Osmangazi Journal of Med, 2025;47(6):951-963
DOI: 10.20515/otd.1721991

Research Article
Araştırma Makalesi

Osmangazi Journal of Medicine
e-ISSN: 2587-1579

Seizures in Cerebral Venous Sinus Thrombosis: Predictive Variables and Their Effect on Clinical Course

Serebral Venöz Sinüs Trombozunda Nöbetler: Tahmini Değişkenler ve Klinik Seyir Üzerindeki Etkileri

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Ethics Committee Approval: The study was approved by Mersin University Noninterventional Clinical Research Ethical Committee (Decision no: 2018-42 Date: 06. 2018

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

Authorship Contributions: Concept: HG, SHK. Design: HG, SHK. Data Collection or Processing: HG. Analysis or Interpretation: HG. Literature Search: HG. Writing: HG, SHK.

Copyright Transfer Form: Copyright Transfer Form was signed by corresponding author.

Peer-review: Internally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

Acknowledgments: We want to thank all patients who participated as subjects in the study for their time and engagement. Also, we appreciate Asena Ayca Ozdemir for her valuable support and contribution.

Received : 18.06.2025

Accepted :21.08..2025

Published : 05.09.2025

Abstract: This study aimed to evaluate the effect of epileptic seizures on prognosis and the secondary factors accompanying this in patients with cerebral venous sinus thrombosis (CVST).This study was designed as a retrospective, cross-sectional study conducted between Jan 2007 and Dec 2017. Patients diagnosed with CVST aged 18 years or older who applied to the Neurology Clinic of Mersin University Faculty of Medicine Hospital were included in the study. Patients were divided into two groups: those with and without epileptic seizures, and both groups were evaluated with the modified Rankin Scale (mRS) at 1, 3, 6, and 12 months for 1 year. Epileptic seizures were observed in 35.2% of a total of 71 adults of the included patients in the study; 65.4% of these patients (n=17) were female, and the mean age was 36.8±15.8 years. When the prognoses of CVST patients with and without epileptic seizures were compared, a significant difference was found in terms of prognosis in the first month after discharge (p = 0.025). Severe disability (mRS ≥3) was observed more frequently in patients with epileptic seizures, and this difference was statistically significant (p = 0.022). Poor prognostic factors in CVST patients with epileptic seizures were failure to control seizures within the first 24 hours, presence of motor deficit, superior sagittal sinus involvement, frontal lobe involvement, and vasculitic etiology (Behçet's disease), while good prognostic factors were age <65 and absence of parenchymal involvement. Epileptic seizures do not significantly affect the prognosis in CVST patients after the first month after discharge. However, correct identification of risk factors, early diagnosis, and effective treatment can improve the functionality of patients in both the short and long term, thereby providing a better prognosis.
Keywords: Cerebral venous sinus thrombosis, seizure, prognosis, parenchymal involvement, Behçet's disease, focal neurological deficits

Özet: Bu çalışmada serebral venöz sinüs trombozu (SVST) olan hastalarda epileptik nöbetlerin prognoz ve buna eşlik eden ikincil faktörler üzerindeki etkisinin değerlendirilmesi amaçlandı. Bu çalışma Ocak 2007 ile Aralık 2017 tarihleri arasında yürütülen retrospektif, kesitsel bir çalışma olarak tasarlanmıştır. Mersin Üniversitesi Tıp Fakültesi Hastanesi Nöroloji Kliniğine başvuran 18 yaş ve üzeri SVST tanısı almış hastalar çalışmaya dâhil edildi. Hastalar epileptik nöbet geçiren ve geçirmeyen olmak üzere iki gruba ayrıldı ve her iki grup da 1 yıl boyunca 1, 3, 6 ve 12. aylarda modifiye Rankin Ölçeği (mRS) ile değerlendirildi. Çalışmaya dâhil edilen 71 yetişkin hastanın %35,2'sinde epileptik nöbetler gözlendi; bu hastaların %65,4'ü (n=17) kadındı ve yaş ortalamaları 36,8±15,8 yıldı. Epileptik nöbet geçiren ve geçirmeyen SVST hastalarının prognozları karşılaştırıldığında, taburcu olduktan sonraki ilk ayda prognoz açısından anlamlı bir fark bulundu (p=0,025). Epileptik nöbet geçiren hastalarda şiddetli sakatlık (mRS ≥3) daha sık gözlendi ve bu fark istatistiksel olarak anlamlıydı (p = 0,022). Epileptik nöbet geçiren SVST hastalarında kötü prognostik faktörler ilk 24 saat içinde nöbetlerin kontrol altına alınamaması, motor defisit varlığı, superior sagital sinüs tutulumu, frontal lob tutulumu ve vaskülitik etyoloji (Behçet hastalığı) iken, iyi prognostik faktörler <65 yaş ve parankimal tutulumun olmamasıydı. Epileptik nöbetler, taburcu olduktan sonraki ilk aydan sonra SVST hastalarında prognozu önemli ölçüde etkilemez. Ancak risk faktörlerinin doğru tanımlanması, erken tanı ve etkili tedavi, daha iyi bir prognoz sağlamak için hastaların kısa ve uzun vadede işlevselliğini iyileştirebilir.
Anahtar Kelimeler: Serebral venöz sinüs trombozu, epileptik nöbet, prognoz, parankimal tutulum, Behçet hastalığı, fokal nörolojik defisitler

How to cite/ Atıf için: Genç H, Kaleağası HŞ. Seizures in Cerebral Venous Sinus Thrombosis: Predictive Variables and Their Effect on Clinical Course, Osmangazi Journal of Medicine, 2025;47(6):951-963

1. Introduction

Cerebral venous sinus thrombosis (CVST) differs from arterial strokes in several key features: It is more common in younger ages (1), carries a lower risk of developing stroke (2), is associated with more frequent epileptic seizures (3), and has lower mortality rates (4). This rare entity accounts for approximately 0.5-0.7% of all strokes (1), and its annual incidence is conjectured to range between 13.9-20.2 /1,000,000 (5).

