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CLINICAL STUDY

The role of the neutrophil-lymphocyte ratio in the diagnosis of cerebral venous sinus thrombosis

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ABSTRACT

OBJECTIVES: We aimed to assist in the diagnosis of cerebral venous sinus thrombosis (CVST) with the neutrophil-lymphocyte ratio (NLR).

BACKGROUND: Diagnosis of CVST is difficult.

METHODS: Patients, who visited the emergency department between March 1, 2013 and March 1, 2021 and underwent magnetic resonance (MR) venography were included. The patients' MR venography results, ages, gender, NLR, were collected. The patients were categorized according to their CVST diagnosis status, and NLR were compared.

RESULTS: Of the 530 patients included in the study, 366 (69.1 %) were female, and the median age was 40 (31–58) years. CVST was detected in 57 (10.8 %) patients, no pathological diagnosis was detected in 251 (47.4 %) patients. The median NLR of the patients with CVST was statistically significantly higher than in the patients without CVST and in the patients without any diagnosis ((3.94 [2.5–6.47] vs 3.03 [1.93–5.43], p=0.023) (3.94 [2.5–6.47] vs 2.92 [1.86–4.95], p=0.009). In the ROC analysis performed with reference to the patients without any diagnosis, NLR obtained 0.612 AUC.

CONCLUSION: Significantly higher NLR levels were found in CVST patients compared to the patients, who were not diagnosed with CVST and the patients without any diagnosis *(Tab. 5, Fig. 2, Ref. 22)*. Text in PDF *www.elis.sk*

KEY WORDS: cerebral venous sinus thrombosis, diagnosis, neutrophil, lymphocyte.

Introduction

Cerebral venous sinus thrombosis (CVST) is a rare disease with poor outcomes such as death (1). Differential diagnosis of CVST from other neurological emergencies is difficult because it has non-specific symptoms such as headache (2, 3). The incidence of CVST is 2–5 million per year (4). Since it is not a disease frequently encountered by physicians, its diagnosis becomes difficult in the emergency department (5). In the study, one out of 30 patients was misdiagnosed with CVST (5). Late diagnosis increases morbidity, while early diagnosis improves prognosis (6). The diagnosis of CVST in emergency services is therefore important. Although several imaging modalities are used for the diagnosis of CVST, magnetic resonance (MR) venography has an excellent diagnostic performance (7). There is a need for laboratory parameters to assist in the diagnosis of CVST, which is rare among patients, who visit the emergency department with a common complaint such as headache and is diagnosed with imaging methods such as MR that cannot be completed in a short time.

There is a relationship between high neutrophil and low lymphocyte levels and inflammation and thrombosis (8). A high neutrophil-lymphocyte ratio (NLR) has been reported in the patients with CVST, including patients with CVST with poor clinical outcomes (8, 9).

We aimed to investigate whether a high NLR was associated with the rate of detection of CVST in the patients, who visited to the emergency department and had MR venography.

Methods

Approval was obtained from the local ethics committee for this study. Medical records of the patients, who visited the emergency department of a tertiary university hospital were examined retrospectively. The inclusion criteria were patients, who underwent MR venography between March 1, 2013 and March 1, 2021. Patients under the age of 18 and patients whose file information could not be accessed were excluded from the study. The hospital, where the study was conducted, is one of the 3 largest hospitals in a city with a population of 2,277 million, with approximately 70,000 emergency department visits annually.

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Tab. 1. Participant characteristics.

