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Risk factors for acute symptomatic seizure in children with cerebral sinovenous thrombosis: Experience from a tertiary center

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ABSTRACT

Objective: To investigate the risk factors for acute symptomatic seizure (ASS) in children with Cerebral Sinovenous Thrombosis (CSVT) and to evaluate the effect of ASS on outcome.
Methods: Cross-sectional, single-center, hospital-based retrospective analysis of 42 children with neuroimaging-confirmed CSVT recorded between December 2009 and January 2023. ASS was defined as a seizure occurring within 7 days after CSVT. Predictors for ASS were analyzed by univariate and multivariate logistic regression. Functional outcomes were evaluated using the Pediatric Stroke Outcome Measure (PSOM).
Results: The average age of the 42 patients included in the study sample was 105.36 ± 63.1 months. Almost one-third (28.6 %) of patients with CSVT developed ASS. In univariate analysis, factors associated with seizure risk were young age, low Glasgow Coma Scale at admission, long hospital stay, headache, change of consciousness, focal neurological findings, cerebral hemorrhage, motor deficit and high D-dimer level (p=0.018, p<0.001, p= 0.016, p= 0.001, p=0.014, p<0.001, p < 0.001, p=0.019 and p=0.013, respectively). In multivariate analysis young age, focal neurological findings and D-dimer levels were potential predictors of ASS (p=0.004, p=0.003, p=0.036, respectively). Receiver operating characteristic (ROC) analysis for D-dimer diagnostic accuracy in patients with CSVT revealed D-dimer > 498 ng/mL (AUC=0.743). In both cohorts, PSOM scores at last follow-up were worse in those with acute seizures compared to those without (p<0.001).
Conclusion: Acute seizures occurred in approximately one-third of our cohort. Young age, focal neurological findings, and high D-dimer levels are potential predictors of ASS in children. Children with ASS had worse outcomes than those without.

1. Introduction

Cerebral sinovenous thrombosis (CSVT) is rare in the pediatric age group, with an estimated incidence of 0.4–0.7 per 100,000 children per year [1–4]. CSVT is a serious stroke that can cause acute brain damage, acute symptomatic seizures (ASS), and epilepsy in children. Previous pediatric stroke registries have reported that 20–58 % of patients with CSVT develop ASS and 21–25 % develop epilepsy [3–11]. Due to the rarity of CSVT in children, there are few studies focusing on potential risk factors of ASS [11]. Adult studies dominate the literature. A multicenter, large-cohort study using data from the International CSVT Consortium found that the main determinants of ASS were intracerebral hemorrhage, cerebral edema, ischemic infarction, sulcal subarachnoid hemorrhage, cortical vein thrombosis, superior sagittal sinus thrombosis, focal neurological deficits, and female-specific risk factors (pregnancy and/or puerperium) [12].

Patients presenting with CSVT are likely to have seizures; 89 % have more than one seizure in the acute period and 67 % require antiseizure

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medication (ASM) [10]. The high frequency of recurrent ASS in children with CSVT, especially within the first seven days, raises the question of whether short-term prophylactic ASM is necessary [10]. However, there is little data to guide the prevention of ASS in the pediatric age group [13]. Therefore, recommendations for treating CSVT in children are based on recommendations for adults. European and American guidelines recommend ASM to prevent further seizures in patients with ASS [14,15]. However, there is insufficient evidence to recommend prophylactic ASM in patients without ASS.

The aims of the current study were to investigate clinical, laboratory, and radiological risk factors for the development of ASS in children with CSVT and to examine the relationship between ASS and functional outcome.

2. Methods

2.1. Study design and patient selection

It is a retrospective, cross-sectional, single-center, hospital-based study. Medical records of a consecutive cohort of children and adolescents (aged 29 days to 18 years) with CSVT followed at a university hospital child neurology clinic between December 2009 and January 2023 were retrospectively reviewed. Venous infarction was defined as a region of reduced diffusion on the diffusion-weighted imaging/apparent diffusion coefficient map on magnetic resonance imaging (MRI) that did not correlate with the arterial vascular area and was attributed to venous thrombosis. The diagnosis of CSVT was confirmed by magnetic resonance venography [15]. Patients with a previous diagnosis of epilepsy, patients with arterial ischemic stroke, and patients with isolated cortical vein or cavernous sinus thrombosis were excluded from the study. The neonatal group was not included in our study due to different underlying etiologies and concomitant hypoxic ischemic encephalopathy or frequent additional brain injury patterns.