The clinical picture of CVST has a broad spectrum. It can present with different symptoms, ranging from headache, visual field defects, and focal neurological deficits to changes in consciousness (6). Epileptic seizures are one of the numerous frequently marked clinical findings and are observed in 23.7-40% of patients (2,6-8). Although there are different classifications according to the time of the beginning of epileptic seizures, the classification made by Ferro et al. is generally accepted. According to this classification, seizures are divided into three groups: those that develop before the diagnosis of CVST, early seizures that emerge within the first 14 days after diagnosis, and late seizures that emerge after 14 days (9).

While 28.8-44.3% of patients may present with epileptic seizures (8,10,11), 9.5% may experience epileptic seizures in the late period (10). Mortality rates in CVST have decreased over time with the help of advances in diagnosis and treatment, and the prognosis has improved (12). Various studies have shown factors such as age, male gender, presence of cerebral hematoma/infarction, neurological deficits, seizures, coma, thrombosis of superior sagittal sinus (SSS)/cortical veins/deep cerebral sinuses, pulmonary embolism, malignancy, sepsis, and central nervous system infections as prognostic determinants (2,13-15). The influences of epileptic seizures on prognosis are contradictory. While some investigations found no effect on prognosis in multiple analyses (2), others showed that they only had an effect in the early period (16). Another study found that epileptic seizures may increase mortality in patients with CVST by 3-fold (17). Our primary aim in this study was to evaluate the effect of epileptic seizures on prognosis in patients with CVST and the secondary factors contributing to this effect. Our secondary aim was to discuss the incidence, semiology, characteristics, treatments, and predictive factors for seizures in CVST.

2. Materials and Methods

This study was designed as a cross-sectional and retrospective investigation. The study population consisted of patients with CVST aged ≥18 who applied to the Neurology Clinic of Mersin University Faculty of Medicine Hospital between 01.01.2007 and 31.12.2017. CVST was diagnosed according to the clinical manifestation of the patients and neuroimaging findings [Cranial computed tomography (CT) scan, magnetic resonance imaging (MRI), magnetic resonance venography (MRV)] and the diagnostic criteria determined based on thrombosis in the cerebral venous sinuses (18). The diagnosis of CVST was confirmed by taking reference to the American Heart Association/American Stroke Association (AHA/ASA) guide issued in 2011 (19). The onset of CVST was categorized as acute (<48 hours), subacute (48 hours-1 month), and chronic (>1 month). Then, it was evaluated by dividing it into two groups: those who had and those who did not have epileptic seizures. Epileptic seizures that developed secondary to CVST were divided into three groups: those that developed before the diagnosis of CVST, early seizures that occurred within the first 14 days after diagnosis, and late seizures that occurred after 14 days.

In the literature, a study including 1144 patients reported a rate of 23.7% epileptic seizures in individuals diagnosed with CVST (6). For this difference to be statistically significant, it was calculated that at least 10 cases should be studied in each group when the Type I error was accepted as 5%, and the test power was accepted as 80%.

A total of 71 CVST patients (26 with epileptic seizures and 45 without seizures) who applied to the Neurology Clinic of Mersin University Faculty of Medicine Hospital between the specified dates were included in the study. It was stated that reaching at least 40% of the population was sufficient to represent the population (20). Accordingly, it was planned to work with at least 28 cases, including 10 with epileptic seizures and 18 without seizures. This study was performed with approval from the meeting of the Mersin University Presidency Clinical Research Ethics Committee, which was held on 25.01.2018 and was numbered 2018/49 [Appendix-1].

Patients diagnosed with CVST who applied to the Neurology Clinic of Mersin University Faculty of

Medicine Hospital were retrospectively examined. The patients were separated into two groups based on the presence or absence of epileptic seizures. This division was made to compare the clinical features, treatment processes, and prognosis between these two groups, providing a comprehensive understanding of the impact of epileptic seizures on CVST patients.

Each patient was evaluated for the following variables:

• Demographic data: Age, gender

• Clinical features: Type of disease onset, time of onset, and type of first symptom

• Variables related to epileptic seizures: Status of presentation with epileptic seizures, seizure types, frequency of seizures in the acute period

• Treatment process: Medical treatments administered in the emergency department, during hospitalization, and at discharge

• Risk factors: Predisposing factors for cerebral venous thrombosis and epilepsy

• Diagnostic data: Neuroimaging (CT, MRI, MRV) and neurophysiological findings

• Stroke severity rating: National Institutes of Health Stroke Scale (NIHSS) score (21)

• Epileptic seizure classification: Seizure types of patients with epileptic seizures were determined according to the International League Against Epilepsy (ILAE) 2017 classification.

• Prognosis assessment: The patients' prognosis and the effects of other variables on prognosis were examined utilizing the Modified Rankin Scale (mRS) (22). The mRS, a scale that evaluates between 0-6 points, is a crucial tool in measuring the degree of disability and dependency due to stroke or other neurological diseases. It is an important indicator in terms of prognosis. It is classified as 0 points = No symptoms, 1 point = No significant disability, 2 points = Mild disability, 3 points = Moderate disability, 4 points = Severe disability, 5 points = Very severe disability, 6 points = Death. Patients with 0-2 points were evaluated in the mild disability group, patients with 3 points were evaluated in the moderate disability group, and patients with 4-6 points were evaluated in the severe disability group. Data regarding the investigated criteria and follow-up evaluations at 1, 3, 6, and 12 months after CVST diagnosis were obtained from the patients' medical records through the study form [Appendix-2]. Missing data were completed through direct or indirect interviews with the patients.