Number of Patients	530 (100%)
Age (years)	40 (31–58)
Gender	
Male	164 (30.9%)
Female	366 (69.1%)
Length of Hospital Stay (Day)	4 (0–13)
Vital Signs	
Fever (C°)	36.5 (36.4–36.6)
Pulse (per minute)	85 (72–92)
Systolic blood pressure (mmHg)	120 (110–130)
Diastolic blood pressure (mmHg)	80 (70–80)
Saturation (%)	97 (95–99)
Laboratory Results	
WBC (10^3µL)	8.9 (7.03–11.4)
Neutrophil (10^3µL)	6.2 (4.3–8.66)
Lymphocyte (10^3µL)	1.9 (1.31–2.5)
NLR	3.19 (1.96–5.66)
BUN (mg/dL)	12.04 (9–17.03)
Creatinine (mg/dL)	0.7 (0.62–0.83)
Medical History	
Hypertension	91 (17.2%)
Pregnancy	59 (11.1%)
Diabetes Mellitus	56 (10.6%)
Cerebrovascular event	41 (7.7%)
Coronary artery disease	32 (6%)
Rheumatic disease*	30 (5.7%)
Malignancy	23 (4.3%)
Migraine	21 (4%)
History of prior CVST	16 (3%)
Complaints	
Headache	275 (51.9%)
Nausea – vomiting	62 (11.7%)
Weakness – Focal neurologic deficits	52 (9.8%)
Visual impairment-diplopia	46 (8.7%)
Dizziness	44 (8.3%)
Seizure	26 (4.9%)
Fever	22 (4.2%)
Clouding of consciousness	21 (4%)
Speech disorder	14 (2.6%)
Emergency Service Outcome	
Discharged	180 (34%)
Ward Unit	223 (42.1%)
ICU	106 (20%)
Discharged against medical advice	16 (3%)
Transferred to other hospitals	5 (0.9%)
Hospital Outcome	
Discharged	474 (89.4%)
Ex	23 (4.3%)
Discharged against medical advice	26 (4.9%)
Transferred to other hospitals	7 (1.3%)
In-Hospital Mortality	
Survivor	507 (95.7%)
Nonsurvivor	23 (4.3%)
MR venography result	
CVST	57 (10.8%)

WBC – White blood cell; NLR – Neutrophil-lymphocyte ratio; BUN – Blood urea nitrogen; CVST – Cerebral venous sinus thrombosis; MR – Magnetic resonance, * Behçet, rheumatoid arthritis, systemic lupus erythematosus, sarcoidosis, familial mediterranean fever

Tab. 2. Diagnostic features of patients without CVST.

Normal	251 (47.4%)
Ischemic cerebrovascular event	79 (14.9%)
Haemorrhagic cerebrovascular event	34 (6.4%)
Epilepsy	15 (2.8%)
Encephalitis	11 (2.1%)
Brain tumours	11 (2.1%)
Vascular malformation	11 (2.1%)
Meningitis	10 (1.9%)
Pseudotumor cerebri	10 (1.9%)
Migraine	5 (0.9%)
Behcet	5 (0.9%)
Increases intracranial pressure-oedema	5 (0.9%)
Guillain barre syndrome-transverse myelitis	5 (0.9%)
Pacchioni granulation	4 (0.8%)
Vasculitis	4 (0.8%)
Cervical discopathy	3 (0.6%)
Optic neuritis	2 (0.4%)
Other*	7 (1.3%)

CVST – Cerebral venous sinus thrombosis, * Diffuse axonal injury, fahr syndrome, facial paralysis, hypertensive encephalopathy, multiple sclerosis, trigeminal neuralgia

The patients' MR venography results (with a diagnosis status of CVST), ages, gender, presenting complaints, history, vital signs, white blood cell count (WBC), blood urea nitrogen (BUN), creatinine, neutrophil, lymphocyte, and NLR values, comorbidities, emergency and hospital outcomes, and in-hospital mortality status were recorded. The final diagnosis of the patients, who were not diagnosed with CVST was also recorded, and the patients were categorized according to their CVST diagnosis status. The collected parameters were compared between the patients, who were diagnosed with CVST and those who were not. The primary outcome of the study was to evaluate whether the NLR differs between those with and without a CVST diagnosis, and between those with CVST and without any diagnosis.

