente maiores no grupo com TVC ($p < 0{,}001$; $p = 0{,}003$; e $p = 0{,}014$, respectivamente). A NLR e a PLR apresentaram correlação positiva significativa com o escore de TVC ($p = 0{,}003$, $r = 0{,}464$; e $p = 0{,}040$, $r = 0{,}326$, respectivamente). A NLR foi significativamente maior no grupo 1 em comparação aos grupos 2 e 3 ($p = 0{,}016$ e $p = 0{,}014$, respectivamente). No grupo 1, houve correlação mais forte entre o escore de TVC e a NLR ($p = 0{,}026$, $r = 0{,}591$) e a PLR ($p = 0{,}012$, $r = 0{,}648$). A análise de regressão linear múltipla identificou a NLR como fator-chave na predição do escore de TVC ($p = 0{,}019$).

Conclusão A NLR e a PLR estão associadas à carga trombótica na TVC, especialmente em pacientes admitidos precocemente, e a RNL é um fator independente na previsão da carga trombótica.

Palavras-chave
- Trombose dos Seios Intracranianos
- Biomarcadores
- Inflamação

INTRODUCTION

Cerebral venous sinus thrombosis (CVST) is a rare cause of stroke that only occurs in 0.5% to 1% of all stroke cases. It typically affects young and middle-aged individuals,[1] with a higher incidence in women and in developing countries, particularly during the postpartum period.[2] Clinically, it can cause a wide range of symptoms, including seizures, neurological deficits, and increased intracranial pressure (ICP).[3] It can occur due to inflammatory causes, such as infection and non-specific inflammation, or non-inflammatory causes, such as hypercoagulability, venous stasis, vascular wall injury, and intracranial hypotension.[4]

The inflammatory mechanisms associated with CVST have been an important subject of molecular studies[5,6] for many years, and it has been revealed that inflammation plays a predisposing role in the formation and development of CVST.[7] The neutrophil-to-lymphocyte ratio (NLR)[1,4,8,9] and the platelet-to-lymphocyte ratio (PLR)[4,9] are emerging inflammatory biomarkers used in patients with CVST. The monocyte-to-lymphocyte ratio (MLR) has been identified as a predictor biomarker for portal vein thrombosis[10] and deep vein thrombosis.[11,12] While a low MLR has been shown to be an indicator of poor prognosis in CVST,[13] there are not sufficient studies specifically focusing on the MLR.

The superior sagittal sinus (SSS) and the right/left lateral sinuses (LSs) are the most commonly affected venous sinuses in CVST. The cavernous sinus, the straight sinus, and the deep venous sinuses are rarely affected.[14] Various scoring systems have been developed to assess the thrombus burden in CVST.[3,15,16] Although the existing scoring methods roughly define thrombus burden by identifying the location and number of occluded sinuses, they do not differentiate among the thrombus burdens of different segments or evaluate the dominant transverse sinus (TS). The newly-developed CVST-Score can accurately determine the thrombus burden in each segment and provide information on the dominant TS.[17]

Despite the increasing research on inflammatory biomarkers in CVST in recent years, the relationship between thrombus burden and the NLR, PLR, and MLR remains unclear. Therefore, in the present study, we aimed to investigate the relationship between these inflammatory biomarkers and thrombus burden evaluated using the CVST-Score.

METHODS

The present study involved the retrospective evaluation of the data of 40 patients diagnosed with CVST for the first time

using cranial magnetic resonance imaging (MRI) and contrast-enhanced magnetic resonance venography (MRV) at Bezmialem Foundation University's Faculty of Medicine Hospital from January 2014 to January 2022. A total of 40 age- and sex-matched patients who presented with a diagnosis of primary headache and were admitted to the neurology outpatient clinic were included in the sample as the control group. The study was approved by the Clinical Research Ethics Committee of the university (approval number: E-54022451–050.05.04–104344; date: April 5, 2023) and conducted in accordance with the principles of the Declaration of Helsinki.