2.1. Statistical Analysis

The Shapiro-Wilk test was used to provide the normality control of the data. An Independent Sample t-test was used for comparing two independent group means with normal distribution, a One-Way Analysis of Variance (ANOVA) was used for comparing more than two independent group means, and the Tukey test was used as a post hoc test. Descriptive statistics were expressed with mean and standard deviation. The Chi-Square test was used for categorical data analysis, Fisher's Exact test for 2x2 tables with more than 20% observations under 5, and the Linear Association test for ordinal data with categories greater than 2. Two ratio comparisons were applied for the results found significant in the analysis of categorical data greater than two. Descriptive statistics were expressed with frequency and percentage. Univariate and Multiple Logistic Regression analyses were used to investigate the factors affecting epileptic seizures. Descriptive statistics were expressed with the Odds ratio [95% Confidence Interval]. The statistical significance level was taken as 0.05 in all analyses. Analyses were executed in the SPSS 21.0 program.

3. Results

Seventy-one patients were included in the study; their mean age was 37.7±15.8 years, and 63.4% were female (63.4%). Clinical symptoms were generally subacute in onset, and the most common and foremost complaint was headache. Epileptic seizures developed in 25 patients (35.2%) due to CVST. Two of these patients had previously known epilepsy, and one had under-controlled seizures. One patient whose seizures were under control was included in this group because his epileptic seizures were re-provoked after CVST. The reason for emergency visits in 19 patients (26.8%) with CVST was epileptic seizures. Seven of these patients (28%) presented with status epilepticus, while epileptic seizures started early in 24 patients (33.8%). In one patient, the first epileptic seizure developed one year later. The mean age of patients with epileptic seizures secondary to CVST was 36.8±15.8 years, and 65.4% of these patients were female. The most common seizure type was focal onset seizures with or without secondary generalized tonic-clonic seizures (60%). Other seizure subtypes observed in the patients are shown in Figure 1, using the ILAE

2017 classification as a reference. Maintenance anti-seizure treatment was given to 22 patients. The most preferred treatment was levetiracetam (73.9%), followed by carbamazepine (8.7%), phenytoin (8.7%), lamotrigine (4.3%), and valproic acid (4.3%). An electroencephalography (EEG) examination was performed on only 11 patients who experienced epileptic seizures. While the EEG examination of 6 patients was normal, two patients had an epileptiform anomaly localized on the temporal, two patients had an epileptiform anomaly localized on the frontocentrotemporal, and one had an epileptiform anomaly localized on the frontotemporal. Two of the patients with epileptiform anomaly on EEG had no parenchymal involvement, one had SAH, one had hemorrhagic venous infarct, and one had parenchymal involvement in the form of venous infarct. The EEG change and sinus involvement were on the same side in 3 patients. Nausea-vomiting, Jacksonian spread, sensory, orofacial, cognitive, memory impairment, hallucination, aphasia, dysphasia, visual, and dysarthria were among the behavioral descriptors commonly observed during or after the seizure.

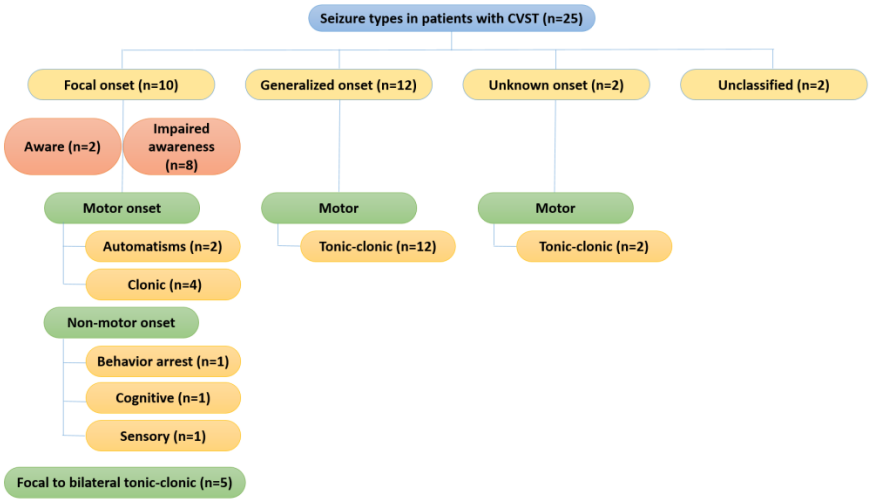

Figure 1. Seizure types in patients with CVST according to the ILAE 2017 classification of seizure types expanded version *(**CVST:** Cerebral venous sinus thrombosis; **ILAE:** The International League Against Epilepsy)*

There was no substantial difference between patients with CVST who had epileptic seizures and those who did not in terms of gender (p=0.790), age (p=0.697), and CVST symptom onset time (p=0.582). The rate of seizures was higher in patients with an acute onset of CVST (p=0.006). In patients, the SSS was involved in 38%, sigmoid sinus in 66.2%, transverse sinus in 80.3%, confluens sinuum in 8.5%, internal jugular vein in 31%, cortical veins in 19.7%, Labbe vein in 1.4% and deep venous system in 14.1%. However, cavernous sinus involvement was not observed. Involvements associated with the risk of epileptic seizures; left cortical veins (p=0.047), bilateral transverse sinuses (p=0.029), and confluens sinuum thrombosis (p=0.016). Different presentations were observed in patients secondary to venous thrombosis, such as infarction, hemorrhage, hemorrhagic infarction, and subarachnoid hemorrhage. No parenchymal involvement was detected in 57.7% of the patients. The most commonly affected parts of the cerebral parenchyma were recorded as the parietal lobe (18.6%) and the temporal lobe (18.6%). Infarction was observed in 46.4% of the patients, hemorrhage in 12.1%, and hemorrhagic infarction in 37.5%. Parenchymal involvement, especially supratentorial, was found to be associated with the risk of developing epileptic seizures in patients with CVST (p=0.001). Hemorrhagic infarction was encountered to be associated with epileptic seizures (p=0.007); hemorrhage (p=0.567) and infarction (p=0.13) were not. However, hemorrhagic infarction and hemorrhage were found to be associated with the risk of epileptic seizures when evaluated in the same group (p=0.014). In addition, involvement of the left temporal lobe (p=0.001), right temporal lobe (p=0.005), and left parietal lobe (p=0.003) significantly increased the risk of epileptic seizures. Univariate and multiple analyses were performed for patients with epileptic seizures according to the type of CVST onset, parenchymal involvement, and temporal and parietal lobe involvement. Accordingly, the rate of epileptic seizures was found to be 0.242 times higher in those with subacute CVST onset, likened to those with acute CVST onset [95% Confidence Interval (CI): 0.073-0.809, p=0.021] and 0.136 times higher in those with chronic CVST onset [95% CI: 0.027-0.682,