The statistical analysis of the data was performed using the SPSS 20.0 statistical package program (SPSS Inc., Chicago, IL, USA). Histograms and the Kolmogorov-Smirnov test were used to test the normality of the data. The quantitative data are expressed as medians (25–75 % percentiles), and the categorical variables are expressed as frequencies (percentages). Differences between the groups were investigated using the Mann-Whitney U test. Intragroup comparisons of the categorical variables were performed using the chi-square and Fisher's exact tests. Receiver -operating characteristic (ROC) analysis was performed to determine the CVST predictive power of the laboratory parameters that showed statistically significant differences between the groups in the Mann-Whitney U test. The optimum cut-off values of the laboratory parameters included in the ROC analysis were determined using the Youden index (sensitivity, 1 − specificity). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the parameters included in the ROC analysis were calculated for the optimum cut-off values. A logistic regression analysis was performed to evaluate the effects of the categorical variables that were found to have statistically significant differences in the chi-square and Fisher's exact tests and the quantitative laboratory variables that were found to have statistically significant differences in the Mann-Whitney U test.

Tab. 3. Comparison data according to patients without CVST.

MR venography result	CVST (+) (n=57)	CVST (–) (n=473)	p
Age (years)	38.5 (29–53)	41 (31–59)	0.154
Male gender	20 (35.1%)	144 (30.4%)	0.474
Length of Hospital Stay (Day)	11.5 (4–14)	4 (0–13)	<0.001
Fever (ºC)	36.6 (36.4–36.7)	36.5 (36.4–36.6)	0.951
Pulse (per minute)	88 (77.5–105.25)	85 (72–91)	0.01
SBP (mmHg)	120 (110–130)	120 (110–133)	0.429
DBP (mmHg)	80 (70–88.75)	80 (70–80)	0.251
Saturation (%)	97 (95–99)	97 (95–99)	0.653
WBC (10^3µL)	9.85 (6.92–11.62)	8.8 (7–11.3)	0.744
Neutrophil (10^3µL)	7.17 (4.28–9.17)	6 (4.26–8.5)	0.257
Lymphocyte (10^3µL)	1.68 (1.21–2.17)	1.95 (1.4–2.53)	0.033
NLR	3.94 (2.5–6.47)	3.03 (1.93–5.43)	0.023
BUN (mg/dL)	12.04 (8.58–17.36)	12.04 (9.05–16.61)	0.694
Creatinine (mg/dL)	0.7 (0.56–0.84)	0.7 (0.62–0.83)	0.539
Hypertension	8 (14%)	83 (17.5%)	0.506
Pregnancy	6 (10.5%)	53 (11.2%)	0.878
Diabetes Mellitus	4 (7%)	52 (11%)	0.356
Cerebrovascular event	6 (10.5%)	35 (7.4%)	0.428*
Coronary artery disease	2 (3.5%)	30 (6.3%)	0.561*
Rheumatic disease**	4 (7%)	26 (5.5%)	0.551*
Malignancy	4 (7%)	19 (4%)	0.296*
Migraine	2 (3.5%)	19 (4%)	0.999*
Sinus vein thrombosis	6 (10.5%)	10 (2.1%)	0.004*
Headache	28 (49.1%)	247 (52.2%)	0.658
Nausea–vomiting	11 (19.3%)	51 (10.8%)	0.059
Weakness– Focal neurologic deficits	4 (7%)	48 (10.1%)	0.453
Visual impairment–diplopia	8 (14%)	38 (8%)	0.135*
Dizziness	7 (12.3%)	37 (7.8%)	0.304*
Seizure	3 (5.3%)	23 (4.9%)	0.752*
Fever	1 (1.8%)	21 (4.4%)	0.495*
Clouding of consciousness	3 (5.3%)	18 (3.8%)	0.485*
Speech disorder	3 (5.3%)	11 (2.3%)	0.183*
In-Hospital Mortality	5 (8.8%)	18 (3.8%)	0.089*