All cranial MRI and MRV scans were performed on the Magnetom Aera 1.5T system (Siemens Healthineers, Erlangen, Germany) using a 24-channel head coil. The analyzed sequences consisted of 5-mm sections. Patients without MRI and MRV scans at the time of the diagnosis were not included in the study. The other exclusion criteria were defined as follows: arterial stroke, acute myocardial infarction, infection, autoimmune diseases, hematological disorders, liver failure, peripheral vascular diseases, any inflammatory conditions, malignancy, use of anti-inflammatory, antiplatelet, anticoagulant, or lipid-regulating medications, incomplete clinical data, and insufficient imaging data.

Collected data

Demographic data, including age, gender, onset-to-door time, clinical symptoms at the time of diagnosis (confusion, headache, nausea and vomiting, visual deficits, tinnitus, dizziness, diplopia, focal neurological deficits, and seizures), risk factors (such as hypertension, diabetes mellitus, pregnancy, and postpartum period), and the presence of parenchymal lesions (venous infarction or hemorrhage), were recorded.

The time from symptom onset to diagnosis was recorded in days, and the patients with CVST were classified into 3 groups: group 1 (onset-to-door time: 0–3 days), group 2 (onset-to-door time: 4–7 days), and group 3 (onset-to-door time: 8–30 days).

Serum inflammatory biomarkers

Biomarkers such as the level of C-reactive protein (CRP), absolute neutrophil count, absolute lymphocyte count, absolute monocyte count, absolute platelet count, NLR, PLR, and MLR were evaluated from peripheral venous blood samples obtained at the time of presentation.

CVST assessment and scoring

The diagnosis of CVST was established based on clinical findings, such as headache, focal neurological deficits, compatible signs of ICP, seizures, or encephalopathy, along with confirmatory imaging findings, including those of the cranial MRI and contrast-enhanced MRV scans. Thrombus burden was assessed using the CVST-Score developed by Wang et al.[17]

The CVST-Score was calculated by dividing the cerebral venous sinuses into 15 segments, including the SSS, with a weight of 3, the TS, with a weight of 2, the sigmoid sinus (SS), with a weight of 2 for each side, and the straight sinus, torcular Herophili, and intracranial jugular veins (IJVs), with a weight of 1 for each side. Each segment was scored individually. The CVST-Score was calculated as follows:

- Absence of thrombus: 0;
- Presence of thrombus $\leq$ 50%: 1 point;
- Presence of thrombus 51% to 99%: 2 points; and
- Presence of thrombus = 100%: 3 points.

Since unilateral dominance is commonly observed in the TS, the maximum cross-sectional area of each TS was manually measured. The weighted drainage of the right TS (TS_R) was calculated using the formula $W_R = CS_R / (CS_L + CS_R)$, in which CS represents the maximal cross-sectional area of the TS. The exact process was repeated for the left TS (TS_L). For the TS_R, the final score was determined using the following formula:

$$A_R = (\text{total } TS_R \text{ score} + \text{total } SS_R \text{ score} + \text{total } IJV_R \text{ score}) \times W_R$$

After the TS_L was obtained using the same formula, a CVST-Score of 0 to 30 was calculated as follows:

$$\text{CVST-Score} = \text{total SSS score} + \text{total straight sinus score} + \text{total torcular Herophili score} + A_R + A_L$$

Statistical analysis

We analyzed the data using IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY, United States) software, version 26. The continuous variables were expressed as mean $\pm$ standard deviation and median with minimum and maximum values. The categorical variables were expressed as frequency and percentage values. Normality was assessed using the Shapiro-Wilk test. We used an independent-samples *t*-test and the Mann-Whitney U test to analyze quantitative independent data. The Chi-squared test was applied for the categorical variables. The Kruskal-Wallis test was conducted for group comparisons, and the Spearman correlation test was used to assess the relationship between the investigated biomarkers and the CVST-Score for non-parametric continuous variables. In the subgroup analyses to evaluate confounding factors, the Mann-Whitney U-test was performed. The receiver operating characteristic (ROC) curve was used to determine the optimal cut-off value for each inflammatory biomarker, applying the maximum value of the Youden index (J). The MedCalc statistical software (MedCalc Software Ltd, Ostend, Belgium), version 12.3, was used for the ROC curve analysis. Multiple linear regression was then used to investigate the relationship between the CVST-Score and potential independent factors. Variables that were significant in the univariate analysis were included in this model. The statistical significance level was accepted as 0.05.