The current research was approved by the related Ethics Committee of Inönü University (protocol no: 2023/4531). Since this study was designed as a retrospective cohort study, informed consent was not obtained from the participants.

2.2. Data collection

The search was performed through electronic medical record review using the International Classification of Diseases 10th (ICD-10) of patients followed in child neurology and hematology/oncology clinics. ICD-10 codes I.82.0, I82.8, I82.9, I.63.0, I.63.6, were used in the search (all codes refer to pathologies that may include CSVT as a clinical presentation).

Clinical data; It includes age, gender, current symptoms (seizures, focal neurological motor and/or sensory disorders, altered consciousness, papilledema and sixth cranial nerve palsy), predisposing risk factors, treatment and management information. Age at thrombosis was defined as the date of onset of the first symptoms/signs confirmed by MRI/MR venography in patients due to CSVT or without significant symptoms/signs.

Laboratory studies; Complete blood count, biochemical, metabolic, infection and hematological tests, thrombophilia panel and D-dimer level at the time of admission were recorded.

Neuroimaging data; Taken from clinical reports showing brain MRI and gadolinium contrast-enhanced MR venography interpreted by an expert neuroradiologist. Characterization of thrombosis included the following; occlusive versus partially occlusive thrombus, thrombus location, anatomic variants of the venous system, presence of hemorrhage, presence and location of venous infarct. Occlusive thrombus was defined as a thrombus occupying the entire diameter of the vessel with immediate distal flow deficiency. Reports with unclear or conflicting findings at initial interpretation were reviewed by an expert pediatric neuroradiologist (SDT) to confirm the diagnosis of CSVT and affected areas.

Seizures and Electroencephalography (EEG) data; It includes timing relative to CSVT symptoms, seizure semiology, application of ASMs, EEG background, and the presence and characterization of epileptiform abnormalities. Seizures were classified as focal or bilateral tonic-clonic seizures in accordance with recommendations of the International League Against Epilepsy [16]. The number of seizures was recorded as single, multiple and status epilepticus. Since EEG is performed only on patients with clinical seizure activity, it does not include subclinical electrographic seizures detected only in EEG monitoring. Seizure classifications were based on clinical seizure activity and did not include subclinical electrographic seizure or electroclinical seizure activity.

The beginning of the follow-up period was considered to be the beginning after the patients were discharged. Follow-up data included epilepsy development and functional outcome.

2.3. Seizure definitions

Acute seizures were seizures that occurred within 7 days of the onset of CSVT symptoms [12,17,18]. Seizures that occurred as the first clinical symptom of CSVT were defined as acute seizures. Remote seizures were defined as a single unprovoked seizure that occurred more than 7 days after CSVT symptom onset [17]. Epilepsy was defined as two or more remote seizures occurring at least 24 hours apart [12,17–19]. Status epilepticus was defined as convulsive tonic-clonic activity lasting more than five minutes, sustained focal seizure activity lasting more than 10 minutes, or seizure activity occurring more than 20 % of any 60-minute EEG recording period [20].

2.4. Outcomes

Functional result; was assessed using the Pediatric Stroke Outcome Measure (PSOM) calculated by follow-up neurological examination at approximately 12 months for all patients. PSOM was calculated by the pediatric neurologist (GY) based on review of follow-up neurological examinations performed and recorded by expert pediatric neurologists (GY, BÖ, and SG) during the patients' clinic visits.

PSOM is a structured pediatric neurological examination scale with proven inter-rater reliability, aiming to evaluate post-stroke patients' language skills, cognitive, cranial nerves, motor, sensory, cerebellar functions and gait [21]. At the end of the examination, scoring is done in a total of 5 areas (Right sensory-motor, left sensory-motor, expressive language, receptive language, cognitive/behavioral). It measures the degree of disability on a scale between 0 and 2 points (0 = no deficit, 0.5 = mild deficit, function is normal, 1 = moderate deficit, function is impaired, 2 = severe deficit, function is lost). The PSOM total score is the sum of the scores in each domain and ranges from 0 to 10. The total score is classified as follows: Good (Normal = score 0 in all domains and mild deficit = score 0.5 in only one domain). Poor (Moderate deficit = score 0.5 in two, three or four domains; score 1 in one area and score 0.5 in another area; score 1 in only one area. Severe deficit = score 0.5 in all areas; score 1 in one domain and score 0.5 in two domains; score 1 in at least 2 areas; score 2 in at least one domain)