MR – Magnetic resonance; CVST – Cerebral venous sinus thrombosis; SBP – Systolic blood pressure; DBP – Diastolic blood pressure; WBC – White blood cell; NLR – Neutrophil-lymphocyte ratio; BUN – Blood urea nitrogen, * Ficher exact test was used, ** Behçet, rheumatoid arthritis, systemic lupus erythematosus, sarcoidosis, familial mediterranean fever

The quantitative laboratory variables were included in the regression analysis after categorizing them according to their optimum cut-off values. First, univariate logistic regression analysis was performed. Then, a multivariate logistic regression analysis was performed with the backward Wald method for the parameters with p values <0.25 in the univariate logistic regression analysis. The Hosmer-Lemeshow test was used to assess the model fit of the multivariate logistic regression analysis. Statistical significance was set at $p < 0.05$.

Results

A total of 575 patients, who visited the emergency department over 8 years and who underwent MR venography, were included in the study. Three patients whose MR venography results could not be found, 5 patients with missing laboratory data, 30 patients with missing comorbidity data, and 7 patients with missing complaint data were excluded from the study. The remaining 530 patients were included in the study. The median age of the patients was 40 (31–58) years, and there were 366 (69.1 %) females. The three most common complaints were headache, nausea-vomiting, and weakness-focal neurologic deficits, and the three most common comorbidities were hypertension, pregnancy, and diabetes mellitus. A total of 23 (4.3 %) patients died in the hospital. CVST was detected in 57 (10.8 %) patients, according to their MR venography results. Detailed characteristics of the patients are given in Table 1.

According to the MR venography results, CVST was not detected in 473 (89.2 %) patients. No pathological diagnosis was detected in 251 (47.4 %) patients, ischemic cerebrovascular events were detected in 79 (14.9 %) patients, and haemorrhagic cerebrovascular events were detected in 34 (6.4 %) patients. The final diagnoses of the patients without CVST are shown in Table 2.

The patients were categorized according to their diagnostic status of CVST using MR venography. The parameters between the groups were compared. The median length of hospital stay of the patients with CVST was statistically significantly higher than that of the patients without CVST (11.5 [4–14] days, 4 [0–13] days, $p < 0.001$). The median pulse of the patients with CVST was statistically significantly higher than that of the patients without CVST (88 [77.5–105.25], 85 [72–91], $p = 0.01$). The median lymphocyte value of the patients with CVST was statistically significantly lower than that of the patients without CVST (1.68 [1.21–2.17] 10^3/uL, 1.95 [1.4–2.53] 10^3/uL, $p = 0.033$) (lymphocyte reference range: 0.8–5.5 10^3/uL). The median NLR of the patients with CVST was statistically significantly higher than that of the patients without CVST (3.94 [2.5–6.47], 3.03 [1.93–5.43], $p = 0.023$). The history of prior CVST rate of the patients with CVST was statistically significantly higher than that of the patients without CVST (6 [10.5%], 10 [2.1%], $p = 0.004$). The detailed comparison data between the groups are presented in Table 3.

We included the lymphocyte parameter and the NLR in our ROC analysis based on the patients, who were not diagnosed with CVST. The area under the curve (AUC) values of the lymphocyte parameter and the NLR were 0.587 and 0.592, respectively (Fig. 1). With a cut-off value of 2.23 for the lymphocyte value, 80.7 % sensitivity, 35.7 % specificity, 13.6 % PPV, and 93.6 % NPV were obtained. With a cut-off value of 3.74 for the NLR,