RESULTS

The study included 80 participants, 40 with CVST (24 female [60%] and 16 male subjects [40%] with a mean age of

Table 1 Demographic characteristics of all participants

Characteristics	CVST group: n = 40	Control group: n = 40	*p*
Female: n (%)	24 (60)	24 (60)	1[a]
Age (years): mean ± SD	39.67 ± 14.59	39.7 ± 14.55	0.994[b]
Hypertension: n (%)	11 (27.5)	10 (25)	0.827[a]
Diabetes mellitus: n (%)	4 (10)	6 (15)	0.527[a]
Alcohol consumption: n (%)	7 (17.5)	5 (12.5)	0.564[a]
Smoking: n (%)	10 (25)	6 (15)	0.317[a]
Pregnancy: n (%)	2 (5)	0 (0)	–
Postpartum period: n (%)	5 (12.5)	0 (0)	–

Abbreviations: CVST, cerebral venous sinus thrombosis; SD, standard deviation.
Notes: [a]Chi-squared test. [b]Independent-samples *t*-test.

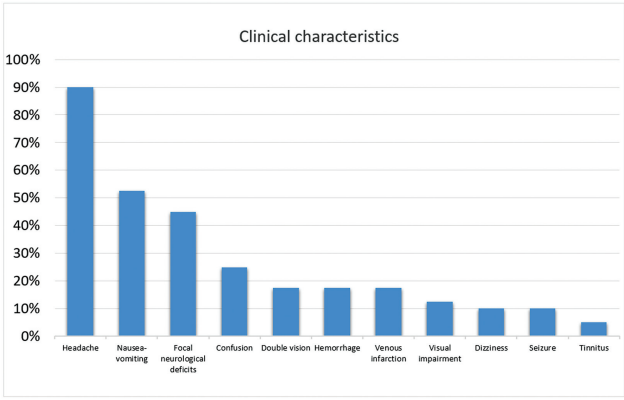


Figure 1 Clinical findings of the cerebral venous sinus thrombosis (CVST) group.

39.67 ± 14.59 years) and 40 age- and sex-matched healthy controls. In total, 2 (5%) patients were pregnant, and 5 (12.5%) were in the postpartum period (►**Table 1**). The typical clinical presentation included headache in 36 patients (90%), nausea in 21 patients (52.5%), and focal neurological deficits in 18 patients (45%). The MRI findings showed hemorrhage in 7 patients (17.5%) and venous infarction in 7 (17.5%) subjects as well (►**Figure 1**). In the CVST group, the median onset-to-door time was of 4.5 (range: 1–30) days, and the mean CVST-Score was of 8.33 ± 5.53 points.

The platelet count, monocyte count, and MLR did not significantly differ between the CVST and control groups. The CRP level, neutrophil count, and lymphocyte count were significantly higher in the CVST group ($p < 0.001$; $p = 0.004$; and $p = 0.027$ respectively). The NLR and PLR were also significantly higher in patients with CVST than in the controls ($p = 0.003$ and $p = 0.014$ respectively) (►**Table 2**).

Among the 18 patients with focal deficits, motor deficits were observed in 14 (35%), while 4 (10%) patients presented abducens paralysis. The mean values of the NLR, PLR, and CRP for the 4 patients (10%) who presented with seizures did not show a statistically significant difference compared with those without a history of seizures ($p = 0.964$; $p = 0.528$; and $p = 0.279$ respectively). Similarly, there was no statistically significant difference between the mean NLR, PLR, and CRP values of patients with venous infarction detected on MRI and those without infarction ($p = 0.735$; $p = 0.488$; and $p = 0.383$ respectively). Furthermore, there was no statistically significant difference in the mean NLR, PLR, and CRP values between cases with parenchymal hemorrhage and those without ($p = 0.310$; $p = 0.510$; and $p = 0.957$ respectively). No statistically significant relationship was found between patients with any other factors (such as hypertension, diabetes mellitus, pregnancy, postpartum period, and seizures) and those without, in terms of the mean NLR, PLR, and CRP values ($p > 0.05$).