p=0.015]. The rate of epileptic seizures was 4.714 times higher in patients with parenchymal involvement in the form of infarction compared to those without parenchymal involvement [95% CI: 1.317-16.871, p=0.017], and 11 times higher in those with parenchymal involvement in the form of hemorrhagic infarction [95% CI: 2.369-51.072, p=0.002]. When examined according to anatomical localization, the rate of epileptic seizures was 15.4 times higher in patients with parietal and temporal lobe involvement compared to those without parenchymal involvement [95% CI: 3.054-77.652, p=0.001] (Table 1).

Table 1. Evaluation of the risk of developing seizures in patients with CVST based on CVST onset, parenchymal involvement, parietal and temporal lobe involvement using uni- and multiple analyses

	Univariate			Multiple		
Seizure	**OR**	**95% Cl**	**p**	**OR**	**95% Cl**	**p**
CVST onset						
Acute	Reference					
Subacute	0.242	0.073-0.809	**0.021**	0.470	0.108-2.051	0.315
Chronic	0.136	0.027-0.682	**0.015**	0.396	0.061-2.573	0.332
Parenchymal involvement						
No	Reference					
Infarct	4.714	1.317-16.871	**0.017**	1.918	0.344-10.684	0.457
Hemorrhage	4.125	0.502-33.911	0.187	2.350	0.226-24.391	0.474
Hemorrhagic infarct	11.000	2.369-51.072	**0.002**	4.991	0.752-33.144	0.096
Temporal lobe involvement						
No	Reference					
Yes	15.400	3.054-77.652	**0.001**	1.012	0.158-6.468	0.990
Parietal lobe involvement						
No	Reference					
Yes	15.400	3.054-77.652	**0.001**	6.387	0.929-43.930	0.059

CVST: *Cerebral venous sinus thrombosis;* ***OR:*** *Odds ratio;* ***CI:*** *Confidence Interval*

CVST risk factors in all patients: Thrombophilia (29.4%), puerperium (27.3%), drugs (21.1%), and local infections (16.9%) were in the first place. When CVST risk factors were evaluated separately, no significant difference was found in terms of the risk of seizure occurrence. However, when the relationships between local infection types and epileptic seizures were evaluated separately, the presence of mastoiditis infection was a risk for the development of seizures (p=0.046) (Table 2).

Table 2. Evaluation of the relationship between venous thrombosis risk factors and seizures in patients with CVST

		Without seizure			With seizure			p value
		n	**Missing data**	**%**	**n**	**Missing data**	**%**	
Pregnancy		1	–	3.6	1	–	5.9	0.719
Puerperium		5	–	17.9	7	–	43.8	0.067
Coagulation factor mutations		5	24	11.1	4	14	15.4	0.839
Nephrotic syndrome		1	–	2.2	0	–	0	0.337
Systemic infection		1	–	2.2	1	–	3.8	0.696
Local infection		6	–	13.3	6	–	23.1	0.291
Subtypes of local infection	Sinusitis	1		16.7	0		0	
	Mastoiditis	3	–	50	6	–	100	0.075
	Otomastoiditis	2		33.3	0		0	
Vasculitis	Behcet's Disease	3		6.8	0		0	
	SLE	1	1	2.3	0	–	0	0.125
	Sjogren's Disease	0		0	1		3.8	
History of VTE		3	4	7.3	3	–	11.5	0.670
Malignancy		3	4	7.2	3	1	11.8	0.666
Thyroid disease		3	1	6.8	1	–	3.8	1.00

Ulcerative colitis	1	1	2.3	0	–	0	0.333
Drugs	10	3	23.8	3	2	12.5	0.345
Dural AVF	1	–	2.2	1	–	3.8	0.696
Family history of CVST	0	5	0	1	3	4.3	0.153
Dehydration/Hypovolemia	1	4	2.4	2	3	8.7	0.268

CVST: *Cerebral venous sinus thrombosis,* ***VTE:*** *Venous thromboembolism,* ***AVF:*** *Arteriovenous fistula,* ***SLE:*** *Systemic lupus erythematosus*

Family history of epilepsy, smoking and alcohol use, age ≥65, substance use, history of cerebral infection and hypoxic birth, thyroid diseases, and head trauma, which may increase the risk of epilepsy, were meticulously questioned in the patients. There was no patient with a history of cerebral infection.

Cerebral lesions are a general risk factor for epilepsy; parenchymal involvement, which was detected in our patients and was statistically significant, can be examined in this category. Other parameters, except parenchymal involvement, were not related to epilepsy risk (Table 3).