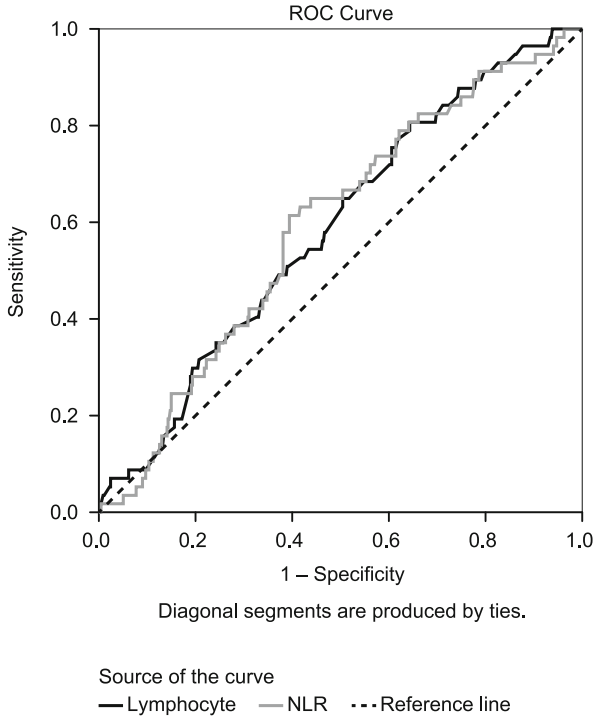

Fig. 1. Roc curve according to patients without CVST.

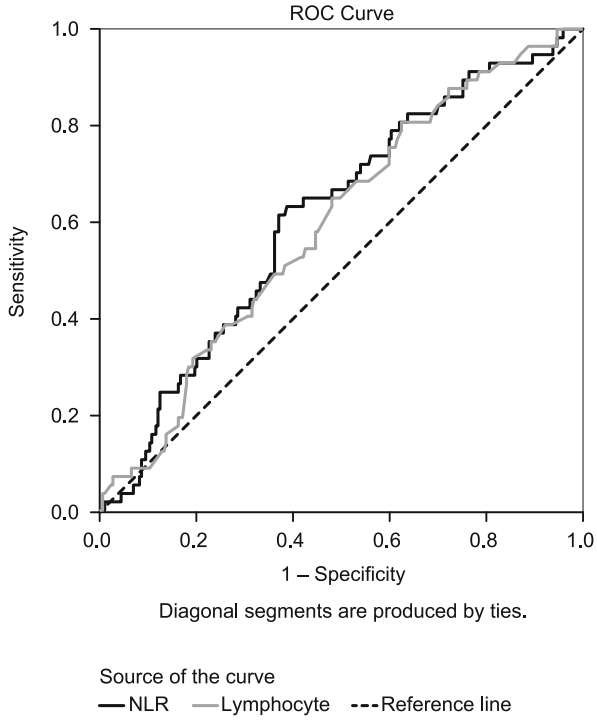

Fig. 2. Roc curve according to patients without any diagnosis.

61.4 % sensitivity, 60.6 % specificity, 16.4 % PPV, and 92.6 % NPV were obtained.

We included lymphocyte and the NLR as laboratory parameters and the history of prior CVST rate as categorical variables in the logistic regression analysis. We categorized the linear variables for inclusion in the regression analysis according to their optimal cut-off values. According to the results of the multivariate logistic regression analysis performed with reference to the patients, who were not diagnosed with CVST, the presence of a history of prior CVST obtained a 6.736 odds ratio, while an NLR value >3.74 obtained an odds ratio of 2.709. The logistic regression analysis results are shown in Table 4.

In our study, patients with CVST detected according to MR venography results were compared to the patients without any diagnosis. Out of a total of 530 patients, 221 patients with any diagnosis other than CVST were excluded, and 309 patients were evaluated. The patients with CVST had a significantly higher NLR and lower lymphocyte levels compared to the patients without any diagnosis (Tab. 5). In the ROC analysis performed with reference to the patients without any diagnosis, lymphocyte obtained 0.595 AUC, while NLR obtained 0.612 AUC (Fig. 2).

Discussion

It is difficult for emergency physicians to suspect CVST, which is rare among crowded patients presenting to the emergency department with non-specific symptoms such as headache. Laboratory parameters are needed to assist with imaging methods that make a definitive diagnosis. In our study, a high NLR value were found in CVST patients compared to the patients, who were not diagnosed with CVST and the patients without any diagnosis.