The optimal cut-off value of each statistically significant inflammatory biomarker was as follows: CRP – 1.61; neutrophil count – 5.64×10^9/L; lymphocyte count – 1.710^9/L; NLR –3.65; and PLR – 157.89 (►**Table 3**).

In the correlation analysis, the neutrophil count ($p = 0.009$, $r = 0.410$), NLR ($p = 0.003$, $r = 0.464$), and PLR ($p = 0.040$, $r = 0.326$) presented a significant positive correlation with the CVST-Score. The lymphocyte count ($p = 0.012$, $r = -0.393$) presented a significant negative correlation with the CVST-Score.

To analyze inflammatory biomarkers according to the onset-to-door time, we divided the patients with CVST into three groups. The NLR was significantly higher in group 1 ($n = 14$; 35%) when compared with group 2 ($n = 10$; 25%) and group 3 ($n = 16$; 40%) ($p = 0.016$ and $p = 0.014$ respectively) (►**Figure 2**). We also analyzed the correlation between inflammatory biomarkers and the CVST-Score according to the onset-to-door time. We observed a significant positive correlation between the CVST-Score and the NLR ($p = 0.026$, $r = 0.591$) and PLR ($p = 0.012$, $r = 0.648$) in group 1 (►**Table 4**).

The multiple linear regression analysis included the NLR and PLR rather than the neutrophil or lymphocyte counts, since these biomarkers were already used to calculate the NLR and PLR. According to the results, the NLR successfully predicted the CVST-Score (►**Table 5**).

When patients with confounding factors such as hemorrhage, venous infarction, and seizures were compared with others, the NLR and PLR values of the patients with hemorrhage did not differ significantly from those of the subjects

Table 2 Laboratory findings of all participants

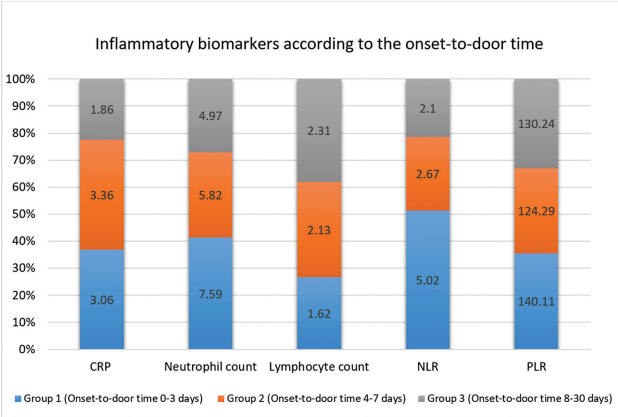
Inflammatory biomarkers	CVST group: n = 40	Control group: n = 40	*p*
CRP (mg/L): median (min–max)	2.70 (0.02–41.03)	0.44 (0.20–4.41)	< **0.001**[a]
Platelet ($\times 10^9$/L): median (min–max)	269 (143–565)	250.50 (114–426)	0.548[a]
Neutrophil ($\times 10^9$/L): median (min–max)	5.87 (0.99–18.75)	4.44 (1.69–9.28)	**0.004**[a]
Lymphocyte ($\times 10^9$/L): mean ± SD	2.09 ± 0.74	0.44 ± 0.63	**0.027**[b]
Monocyte ($\times$ 10^9/L), mean ± SD	0.64 ± 0.26	0.61 ± 0.17	0.611[b]
NLR: median (min–max)	2.88 (0.92–21.96)	2.08 (0.77–3.65)	**0.003**[a]
PLR: median (min–max)	131.78 (57.50–391.74)	107.45 (42.29–191.52)	**0.014**[a]
MLR: median (min–max)	0.28 (0.08–1)	0.25 (0.13–0.44)	0.071[a]

Abbreviations: CRP, C-reactive protein; CVST, cerebral venous sinus thrombosis; max, maximum; min, minimum; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SD, standard deviation.
Notes: [a]Mann-Whitney U test. [b]Independent-samples *t*-test. *p* value less than 0.05 is considered to be statistically significant.