2.5. Statistical analysis

The variables used in the study were summarized with mean, standard deviation, median, minimum and maximum values, frequency and percentage according to measurement levels. For non-normal distribution, central tendency and dispersion measurements were expressed as median with interquartile range (IQR). The assumption of normal distribution for numerical variables was examined using the Shapiro-Wilk test. For quantitative variables, to examine significance difference between groups, Mann-Whitney U test was performed. For qualitative variables, Yates' chi-square with continuity correction and Fisher's exact tests were used where appropriate. Multiple logistic regression

model was used to model the relationship between acute seizure and predictors. Backward elimination stepwise method was used to obtain optimal model. ROC (Receiver Operating Characteristics) analysis was utilized to define cutoff for relevant predictors. Classification performance of predictors was indicated by overall accuracy, sensitivity, specificity and AUC (Area under the Curve) metrics. $p \leq 0.05$ was accepted as statistical significance level. IBM SPSS Statistics 27 program was used in the analysis.

3. Results

3.1. Demographic, clinical and radiological characteristics of the patients

The average age of the 42 children diagnosed with CSVT included in the study sample was 105.36 ± 63.1 (range: 9–200) months and 56 (66.7 %) were male. The average follow-up period of the patients was 42 months (4−121). Multiple genetic and/or acquired risk factors associated with stroke were detected in 76.2 % of CSVT patients. Prothrombotic/hematological diseases were the most common risk factors, and 37 (88.1 %) patients had at least one prothrombotic risk factor. The most common genetic thrombophilic mutations were PAI-1 4G>5G, MTHFR C677T and MTHFR A1298C. The most common acquired causes included infections 25 (59.5 %) and chronic systemic diseases 17 (40.5 %). The distribution of predisposing risk factors of the patients is given in Table 1. At the time of admission, 9 (21.43 %) patients had a Glasgow Coma Scale (GCS) score of < 8 points and were monitored in intensive care. Focal neurological symptoms and findings were detected in 17 (45 %) of the patients with CSVT at the time of admission, the most common being external gaze limitation in 7 (41.2 %) and hemiparesis in 3 (17.6 %) patients. Among diffuse neurological symptoms and findings (some patients had more than one symptom), the most common were headache in 25 (59.5 %), vomiting in 13 (31 %) and papilledema in 21 (50 %).

The diagnosis of CSVT was confirmed by brain MRI and MR venography. In terms of the distribution of thrombi in the brain venous circulation system, 27 (64.3 %) thrombosis was most frequently detected in the superficial circulation. The superior sagittal sinus was the most common site of thrombus occlusion, followed by the transverse sinus. The least thrombosis was in the internal jugular vein. In terms of parenchymal effects resulting from CSVT, venous infarction and cytotoxic cerebral edema in the drainage area of the affected vein were observed in 15 (35.7 %) patients. There was bleeding within the venous infarct in 10 (23.8 %) patients. (Table 2). In repeated/control MRI, 21 (25 %) patients had an area of gliosis and 13 (15.5 %) had infarct resolution. In repeated/control MR venography, there was complete recanalization in 43 (51.2 %) of the sinuses and partial recanalization in 29 (34.5 %). No stroke-related deaths were detected in our patients during the follow-up period. Stroke recurrence was observed in 4 (9.5 %) patients with CSVT.

Anticoagulation treatment was started in the acute period in patients diagnosed with CSVT. All patients were treated with low molecular weight heparin for 7 days followed by warfarin. International Normalized Ratio (INR) was kept between 2.0 and 2.5. Anticoagulation and antiplatelet therapy were administered together in 2 patients. In CSVT patients, in addition to antithrombotic treatment, 11 (26 %) patients were administered excretory LP and 7 (16.7 %) patients were administered acetazolamide for the medical treatment of cerebral edema.

3.2. Presentation of acute symptomatic seizures

ASS was observed in 12 (28.6 %) of CSVT patients (9 bilateral tonic-clonic, 3 focal seizures). In terms of seizure frequency in the acute period, status epilepticus was observed in 3 (7.1 %) patients, more than one seizure in 4 (.9.5 %) patients, and a single seizure in 5 (11.9 %) patients. 5 (11.9 %) of the patients were discharged with monotherapy and 7 (16.7 %) with multiple ASMs. The most commonly used ASM in patients with acute seizures was levetiracetam. 7 patients took levetiracetam, 4 took valproic acid, 3 took phenytoin, 3 took carbamazepine, and 2 took phenobarbital. All patients using ASMs at the time of discharge continued prophylactic ASMs for at least a 3-month follow-up. 5 of 12 (41.7 %) patients who had acute seizures were diagnosed with epilepsy during follow-up.