High neutrophil and low lymphocyte levels are strong indicators of an inflammatory response (10). Their value increases in many diseases, in which the inflammatory process is activated, which includes CVST (11). In the study by Dias et al of 78 patients with CVST, high NLR values and lymphopenia without a change in the leukocyte count occurred in the acute phase of the disease (12). In our study, low lymphocyte values and a high NLR were

Tab. 4. Logistic regression analysis results.

Univariate			Multivariate		
Parameters	Odds rate	95% CI	Parameters	Odds rate	95% CI
Lymphocyte <2.23	2.32	1.169–4.604			
NLR>3.74	2.444	1.388–4.303	NLR>3.74	2.709	1.511–4.857
History of prior CVST	5.447	1.901–15.607	History of prior CVST	6.736	2.253–20.141

CI – Confidence interval; NLR – Neutrophil-lymphocyte ratio; CVST – Cerebral venous sinus thrombosis

Tab. 5. Comparison data according to patients without any diagnosis.

MR venography result	CVST (+) (n=57)	Normal (n=251)	p
Age (years)	38.5 (29–53)	37 (30–50.75)	0.814
Male gender	20 (35.1%)	61 (24.2%)	0.092
Length of Hospital Stay (Day)	11.5 (4–14)	0 (0–4)	<0.001
Fever (Cº)	36.6 (36.4–36.7)	36.5 (36.4–36.6)	0.975
Pulse (per minute)	88 (77.5–105.25)	86 (72–91.75)	0.027
SBP (mmHg)	120 (110–130)	120 (110–130)	0.846
DBP (mmHg)	80 (70–88.75)	75 (70–80)	0.081
Saturation (%)	97 (95–99)	97 (95–99)	0.826
WBC (10^3µL)	9.85 (6.92–11.62)	8.43 (6.9–10.5)	0.288
Neutrophil (10^3µL)	7.17 (4.28–9.17)	5.57 (4.11–7.9)	0.082
Lymphocyte (10^3µL)	1.68 (1.21–2.17)	2 (1.4–2.6)	0.027
NLR	3.94 (2.5–6.47)	2.92 (1.86–4.95)	0.009
BUN (mg/dL)	12.04 (8.58–17.36)	10.59 (8.68–13.94)	0.251
Creatinine (mg/dL)	0.7 (0.56–0.84)	0.66 (0.59–0.78)	0.5
Hypertension	8 (14%)	30 (11.9%)	0.658
Pregnancy	6 (10.5%)	39 (15.5%)	0.339
Diabetes Mellitus	4 (7%)	23 (9.1%)	0.797*
Cerebrovascular event	6 (10.5%)	11 (4.4%)	0.099*
Coronary artery disease	2 (3.5%)	13 (5.2%)	0.999*
Rheumatic disease**	4 (7%)	8 (3.2%)	0.244*
Malignancy	4 (7%)	7 (2.8%)	0.125*
Migraine	2 (3.5%)	14 (5.6%)	0.745*
Sinus vein thrombosis	6 (10.5%)	8 (3.2%)	0.027*
Headache	28 (49.1%)	170 (67.5%)	0.009
Nausea–vomiting	11 (19.3%)	29 (11.5%)	0.114
Weakness– Focal neurologic deficits	4 (7%)	16 (6.3%)	0.771*
Visual impairment–diplopia	8 (14%)	20 (7.9%)	0.147
Dizziness	7 (12.3%)	26 (10.3%)	0.665
Seizure	3 (5.3%)	5 (2%)	0.168*
Fever	1 (1.8%)	13 (5.2%)	0.479*
Clouding of consciousness	3 (5.3%)	2 (0.8%)	0.045*
Speech disorder	3 (5.3%)	2 (0.8%)	0.045*
In–Hospital Mortality	5 (8.8%)	3 (1.2%)	0.007*