Table 3 Results of the ROC curve analysis to determine the optimal cut-off value of each investigated parameter in the prediction of CVST

	Optimal cut-off value	AAUC	95%CI		Sensitivity	Specificity	*p*
			Lower limit	Upper limit			
CRP	1.61	0.760	0.651	0.848	65	80	< **0.001**
Neutrophil count	5.64 $\times$ 10^9/L	0.686	0.572	0.785	60	70	**0.018**
Lymphocyte count	1.71 $\times$ 10^9/L	0.635	0.520	0.740	37.50	92.50	**0.031**
NLR	3.65	0.680	0.566	0.779	68	97.50	**0.003**
PLR	157.89	0.650	0.534	0.752	70	95	**0.001**

Abbreviations: 95%CI, 95% confidence interval; AUC, area under the curve; CRP, C-reactive protein; CVST, cerebral venous sinus thrombosis; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; ROC, receiver operating characteristic.
Notes: *p*-value less than 0.05 is considered to be statistically significant.



Abbreviations: CRP, C-reactive protein; CVST, cerebral venous sinus thrombosis; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio. Note: Continuous variables are presented as median values.
Figure 2 Comparison of inflammatory biomarkers between the CVST groups formed according to the onset-to-door time.

without hemorrhage ($p = 0.310$ and $p = 0.957$ respectively). There was no significant difference between the NLR and PLR values of patients with venous infarction and of those without it ($p = 0.735$ and $p = 0.383$ respectively). No significant difference was observed between the NLR and PLR values of patients presenting with and without seizures ($p = 0.964$ and $p = 0.279$ respectively).

DISCUSSION

It is well known that inflammation plays a crucial role in arterial stroke.[18] After ischemic stroke, brain tissue rapidly activates proinflammatory pathways due to oxygen and glucose deprivation, releasing cytokines, chemokines, and activating adhesion molecules. This leads to the swift accumulation of neutrophils and monocytes at the injury site, hindering microvascular perfusion by blocking cerebrovascular microvessels.[19] Lymphocytes play a significant role in determining the neuroinflammatory outcome as a subset of leukocytes, while platelets are critical in acute arterial thrombosis following plaque rupture, speeding up fibrin formation.[20] The NLR, PLR, and MLR are biomarkers that can indicate inflammation and are calculated using the counts of lymphocytes, neutrophils, platelets, and monocytes in venous blood samples. Multiple meta-analyses and studies[21–24] have shown the association of the NLR and PLR with prognosis in patients with ischemic stroke. Furthermore, elevated MLRs have been found in the thrombus analysis of cryptogenic stroke patients.[25]

Table 4 Correlation between inflammatory biomarkers and the CVST-Score according to the onset-to-door time

	CVST groups (onset-to-door time)					
Inflammatory biomarkers	*Group 1 (0–3 days)*		*Group 2 (4–7 days)*		*Group 3 (8–30 days)*	
	p	*rho*	*p*	*rho*	*p*	*rho*
CRP	0.493	-0.200	0.934	-0.030	0.274	0.291
Neutrophil count	0.135	0.420	0.580	0.200	0.460	0.199
Lymphocyte count	**0.026***	-0.592	0.327	0.347	0.311	-0.271
NLR	**0.026***	0.591	0.489	-0.248	0.374	0.238
PLR	**0.012***	0.648	0.777	-0.103	0.405	0.224

Abbreviations: CVST, cerebral venous sinus thrombosis; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; rho, Spearman correlation coefficient.
Notes: *p* value less than 0.05 is considered to be statistically significant.

Table 5 Multiple linear regression model for the CVST-Score

CVST-Score	β	SE	95%CI	*p*
CRP	-0.105	0.087	-0.282:0.072	0.236
NLR	0.561	0.228	0.099:1.023	**0.019**
PLR	0.015	0.013	-0.012:0.042	0.273

Abbreviations: 95%CI, 95% confidence interval; CRP, C-reactive protein; CVST, cerebral venous sinus thrombosis; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SE, standard error; β, regression coefficient.
Note: Overall significance of the model: $p = 0.0016$; method: enter. *p* value less than 0.05 is considered to be statistically significant.