Table 3. Evaluation of the relationship between epilepsy risk factors and seizures in patients with CVST

		Without seizure			With seizure			p value
		n	Missing data	%	n	Missing data	%	
Parenchymal involvement	Infarct	7		15.6	8		30.8	**0.003**
	Hemorrhage	2	_	4.4	2	_	7.7	
	Hemorrhagic infarct	3		6.7	8		30.8	
Epilepsy history on family		1	7	25	3	6	75	0.086
Smoking	No	25		58.1	17		70.8	
	Yes	15	2	34.9	5	2	20.8	0.471
	Quitted	3		7	2		8.3	
Alcohol	No	37		88.1	21		87.5	
	Yes	5	3	11.9	2	2	8.3	0.330
	Quitted	0		0	1		4.2	
≥ 65 years		4	2	9.3	2	–	7.7	0.817
Substance Use		0	5	0	1	4	4.5	0.147
History of cerebral infection		0	6	0	0	3	0	–
History of hypoxic birth		0	7	0	1	5	4.8	0.148
Thyroid diseases		3	1	6.8	1	–	3.8	1.00
History of head injury		2	7	5.3	2	7	10.5	0.476

CVST: *Cerebral venous sinus thrombosis*

Effective treatments were administered to patients who presented to the emergency room with epileptic seizures. Diazepam (42.1%), levetiracetam (36.8%), midazolam (26.3%), phenytoin (21%), and valproic acid (5.3%) were among the treatments used. The average seizure control period was 1.4±1.3 days, and all patients had their seizures stopped within a week at the latest. Before medical treatment, patients had an average of 2±1.4 seizures. Maintenance anti-seizure medication (ASM) was started in 88% of patients, and this treatment was continued for an average of 8.2±15 months. Seizure recurrence was observed in 22.7% of patients during the treatment period.

The mean length of stay of all patients was 10.9±7.9 days. While the admission NIHSS was 1.8±3.4, the discharge NIHSS was 0.7±1.3, indicating significant improvement.

The mRS was used to appraise the patient's prognosis. None of our patients scored 5 or 6 on this scale; they scored between 0 and 6. The patients generally showed a stable or mildly disabled course. When the prognosis of patients with and without epileptic seizures secondary to CVST was compared, a significant difference was found in the prognosis in the first month after discharge (p=0.025) (Figure 2). Accordingly, the mild disability group was observed more in patients

without epileptic seizures (p=0.025). The fact that the severe disability group had a higher rate of patients with seizures was statistically significant (p=0.022). In the one-year follow-up, no difference was found between the groups regarding prognosis in the following months (Figure 2).

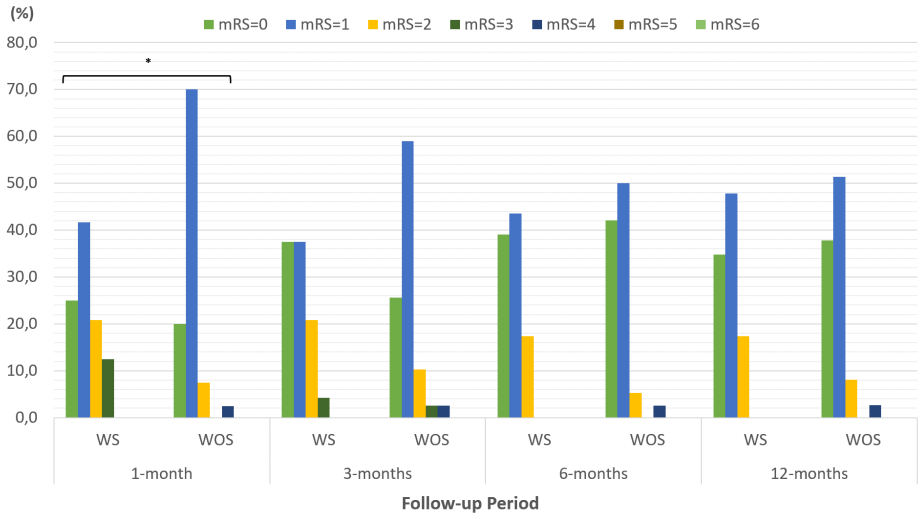

Figure 2. Comparison of the prognoses of patients with cerebral venous thrombosis who have epileptic seizures versus those without seizures at one-year follow-up *(**WS:** With seizure; **WOS:** Without seizure, **mRS:** Modified Rankin Scale; ***:** WS group has a poorer outcome than the WOS group; p=0.025)*

When the prognoses of patients with and without epileptic seizures were compared in terms of age, gender, CVST onset type, and time of onset of symptoms, no significant difference was found. However, when the relationship between motor deficit status and epileptic seizure was examined, an important difference was observed in terms of prognosis in the first month (p=0.002) and third months (p=0.017). This finding has significant implications for patient care and prognosis. In particular, the higher rate of heavy disability in patients with both seizures and motor deficits was found to be statistically significant, highlighting the importance of early intervention and comprehensive care for these patients.

Our study revealed a marked difference in prognosis in the first month between patients with SSS involvement and those with seizures (p=0.025). Notably, the rate of mild disability was higher in patients with seizures but no SSS involvement (p=0.007). In comparison, the rate of moderate disability was higher in patients with seizures and SSS involvement (p=0.027). No difference was found in terms of prognosis in the other months. When evaluated in terms of deep vein involvement, the prognosis in patients without seizures showed a statistically consequential difference in the first month (p=0.009), sixth months (p=0.002), and twelfth months (p=0.001). In particular, it was found that the proportions of severe disability were higher in patients without seizures but with deep vein involvement. No relationship was found with other sinus involvements. Again, no significant difference was noticed between epileptic seizures and the number of involved venous sinuses in terms of prognosis.

Our comprehensive research uncovered a significant relationship between parenchymal involvement status and epileptic seizure in the first month (p=0.05). This finding, along with the higher rate of mild disability in patients who had seizures but did not have parenchymal involvement, which was found to be statistically significant (p=0.014), provides a robust basis for our conclusions. No statistically significant difference was found between parenchymal involvement types of CVST in the form of infarction, hemorrhage, or hemorrhagic infarction, and seizures in terms of prognosis. Similarly, no meaningful relationship was found with subarachnoid hemorrhage (SAH).

A significant disparity was found between patients with epileptic seizures and frontal lobe involvement in terms of prognosis in the first month. The higher rate of severe disability in patients with frontal lobe involvement and seizures was statistically significant (p=0.013). There was no statistically significant difference in prognosis between other parenchymal involvement areas and seizure status.