MR – Magnetic resonance; CVST – Cerebral venous sinus thrombosis; SBP – Systolic blood pressure; DBP – Diastolic blood pressure; WBC – White blood cell; NLR – Neutrophil-lymphocyte ratio; BUN – Blood urea nitrogen, * Ficher exact test was used, ** Behçet, rheumatoid arthritis, systemic lupus erythematosus, sarcoidosis, familial mediterranean fever

also obtained without a significant change in neutrophil values in the patients diagnosed with CVST compared to the patients without a diagnosis of CVST. Disruption of the blood-brain barrier has been shown to cause an increased inflammatory process in CVST (13). Inflammation has also been shown to increase in other neurological diseases, such as ischemic cerebrovascular events, which increase intracranial pressure where the blood–brain barrier may be impaired (14). Increased inflammation has also been reported pathophysiologically in cases of hypercoagulation resulting in thrombosis (15).

Since CVST is a thromboembolic disease, a high NLR is usual. In our study, an NLR > 3.74 was an independent predictor of the diagnosis of CVST, with an odds ratio of 2.709. A study including 80 patients with CVST and 197 control patients found the NLR to be an independent predictor of the presence of CVST, achieving an odds ratio of 1.442 per one-unit increase in NLR (8). However, NLR was not categorically included in the regression analysis in the mentioned study, (8). In addition, the control group was recruited by excluding conditions that would increase systemic inflammation (8). A strength of our study was that the control group comprised the patients with a pre-diagnosis of CVST. In our study, although CVST was not detected in the control group, diseases such as ischemic cerebrovascular events and encephalitis that increased inflammation were detected. The higher NLR in the CVST group can be attributed to the absence of a pathology that would increase inflammation in approximately half the control group. Compared to the normal patients as the control group in our study, NLR achieved a higher AUC value (0.612 > 0.592).

In our study, the most common complaint was headache. In literature, the most common complaint in CVST patients is also headache (16). Therefore, neurological diseases, such as meningitis and intracranial haemorrhage causing headache, should be suspected in the differential diagnosis (2). We found diseases that would cause headache in our study's control group. In our study, the women had more CVST (64.9 %) than the men, and the median age of the patients with CVST was 38.5 years. In the study conducted with 1144 CVST patients, the percentage of females was 68 %, while 79.8 % of the patients were under the age of 50 years (16). In another study conducted with 624 CVST patients, the median age of the patients was 37 years, while the female ratio was 74.5 % (17). In literature, pregnancy, malignancy, and rheumatic diseases such as Behçet's have been found to be common in the patients with CVST (16, 18, 19). In our study, the medical history of the patients diagnosed with CVST revealed that 10.5 % were pregnant, 7 %, had rheumatic disease, and 7 % had a malignancy. It has been reported that the patients with CVST have a tendency toward thrombosis, which is the etiological cause, and that more CVST appears after thromboembolic events, especially in certain patient groups (2, 20). In our study, the medical history of the patients diagnosed with CVST showed that 10.5 % had ischemic cerebrovascular events, and 10.5 % had a history of prior CVST. The presence of prior CVST in the patient's medical history was found to be an independent predictor with an odds ratio of 6.736 in diagnosing CVST. The study data are generally consistent with literature.

There are some limitations to our study. This was a single-center study, and the data were collected retrospectively. It was not

possible to collect all the parameters that would affect the diagnosis of CVST from the medical records. The inability to evaluate some parameters, such as D-dimer and troponin, that could affect the diagnosis and prognosis of CVST was another limitation (21, 22), as was the small number of patients, especially in the group diagnosed with CVST. MR venography was used for the diagnosis of CVST. However, there are alternative diagnostic methods such as computed tomography for diagnosis. Evaluation of only MR venography method is a limitation in our study. In addition, due to the retrospective nature of the study, the clinical conditions of the patients before MR venography were not standardized. It was not evaluated whether other imaging such as computed tomography was performed before MR.

Conclusion

As the result, significantly higher NLR levels were found in CVST patients compared to the patients who were not diagnosed with CVST and the patients without any diagnosis. In the ROC analysis performed with reference to patients without any diagnosis, NLR obtained 0.612 AUC, while in the ROC analysis performed with reference to the patients without CVST, NLR obtained 0.592 AUC.

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