Recent studies indicate that, as in arterial stroke, inflammation contributes significantly to the development of venous thromboembolism by inducing hypercoagulability and damaging the endothelium.[26] While platelets are primarily responsible for arterial thrombosis,[20,27] they also contribute to the propagation of deep vein thrombosis (DVT). A mouse model revealed that monocytes, neutrophils, and platelets collaborated in the response to disturbed blood flow, linking inflammation and venous thrombosis,[27] and the coagulation system was triggered through the induction of the tissue factor after the onset of inflammation.[26] A recent review by Hu et al.[28] established the significant role of microglia, astrocytes, and neutrophils in the pathophysiology of CVST. Clinical studies[1] have revealed that inflammatory biomarkers, specifically the NLR, are associated with CVST, and elevated NLRs reflect a poor prognosis. In a retrospective study[4] evaluating 90 patients with CVST, the NLR and PLR were found to be helpful in diagnosing CVST. Similarly, a prospective study by Tekesin and Tunç[9] found that the CRP level, the NLR, and the PLR were significantly higher in the CVST group than in the control group. Our analysis also demonstrated significantly elevated CRP levels and NLR and PLR values in the presence of CVST, while the MLR did not differ between the two groups.

Although studies have revealed an association between inflammatory biomarkers and CVST, no study has specifically examined the relationship between thrombus severity and inflammatory processes in patients with CVST. Various scoring systems have been developed to assess the thrombus burden in CVST. Ferro et al.[29] used the cerebral venous occlusion score to evaluate the effect of anticoagulants on post-CVST recanalization. In this scoring system, a score of 1 is assigned for complete occlusion and of 0 for no occlusion or partial occlusion for each dural sinus and cerebral vein. Wu et al.[3] designed the venous occlusion imaging score (VOIS) using computed tomography venography. They assigned 2 points for the absence of thrombus in the SSS and 1 point each for the absence of thrombus in the inferior sagittal sinus, straight sinus, TS_R, TS_L, SS_R, SS_L, IJV_R, and IJV_L; lower VOIS scores indicated a higher thrombus burden. In a study[3] including 56 patients, the VOIS was shown to present an inverse correlation with stroke severity, suggesting that it could be a reliable scoring system to monitor treatment and predict outcomes in patients with CVST. In another study conducted to determine the increased risk of venous thromboembolic events following CVST, Miranda et al.[15] grouped patients based on thrombus burden in ≤ 2 or >2 sinuses and vessel occlusions. These thrombus scoring systems define the severity of thrombosis by roughly indicating the location and number of thrombosed sinuses, using a unified or binary scoring rule for each segment. In another study[2] designed to investigate the relationship between the extent of CVST, clinical severity, MRI lesions, and clinical outcomes, the thrombus burden in MRV was calculated by assigning 1 point for each thrombosed sinus and 3 points for the SSS. Zubkov et al.[16] analyzed the relationship between the location and severity of CVST and the presence of brain lesions by assigning 1 point for each thrombosed sinus to measure the general distribution of sinus thrombosis. The SSS was divided into three segments, each assigned 1 point. Consequently, the severity of thrombosis was

associated with an increased risk of developing brain lesions. Although the SSS was divided into three segments in these two scoring systems, it is challenging to accurately differentiate between the thrombus burdens of other sinuses. Additionally, these systems disregard the impact of the non-dominant TS on the clinical burden of CVST.

The presence of intracranial hypertension in some cases of LS thrombosis in CVST but not in others raises a question concerning the relationship between the development of intracranial hypertension and the unaffected LS patency on the contralateral side. In a study conducted by Glik et al.[14] involving 50 patients, it was observed that patients who developed intracranial hypertension after CVST had a narrower, unaffected LS. The relationship between inflammation and idiopathic intracranial hypertension (IIH), characterized by ICP, has been studied for years.[30,31] A study[32] including 33 patients with IIH reported that the NLR and PLR were significantly higher in the patient group compared with the control group. The linear relationship between papilledema grade and the NLR and PLR, in particular, indicated that, as the ICP increased, the levels of inflammatory biomarkers also increased.[32] In this context, when examining patients with CVST, it is important to consider the effect of increased ICP on inflammatory biomarkers. The thrombus scoring system developed by Wang et al.,[17] which we used to determine the thrombus burden, appears to be the most suitable and sensitive scoring system among those previously described. Compared with previous methods, the CVST-Score divides the unilateral TS and SS into two segments. The CVST-Score seems to be the scoring system that divides the dural venous sinuses into more segments than other scoring systems, and this enables a more detailed and accurate assessment. Additionally, since the patency of the unaffected LS is important for the development of intracranial hypertension, this method calculates the weighted drainage of bilateral transverse sinuses based on the maximum cross-sectional area and CVST-Score; thus, it can predict the severity of intracranial hypertension and help clinicians determine the optimal treatment for patients.[33]