Table 1
Distribution of Risk Factors in Cerebral Sinovenous Thrombosis Patients.

Presence of Risk Factor	n:42 (%)
1 risk factor	10 (23.8)
>1 risk factor	32 (76.2)*
Conditions related to head and neck	1
Tympanomastoidectomy surgery	
Chronic systemic diseases	17/42 (40.5)
Nephrotic syndrome	5
Chronic renal failure	1
Behcet 's disease	2
Congenital heart disease	1
Cardiac septal defects	1
Acute Lymphoblastic Leukemia	2
Acute myeloid leukemia-M3	1
Fanconi aplastic anemia	1
Macrophage activation syndrome	1
Homocystinuria	1
Diabetes mellitus	1
Infection	25/42 (59.5)
Chronic otitis	2
Mastoiditis	11
Meningitis	2
Sinusitis	4
Varicella	1
Osteomyelitis	1
Thrombophlebitis	1
Pneumonia	2
Neutropenic fever	1
Prothrombotic states	
Presence of at least 1 prothrombotic risk factor	37/42 (88.1)
Presence of at least 2 prothrombotic risk factors	25/42 (59.5)
Iron deficiency anemia	7/42 (16.7)
MTHFR 677 (Homozygous)	3/38 (7.9)
MTHFR 1298 (Homozygous)	5/38 (13.2)
Factor V leiden (Heterozygous)	4/38 (10.5)
Factor V leiden (Homozygous)	0
Prothrombin 20210A (Heterozygous)	5/30 (16.7)
Prothrombin 20210A (Homozygous)	0
Plasminogen activator inhibitor−1 (Heterozygous)	9/38 (23.7)
Plasminogen activator inhibitor−1 (Homozygous)	4/38 (10.5)
Factor VIII elevation (in the acute period)	12/33 (36.4)
High total cholesterol or VLDL	10/26 (38.5)
Homocysteine >15 micromoles/litre	9/35 (25.7)
Lipoprotein (a) >30	4/35 (11.4)
Other	
Trauma	2 (4.8)
Dehydration	2 (4.8)
Port catheter insertion	1 (2.4)
Cause undetermined	0

* 76.2 % of patients have more than one risk factor, therefore the same patient can be included in more than one group.

3.3. Risk factors for acute symptomatic seizures

ASSs developed in 12 (28.6 %) of patients with CSVT. The average age of these patients was 57.92 ± 64 (12−186) months and 9 (75 %) patients were male. The age at thrombosis was statistically significantly younger in patients with ASS than in those without ASS (p=0.018). There was no difference between the groups in terms of gender (p = 0.442). The hospital stay of patients with ASS was statistically significantly longer (p = 0.016) (Table 3). Patients who had ASS had lower GCS scores and required intensive care unıt ($p<0.001$). Headache, change of consciousness, focal neurological findings, presence of motor deficits, presence of cerebral hemorrhage in brain MRI and D-dimer levels were detected to be statistically significantly higher in patients with ASS than

Table 2
Comparison of clinical and radiological features between CSVT groups with and without acute symptomatic seizures.