Our study found no important difference in prognosis between epileptic seizures and pregnancy,

puerperium, coagulation disorder, and systemic infection status.

This study revealed a significant difference in prognosis between patients without seizures and those with local infection in the first month (p=0.044). The high rates of severe disability among patients without seizures and those with local infection were statistically significant (p=0.016).

Our study thoroughly investigated the causes of vasculitic etiology in the patients, which were found to be SLE, Sjögren's, and Behçet's disease. We discovered a significant distinction in prognosis between patients without seizures and those with vasculitis in the first month (p=0.002), sixth month (p=0.002), and twelfth month (p=0.003). The high rates of severe disability in patients without seizures and those with vasculitis in the first, sixth, and twelfth months were statistically significant (p<0.001 for all). When the causes of vasculitis were evaluated separately, Behçet's disease was identified as the main reason for this significance. When other factors that could cause CVST and epileptic seizures were evaluated separately, there was no significant difference in prognosis. Among patients with epileptic seizures and <65 years of age, the higher ratios of mild disability in the third month (p=0.001), sixth month (p=0.024), and twelfth month (p=0.024) were statistically significant in terms of prognosis.

There was no notable dissimilarity in terms of prognosis between comorbid diseases, previously known epilepsy, type of anticoagulant treatment, and epileptic seizure status due to CVST.

In patients whose seizures could not be controlled within the first day, the higher rates of severe disability in the first month were statistically significant (p=0.013). Apart from this, there was no significant difference in terms of prognosis with early epileptic seizures, status epilepticus, type of ASM, and recurrence of seizures after antiepileptic treatment.

The hospital stay, hospitalization, and discharge NIHSS of patients with and without epileptic seizures due to CVST were assessed. In patients with CVST, a substantial difference was found between the duration of hospitalization and the presence of epileptic seizures in the first, third, and sixth months. Accordingly, when patients with seizures were evaluated within themselves (p<0.001, p=0.01, p=0.001, respectively), the increase in hospitalization duration from mild to severe disability was statistically significant. No difference was found when patients with and without seizures were compared among themselves. In patients with epileptic seizures with CVST, the increase in hospitalization NIHSS from mild to severe disability in the first month (p=0.002) and from mild to moderate disability in the third and sixth months (p=0.039, p=0.01, respectively) was statistically significant. NIHSS was significantly higher in patients with seizures and mild disability at admission (First month: p=0.018; third month: p=0.008; sixth month: p=0.001; twelfth month: p=0.01). In patients with epileptic seizures with CVST, the progression from mild to severe disability in the first and third months (p<0.001 for both) and from mild to moderate disability in the sixth month (p<0.001) was statistically significant with higher NIHSS at discharge.

4. Discussion

CVST occurred more frequently in middle-aged female patients and usually had an acute-subacute onset. Headache was the most common manifestation in patients, and epileptic seizures were observed in one-third of them. Subacute onset, involvement of left cortical veins, bilateral transverse sinus, and confluens sinuum, parenchymal involvement, left temporal and left parietal lobe involvement, and mastoiditis were factors that increased the risk of epileptic seizures in patients with CVST **(Table 1)**. Epileptic seizures had a negative effect on prognosis in the first month, but this effect did not continue in the following months **(Figure 2)**. In patients with CVST who had an epileptic seizure, failure to handle the seizure within the first day, motor deficit, SSS involvement, frontal lobe involvement, and Behçet's disease had a negative effect on prognosis. In contrast, the absence of parenchymal involvement and age <65 had a positive impact. CVST is an infrequent cerebrovascular disease that usually affects young adult women, especially those between the ages of 20 and 40 (3,6,23,24). The mean age of the patients in our study was 37; 63% were female, similar to the rates reported in the literature (67.9-75%) (6,24,25). Epileptic seizures are one of the most common symptoms in patients with CVST; their frequency has been reported to be between 23.7% and 46.38% in studies (6,25,26). In our study, similar to the literature, 35.2% of patients with CVST developed epileptic seizures. In studies, epileptic seizures have been observed more frequently in young adult women. The mean reported age ranged between 30-39.73, and 70-76.6% of the patients were female (6,25). The results we obtained in this research were similar. The mean age of patients with secondary epileptic seizures due to CVST was 36 years, and 65.4% were female. While a study apprised that

young mothers with CVST and women with preeclampsia had a higher risk of secondary seizures (27), studies by Bertina et al. (28) and Sha et al. (26) did not support this. In another meta-analysis investigating late epileptic seizures in patients with CVST, female gender also was not a predictive factor (3).