In the present study, we showed a statistically significant positive correlation between the CVST-Score and the NLR and PLRs. In a previous study[34] investigating the relationship between thrombus burden and inflammatory biomarkers in DVT, the NLR of 933 patients with DVT was found to be associated with thrombus burden. We have also determined that the NLR is an independent determinant in predicting the CVST-Score in the linear regression model developed to estimate the thrombus burden.

It should be considered that inflammatory biomarkers may be elevated in various conditions. Studies have shown that the NLR and PLR values increase in patients presenting with seizures[35] and are associated with seizure severity.[36] In the study, the proportion of patients with seizures was of 10% (4 subjects). No statistically significant difference was observed between the levels of inflammatory biomarkers in patients with seizures compared with patients without seizures. Although the NLR values have been shown to increase in patients with arterial stroke,[22] no statistically significant difference was found between NLR and PLR values when patients with venous infarction or hemorrhage were compared with the others in the present study. In the study by Wang et al.,[37] no increase in NLR was found in patients with venous infarction and hemorrhage due to CVST. In the present study, other conditions, such as arterial stroke and infections, which may cause an increase in inflammatory biomarker levels, were excluded. This enabled us to obtain more accurate results.

When we divided the patients with CVST into three groups based on the onset-to-door time, we observed that the NLR values were significantly higher in those who presented to the hospital within three days than those with a delayed diagnosis. We also obtained a stronger positive correlation between the CVST-Score and the NLR and PLR in the early stages. Similar to our study, Wang et al.[37] reported that inflammation could develop after CVST and gradually decrease over time. The levels of inflammatory biomarkers were higher in patients with CVST than in the controls, and these levels were significantly higher in the acute and subacute stages than in the chronic stage. Dias et al.[7] conducted a retrospective study with 78 adult patients with CVST to evaluate the relationship between the duration of symptoms and inflammatory biomarkers and obtained higher NLR values in the acute phase. Due to the retrospective design of the present study, follow-up inflammatory biomarker levels could not be included and were only compared with those of the patients presenting in the chronic phase. Nevertheless, the results suggest that increased inflammation in CVST patients is more likely to be a consequence rather than a cause of the thrombotic process.

As a limitation of the present study, the sample size was small, and during the data analysis, cerebrospinal fluid (CSF) pressure could not be evaluated in most cases. It is anticipated that more accurate results can be obtained if this evaluation is included in further studies.

In conclusion, increased inflammation is present in CVST, as evidenced by elevated NLR values, particularly in the early stages. Additionally, there is a positive correlation between thrombus burden and NLR and PLR values in CVST, which is more pronounced in the early phase. Especially when combined with other factors, the NLR seems to be a determinant of thrombus burden in CVST. Determining the onset time of CVST can be difficult, especially when the patient experiences non-specific symptoms such as progressive headache. In cases in which the onset time of symptoms cannot be defined, the diagnosis of CVST may raise questions about whether the patient should be anticoagulated, since the literature on anticoagulation in cases of chronic CVST is limited.[7] Studies[37] have also shown that high inflammatory biomarkers in CVST are associated with poor prognosis. In light of these data, our results suggest that the detection of high NLR values in CVST patients may support the acute onset of the disease, help determine the treatment protocol, and provide useful information to predict prognosis and the severity of the disease, especially in the early stages of CVST. Further studies with larger and more diverse populations are needed.

Authors' Contributions

AYK, TA: conceptualization and design of the work, writing the manuscript; AVK, VG: data acquisition; AYT: analysis; SB: measurements on the imaging. All authors approved the final version of the manuscript and are responsible for all aspects of the work.

Conflict of Interest

The authors have no conflict of interest to declare.

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