Classification	Variables*	Categories	Acute symptomatic seizure		Total	Chi-square statistics	*p*
			No (*n*=30)	Yes (*n*=12)	(*n*=42)		
Clinical features	**Gender**	**Girl**	11a (36.67 %)	3a (25.00 %)	14 (33.33 %)	-	0.719[3]
		Boy	19a (63.33 %)	9a (75.00 %)	28 (66.67 %)		
	Headache	**No**	7a (23.33 %)	10b (83.33 %)	17 (40.48 %)	-	**0.001**[3]
		Yes	23a (76.67 %)	2b (16.67 %)	25 (28.52 %)		
	Vomiting	**No**	19a (63.33 %)	10a (83.33 %)	29 (69.05 %)	-	0.282[3]
		Yes	11a (36.67 %)	2a (16.67 %)	13 (30.95 %)		
	Change of consciousness	**No**	28a (93.33 %)	7b (58.33 %)	35 (83.33 %)	-	**0.014**[3]
		Yes	2a (6.67 %)	5b (41.67 %)	7 (16.67 %)		
	Eye Findings	**No**	7a (23.33 %)	7b (58.33 %)	14 (33.33 %)	5.250	0.08[1]
		Papilledema	18a (60.00 %)	3b (25.00 %)	21 (50.00 %)		
		Abducens paralysis	5a (16.67 %)	2a (16.67 %)	7 (16.67 %)		
	Ataxia	**No**	28a (93.33 %)	12a (100.00 %)	40 (95.24 %)	-	0.999[3]
		Yes	2a (6.67 %)	0a (0.00 %)	2 (4.76 %)		
	Glasgow Coma Scale	**Good (GCS ≥ 8)**	29a (96.67 %)	4b (33.33 %)	33 (78.57 %)	-	**<0.001**[3]
		Bad (GCS< 8)	1a (3.33 %)	8b (66.67 %)	9 (21.43 %)		
	Focal neurological finding	**No**	24a (80.00 %)	1b (8.33 %)	25 (59.52 %)	-	**<0.001**[3]
		Yes	6a (20.00 %)	11b (91.67 %)	17 (40.48 %)		
	Motor Deficit	**No**	30a (100.00 %)	9b (75.00 %)	39 (92.86 %)	-	**0.019**[3]
		Yes	0a (0.00 %)	3b (25.00 %)	3 (7.14 %)		
	Sensory Deficit	**No**	25a (83.33 %)	11a (91.67 %)	36 (85.71 %)	-	0.655[3]
		Yes	2a (6.66 %)	1a (8.33 %)	3 (7.14 %)		
	Facial Paralysis	**No**	30a (100.00 %)	10b (83.33 %)	40 (95.24 %)	-	0.077[3]
		Yes	0a (0.00 %)	2b (16.67 %)	2 (4.76 %)		
Radiological features	**Cerebral edema**	**No**	17a (56.67 %)	10a (83.33 %)	27 (64.29 %)	-	0.158[3]
		Yes	13a (43.33 %)	2a (16.67 %)	15 (35.71 %)		
	Intracerebral Hemorrhage	**No**	29a (96.67 %)	3b (25.00 %)	32 (76.19 %)	-	**<0.001**[3]
		Yes	1a (3.33 %)	9b (75.00 %)	10 (23.81 %)		
	Cortical vein involvement	**No**	27a (90.00 %)	10a (83.33 %)	37 (88.10 %)	-	0.613[3]
		Yes	3a (10.00 %)	2a (16.67 %)	5 (11.90 %)		
	Thrombosis Location	**Superior Sagittal Sinus**	13a (43.33 %)	4a (33.33 %)	17 (40.48 %)	3.865	0.668[1]
		Transverse sinus	10a (33.33 %)	4a (33.33 %)	14 (33.33 %)		
		Sigmoid Sinus	4a (13.33 %)	2a (16.67 %)	6 (14.28 %)		
		Rectus Sinus	1a (3.33 %)	2a (16.67 %)	3 (7.14 %)		
		Internal Juguler Vein	2a (6.67 %)	0a (0.00 %)	2 (4.76 %)		
Outcome	**Functional outcome PSOM (twelve months)**	**Good outcome**	29a (96.67 %)	4b (33.33 %)	33 (78.57 %)	-	**<0.001**[3]
		Poor outcome	1a (3.33 %)	8b (66.67 %)	9 (21.43 %)		
Total			**30 (100.00 %)**	**12 (100.00 %)**	**42 (100.00 %)**		

a, b: Each same subscript letter denotes a subset of acute seizure categories whose column proportions do not differ significantly from each other at the 0,05 level. The statistically significant difference is expressed in bold.
CSVT: Cerebral sinovenous thrombosis; GCS: Glasgow Coma Scale; PSOM: Pediatric Stroke Outcome Measure
*Variables are expressed as frequency (percent).
[1]Pearson chi-square,
[2]Continuity correction
[3]Fisher's exact test

Table 3
Comparison of demographic features and D dimer levels between CSVT groups with and without acute symptomatic seizures.

Variables*	Acute Seizure		Total	*p***
	No (*n*=30)	Yes (*n*=12)	(*n*=42)	
Age at thrombosis (month)	124.33 ± 52.18 | 131 (9–200)	57.92 ± 64 | 19.5 (12–186)	105.36 ± 63.1 | 96.5 (9–200)	**0.018**
D-dimer level	482.73 ± 600.02 | 265 (40–2629)	1314.17 ± 1644.72 | 672 (130–5930)	720.29 ± 1060.63 | 395 (40–5930)	**0.013**
Durationran **Duration of hospital stay (days) (median, IQR)**	12 (8)	15 (12.85)		**0.016**

*: Variables are expressed as mean ± std. deviation | median (minimum-maximum).The statistically significant difference is expressed in bold.
IQR; interquartile range; CSVT: Cerebral sinovenous thrombosis
[1]: Independent samples t-test,
[2]: Mann-Whitney U test

in patients without ASS (p=0.001, p=0.014, p<0.001, p=0.019, p<0.001, p=0.013, respectively) (Table 2).