The literature has insufficient and inconsistent results regarding the seizure types observed in CVST. This may be due to the retrospective design of the studies, discrepancies in seizure recording methods, and the classifications used (25). The most often detected seizure type in our study was focal onset seizures with or without secondary generalized tonic-clonic seizures (60%) (Figure 2). While generalized onset seizures were reported more frequently in the studies conducted by Mahale et al. (29) and Davoudi et al. (30), focal onset seizures were declared more frequently in others (2,11,25). In our study, the reason for emergency visits of 26.8% of the patients with CVST was epileptic seizures. The results of the presentation with epileptic seizures in the study executed by Gazioglu et al. (25) were similar to ours. While status epilepticus can be observed in patients with CVST at a rate of 1-11.1% (10,11,30), in our study, this rate was much higher, and status epilepticus was observed in 28% of the patients. The treatments applied to patients who applied to the emergency department due to epileptic seizures were diazepam, levetiracetam, midazolam, phenytoin, and valproic acid, respectively, according to their frequency. At discharge, levetiracetam was the most preferred ASM at a rate of 73.9%, followed by carbamazepine, phenytoin, lamotrigine, and valproic acid, respectively. In the study executed by Gazioglu et al., all patients with acute seizures were treated with ASMs, primarily levetiracetam, at a rate of 80% (others were carbamazepine, oxcarbazepine, and lamotrigine), and monotherapy was generally sufficient (25). Levetiracetam was the most preferred ASM because of its possible anticonvulsant effects, broad-spectrum, advantageous pharmacokinetic profile, lower risk of drug interactions, and ideal ASM properties (31,32). The mean duration of seizure control was 1.4±1.3 days, and patients had an average of 2±1.4 seizures before medical treatment. In the study by Masuhr et al., patients with no more than two seizures had a reduced need for intensive care, while there was a slight increase in mortality compared to patients without seizures (11). Some studies recommend prophylactic treatment in patients with CVST because of the increased incidence of seizures and the potential harmful consequences on the metabolic status of the brain (33). In contrast, other studies limit the use of ASMs to patients who have seizures, considering that the potential risk of side effects may outweigh the benefits (13). In addition, there is insufficient data on the optimal period of treatment (34). In patients with early-stage seizures and no previously reported risk factors [such as Glasgow coma scale (GCS) score <8, altered mental status, aphasia, paresis, and brain parenchymal involvement (29,31,35)], continuation of antiepileptic treatment for 3 months may be considered (11). In cases of recurrence of epileptic seizures during or after drug reduction (36) or in the presence of the stated risk factors, continuation for at least 1 year is recommended (10). In our study, 88% of the patients were started on monotherapy and maintenance ASM in the subsequent period, and this treatment was continued for an average of 8 months. No prophylactic ASM was given to any patient without an epileptic seizure. Seizure recurrence was observed in 22.7% of the patients during treatment. Epileptiform abnormalities were detected in 5 patients in the EEG findings. Two had no parenchymal involvement, one had SAH, one had hemorrhagic venous infarction, and one had parenchymal involvement in the form of venous infarction. In 3 patients, the EEG changes and sinus involvement were on the same side. A comparison wasn't performed due to insufficient data on EEG in patients with CVST in the literature and EEG could not be performed on all patients in this study.

While the necessity of prophylactic antiepileptic treatment in patients with CVST is being discussed, researchers have conducted studies to define the risk factors for early and late-stage epileptic seizures in order to identify patients in the risk group. While some parameters emerged as common risk factors, differences were observed among the studies in some. Supratentorial involvement (26,30,32), focal neurological deficit (hemiplegia, sensory deficit, aphasia, hemianopia) (8,25,26,30), hemorrhagic brain parenchymal lesion (8,25,30), and cortical vein thrombosis (25,30) were the most commonly mentioned risk factors. In our study, left cortical veins, bilateral transverse sinuses, confluens sinuum thrombosis, left temporal and left parietal lobe involvement, especially hemorrhagic parenchymal involvement, and mastoiditis were identified as factors increasing the risk of epileptic seizures **(Table 1)**. Since cortical veins provide venous drainage of the cortex, thrombosis may impair this drainage and increase the risk of seizures (11,35). The reason why intracranial lesions with hemorrhagic components produce epileptic seizures

more frequently is probably the decompartmentalization of iron (37). In contrast to our study, SSS involvement has been associated with epileptic seizures in many studies (8,16,25), while transverse sinus involvement has been associated with much fewer epileptic seizures (29). One study suggested that lesions in one lobe were more associated with acute symptomatic seizures than lesions in more than one lobe (30). In our study, supratentorial involvement, especially left temporal and parietal lobe involvement, was associated with a 15.4-fold increased risk of epileptic seizures. In contrast, most studies, although not specifying the direction, showed that lesions in the frontal, parietal, and temporal lobes increased the tendency to seizures. It was revealed that the risk of seizures was 5 times higher in supratentorial lesions (2,35). In addition to these, previous studies reported the presence of stupor, coma, and/or a low Glasgow Coma Scale score as hazard factors for acute seizures in CVST (11,29). The patients in our study were not evaluated in this respect. However, it can be considered that focal neurological deficits that supratentorial lesions may cause may be correlated with these risk factors. In our study, no relationship was found between gender, age, and the risk of epileptic seizures. Ding et al. In the study conducted by (8), male gender was highlighted as a risk factor, which was not supported by many studies (25,26). Age also did not stand out as a risk factor in the studies (8,26,30). In our review, the relationship between CVST risk factors and epileptic seizures was only valid for mastoiditis. In the study performed by Ding et al., contrary to our study, infection was not associated with epileptic seizures (8).

While pregnancy and puerperal status were also associated with epileptic seizures in some studies (27,29), this relationship was not found in others (26,28). In the study executed by Uluduz et al. (16), puerperium was found to be associated with epileptic seizures. The study conducted by Uluduz et al. determined that CNS and CV involvement was more common in this group (16). The most critical risk factor for late seizures in patients with CVST is the existence of acute symptomatic seizures, which increases the risk of seizures by 5 times (3). In addition, supratentorial involvement, coma, and hemorrhage are other established risk factors for late seizures (3,32). Our study did not analyze late seizures due to insufficient data. Unlike other studies, we also examined whether general risk factors for epilepsy contribute to the risk of seizures in patients with cerebral venous sinus thrombosis (CVST). However, we did not find any significant results.