According to Hosmer and Lemeshow (HL) test results; The multiple logistic regression model (MLRA) established between the variables of age, presence of focal neurological findings, and D-dimer level was found to be statistically significant. Considering the outputs of the MLRA model, it is seen that the age variable has a negative correlation with the risk of ASS (OR = 0.85, p = 0.004). In other words, each unit decrease in age increases the risk of ASS by 15 %. The presence of focal neurological findings increases the risk of ASS by 32.18 times (p=0.003). When the D-dimer level increases by one unit, the risk increases by 4 in 1000, while every 0.01 unit increase in the D-dimer variable increases the risk of ASS by approximately 1.13 times (p = 0.036) (Table 4). ROC analysis results for the D-dimer variable; D-dimer > 498 ng/mL [AUC=0.743 (0.585 – 0.865) p=0.003] specificity of this value was found to be 85 %, sensitivity 53 % was statistically significant (Table 5). ROC Analysis results for D-dimer are shown in Fig. 1.

3.4. Functional outcomes

At the end of approximately 12 months of follow-up, there were 9 (21.4 %) patients with poor functional outcome calculated by PSOM.

Table 4
Multiple logistic regression analysis results for acute seizure development.

Model significance and goodness of fit statistics			Statistics of model's coefficients			
Hosmer & Lemeshow test			Variable	*ß*	*p*	OR (95 % CI)
χ^2	*df*	*p*				
			Age at thrombosis (month)	−0.163	**0.004**	0.850 (0.761 – 0.949)
			Focal neurological finding	3.471	**0.003**	32.176 (3.364 – 307.728)
8.817	8	0.358	**D –dimer level**	0.004	**0.036**	1.004 (1.001 – 1.008)

ß: Coefficient, *df*: Degree of freedom, CI: Confidence Interval, OR: Odds Ratio
p values which $p \leq 0.05$ are expressed in bold.

Table 5
ROC Analysis results for D-dimer in patients with cerebral sinovenous thrombosis.

Variable	Cut-off value	Metrics with 95 % CI			*p**
		AUC	Sensitivity	Specificity	
D-dimer	>498	0.743 (0.585 – 0.865)	0.533 (0.265 – 0.787)	0.852 (0.66 – 0.958)	**0.003**

AUC: Area under curve, CI: Confidence interval,
* Significance level for AUC

Functional outcomes assessed by PSOM were poor in patients with ASS than in those without ASS ($p<0.001$).

4. Discussion

We examined potential risk factors for the development of ASS using a cohort of children diagnosed with CSVT. ASSs occurred in approximately one-third of patients with CSVT. Young age, focal neurological findings, and high D-dimer level may predict acute seizures in children with CSVT. Children who developed ASS had worse outcomes measured by the PSOM.

ASSs occurred in 28.6 % of patients with CSVT. The incidence of ASS was consistent with previous pediatric stroke registries (20–58 %) [3–11]. In children, younger age was a potential predictor of the development of ASS, and each unit decrease in age increasing the risk of ASS by 15 %. Similarly, young age was shown to be a risk factor for the development of seizures after CSVT in a study conducted in adults [22]. The most common clinical finding in our cohort was headache. Serious clinical findings such as GCS <8 at admission, altered consciousness, and presence of focal neurological findings were more common in patients with ASS, and hospital stays were longer. The presence of focal neurological findings increased the risk of developing ASS by 32.18 times. The presence of intracerebral hemorrhage was associated with the risk of developing ASS. A recent study reported that in children hemorrhage predicted acute seizures, and acute seizures predicted the development of epilepsy [11]. Similarly, adult evidence showed that brain parenchymal lesions, including intracerebral hemorrhage, cerebral edema, and infarction, are basis predictors of ASS [12,23,24]. The location of the lesion also seems to be important in the development of acute seizures after stroke. Previous studies report that lesions in the supratentorial and anterior central sulci are predictive of ASS [23,24]. Superficial system thrombosis, such as cortical vein thrombosis and