Mortality rates have decreased over time with advances in diagnosis and treatment of CVST (12). The prognosis of CVST varies according to the sinus involved, parenchymal damage, underlying cause, and treatments. Patients with CVST associated with pregnancy, puerperium, and oral contraceptive use had a better prognosis in studies (38). In the VENOPORT study, age <45, absence of encephalopathy at admission, absence of deterioration after admission, absence of aphasia, and anticoagulation were reported as good prognostic factors (2,9). In the ISCVT study, which examined 624 patients, coma, mental disturbance, focal neurological deficits, superior sagittal sinus, thrombosis of cortical veins and deep cerebral veins, right-sided intracerebral hemorrhage, posterior fossa lesions, and parenchymal lesions (especially those >5 cm in diameter) were identified as poor prognostic factors (15). Other reported poor prognostic factors are age (>37 years in ISCVT), male gender, infection, malignancy, and seizures (2,15,16,31,39). There are several studies examining the effect of epileptic seizures on prognosis. Some studies have associated them with higher disability and mortality, while others have not found a negative association (31). Koubeissi et al. reported that patients with epileptic seizures secondary to CVST had higher mortality than those without (17). However, Sha et al. found no significant difference in mortality and 90-day recovery rates between the seizure and seizure-free groups (26). In our study, epileptic seizures in patients with epileptic seizures secondary to CVST had an unfavorable prognosis in the first month, but this did not continue in the following months (Figure 2). Similar results were obtained in the study by Uluduz et al. (16). In this study, secondary causes contributing to prognosis, together with epileptic seizures in patients with CVST, were investigated. In patients with epilepsy, failure to control epileptic seizures within the first day, motor deficit, SSS involvement, frontal lobe involvement, and Behçet's disease were secondary poor prognostic factors. In contrast, age <65 and absence of parenchymal involvement were good prognostic factors. ASM type and dosage, seizure type, and EEG findings did not affect prognosis. In one study, the mortality rate increased in patients who had more than two seizures despite antiepileptic treatment (39). In contrast, in another study, having fewer than three seizures did not reveal a significant difference in terms of mortality (11). In our study, the average time for seizures to be controlled was 1.5 days on average, and patients had an average of 2 seizures before antiepileptic treatment. In the study conducted by Masuhr et al. (11), the mortality rate increased 3-fold in patients with status epilepticus, while no deaths were observed in our study. This

may be because our center effectively carries out patient transfer, diagnosis, and treatment processes. Studies have associated parenchymal involvement (26,30,31) and focal neurological deficits, especially hemiplegia (8,25,26,30), with epileptic seizures. In addition, parenchymal involvement, focal neurological deficits, and SSS involvement were also associated with poor prognosis (15). In light of this information, the fact that motor deficit, SSS involvement, and frontal lobe involvement were associated with poor prognosis in patients with epileptic seizures in our study is parallel to the findings in the literature. Again, this can explain the relationship between the absence of parenchymal involvement and good prognosis in our study. In our study, Behçet's disease appears as a poor prognostic factor in epileptic patients; we could not find a similar result in the literature. However, ocular, gastrointestinal, vascular, and neurological involvements of Behçet's disease have been associated with poor prognosis (40). In the studies conducted by Ferro et al. (2) and Stolz et al. (39), advanced age was associated with poor prognosis. In this study, patients with CVST and epilepsy who were younger than 65 years of age had a better prognosis. Other studies did not show any significant difference.

5. Conclusion

The prognosis for patients with CVST has improved thanks to recent approaches. A significant number of studies have been launched to identify risk factors that may affect prognosis and to develop preventive measures. Although epileptic seizures negatively impact prognosis in the early stages, this effect tends to lessen over time.

Several secondary factors contribute to a poor prognosis in CVST patients experiencing epileptic seizures. These include failure to control seizures on the first day, motor deficits, involvement of the superior sagittal sinus, frontal lobe involvement, and the presence of Behçet's disease. On the other hand, being under 65 years of age and the absence of parenchymal involvement have been identified as positive prognostic factors.

Understanding these risk factors can help improve the prognosis for CVST patients. However, further prospective cohort studies are needed to validate these findings.

5.1. Highlights

• This study sheds light on the impact of epileptic seizures in CVST patients, revealing that they negatively affect prognosis in the first month but do not pose a significant risk in the following months.

• This study is the first to provide a detailed classification of epileptic seizures in CVST patients according to the ILAE 2017 classification. The most frequently observed seizure type was focal onset with or without secondary generalized tonic-clonic seizures, and levetiracetam emerged as the most commonly preferred antiepileptic treatment.

• This comprehensive study is the first to investigate whether generally accepted epilepsy risk factors contribute to seizure risk in CVST patients. It found no significant association between these risk factors and seizure occurrence, providing a robust foundation for further research.

• Thrombosis in the left cortical veins, bilateral transverse sinuses, and confluens sinuum, as well as involvement of the left temporal and left parietal lobes, parenchymal involvement, and mastoiditis, were identified as risk factors for epileptic seizures.

• This study is also the first to investigate secondary factors affecting prognosis in CVST patients with epileptic seizures. While poor prognostic factors were uncontrolled seizures within the first 24 hours, SSS thrombosis, frontal lobe involvement, motor deficits, and Behçet’s disease, good prognostic factors were age <65 years and absence of parenchymal involvement.

5.2. Limitations

• This study was performed in a tertiary care hospital. As many patients were referred to specialized centers, there may be a selection bias toward more severe cases. This condition may explain the high rate of status epilepticus detected in the study. So, all eligible cases within the study period were included to minimize selection bias. The findings may not generalize to milder cases not referred to or hospitalized.

• Not all patients had EEG recordings to identify subclinical epilepsy. EEG was performed only in patients who experienced epileptic seizures.

• Due to the retrospective study design, a lack of data was tried to complete by direct or indirect communication with patients. So, there is a possibility of missing or incomplete data due to recall bias.

Abbreviations

AHA/ASA: The American Heart Association/American Stroke Association
ANOVA: Analysis of Variance
ASM: Anti-seizure medication
AVF: Arteriovenous Fistula
CI: Confidence Interval
CT: Computerized Tomography
CVST: Cerebral Venous Sinus Thrombosis
EEG: Electroencephalography
ILAE: The International League Against Epilepsy
MRI: Magnetic Resonance Imaging
MRV: Magnetic Resonance Venography
mRS: Modified Rankin Scale
NIHSS: National Institutes of Health Stroke Scale
OR: Odds Ratio
SLE: Systemic Lupus Erythematosus
SSS: Superior sagittal sinus
WOS: Without Seizure
WS: With Seizure
VTE: Venous Thromboembolism

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