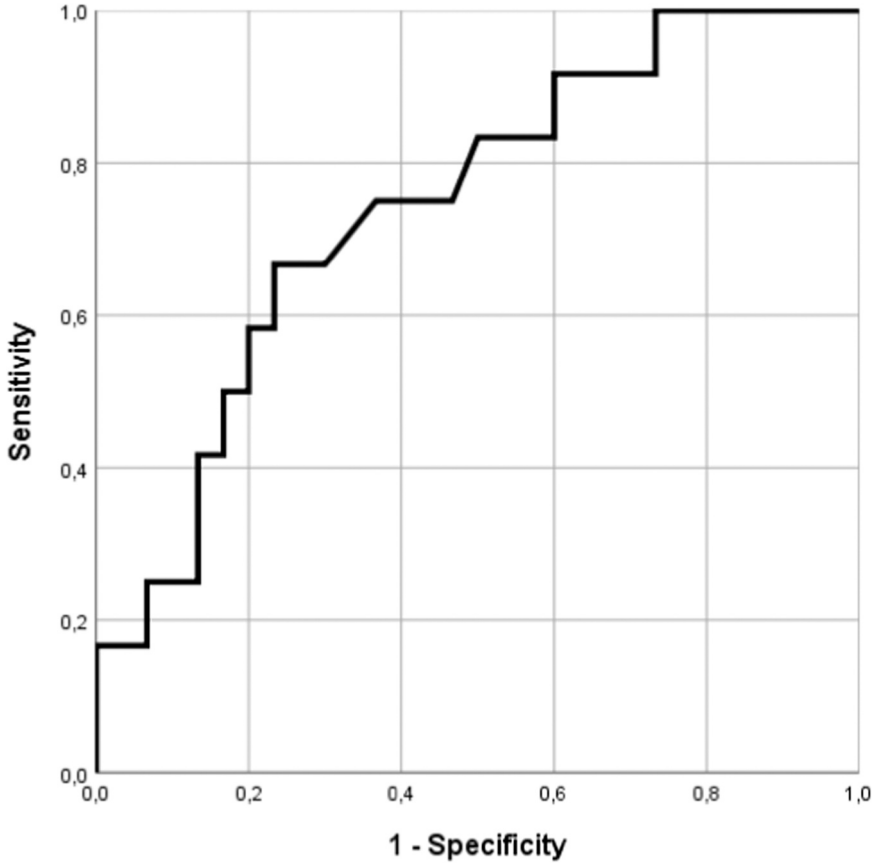


Fig. 1. ROC Analysis results for D-dimer in patients with cerebral sinovenous thrombosis.

superior sagittal sinus thrombosis, are associated with the risk of ASS [12]. In current study, thrombosis was most common in the superior sagittal sinus and transverse sinus, but no significant relationship was found between ASS and the location of the lesion.

It has been reported in the literature that the D-Dimer test is a useful biomarker in the diagnosis and exclusion of CSVT [25–27]. However, there are differences between studies in clinical practice. D-Dimer has been reported to have high sensitivity in distinguishing those with CSVT from those without, especially at values < 300 ng/mL [25]. On the contrary, it has been stated that it may be an indicator for predicting CSVT and further diagnostic procedures, especially in patients with headache, but low D-Dimer levels cannot be taken in clinical practice [26]. High D-dimer level has been associated with shorter symptom duration, more risk factors, and more multiple venous sinus involvement in acute/subacute CSVT patients [27]. It is also associated with complications and fatal course of the disease [26]. In the current study, ROC analysis demonstrated diagnostic accuracy for D-dimer levels > 498 ng/mL in children with CSVT. Additionally, it has been shown that every 0.01 unit increase in D-dimer level increases the risk of developing ASS by approximately 1.13 times. In this context, high D-dimer levels may be one of the candidate risk factors associated with the development of ASS in children with CSVT.

In current study, children who developed ASS at last follow-up (approximately 12 months) had worse outcomes as measured by PSOM. This finding was consistent with a previous study reporting that acute seizures were predictors of neurological outcomes [28]. Conversely, Lindgren et al. [12] reported that there was no significant difference in functional outcomes measured by the modified Rankin Score (mRS) between adults who developed and did not develop ASS, therefore the development of ASS was not associated with poor outcome and mortality. In a recent study, it was reported that worse PSOM scores were detected in newborns and children with CSVT who developed epilepsy compared to those who did not develop epilepsy [11]. A similar neonatal CSVT study showed that no newborns with normal results had epilepsy, and all those with epilepsy had neurological deficits [29]. In contrast to these two studies mentioned, no differences in mRS or King's Outcome Scale results for childhood head trauma were detected between those with and without epilepsy in pediatric CSVT [10]. However, it was reported that this finding may have been influenced by the small number of CSVT cases in the aforementioned study. Previous studies have shown that focal deficits and intracerebral hemorrhage are predictive of poor outcome [13,30]. The development of hemiparesis and epilepsy after stroke-related parenchymal hemorrhage has been associated with poorer health status [31]. In the current study found an epilepsy incidence rate of 12 % (5/42) for up to one year among children with CSVT. Significance tests could not be performed due to the small number of patients who developed epilepsy.

The current approach in children is that patients with ASS should be treated, but prophylactic ASM therapy is controversial when seizures do not occur [13]. Guidelines for the treatment of pediatric severe traumatic brain injury [32] recommend prophylactic ASM when the risk of seizures is high, considering that seizures will increase cerebral blood flow and intracranial pressure. This recommendation is based on an estimated incidence of 12 % of clinical seizures and 20–25 % of electrographic seizures [10]. It has been reported that the risk of distant seizures is reduced when ASM prophylaxis is used in patients with supratentorial lesions and seizures in the acute phase [33]. On the contrary, prophylactic ASM is not recommended because there are no risk factors that adequately predict future seizure development in the absence of ASS [12]. In the current study, five out of 12 children with acute seizures were (41.7 %) diagnosed with epilepsy. However some of the children who have acute seizures did not develop epilepsy. The incidence of epilepsy was found to be lower than reported in the literature [9–11]. This may be due to the fact that all patients with acute seizures receive ASM. In this context further studies are needed to determine which children would benefit from continuing ASMs after acute seizures due to CSVT.

4.1. Limitations

The current study has some limitations; Firstly, due to the relative scarcity of cases developing epilepsy (considering the rarity of CSVT), inferential statistical methods were not used as they would produce poor results in terms of generalizability in terms of epilepsy. Secondly, EEG was performed on patients with clinically symptomatic seizures and altered consciousness. Therefore, the data do not include subclinical seizures and electrographic seizures. Since routine EEG recording was not performed in children without clinical seizure activity, subclinical seizures or non-convulsive electrographic seizures could not be systematically investigated. Third, all patients who developed ASS received ASM, but routine ASM was not started in patients who did not develop ASS. For this reason, an evaluation of the treatment effects of ASMs could not be made. The potential effects of prophylactic ASM on the development of epilepsy and long-term outcomes in patients with CSVT require further investigation.

5. Conclusion

The current study has clinical implications that may be useful for counseling about acute seizure risk and outcomes after CSVT. Young age, presence of focal neurological findings and high D-dimer levels were risk factors associated with the development of ASS after CSVT. Children who developed ASS had poorer outcomes as measured by the PSOM.

Ethical approval

The study was approved by Inönü University Ethics Committee (date: (protocol no: 2023/4531). Written informed consent was not obtained from the participants due to the retrospective nature of the study.

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CRediT authorship contribution statement

Yurday Öncül: Writing – review & editing, Validation, Supervision, Investigation, Conceptualization. **Murat Çağlar Şahin:** Writing – review & editing, Validation, Supervision, Resources, Investigation, Conceptualization. **Bilge Özgör:** Writing – review & editing, Validation, Supervision, Investigation, Conceptualization. **Ahmet Kadir Arslan:** Writing – review & editing, Visualization, Validation, Supervision, Software, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Serdal Güngör:** Writing – review & editing, Validation, Supervision. **Arzu Akyay:** Writing – review & editing, Validation, Supervision. **Sevgi Demiröz Taşolar:** Writing – review & editing, Validation, Supervision, Conceptualization. **Gül Yücel:** Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Conflict of interest

The authors declare that there is no conflict of interest to disclose

References

[1] R. Ichord, Cerebral sinovenous thrombosis, Front. Pedia (5) (2017) 163, https://doi.org/10.3389/fped.2017.00163.
[2] N. Dlamini, L. Billinghurst, F.J. Kirkham, Cerebral venous sinus (sinovenous) thrombosis in children, Neurosurg. Clin. N. Am. 21 (3) (2010) 511–527, https://doi.org/10.1016/j.nec.2010.03.006.

[3] V. Lolli, F. Molinari, J.P. Pruvo, G. Soto Ares, Radiological and clinical features of cerebral sinovenous thrombosis in newborns and older children, J. Neuroradiol. 43 (4) (2016) 280–289, https://doi.org/10.1016/j.neurad.2015.12.001.
[4] A. Ozcan, M. Canpolat, S. Doganay, Cerebral sinus venous thrombosis and prothrombotic risk factors in children: a single-center experience from Turkey, J. Pedia Hematol. Oncol. 40 (6) (2018) e369–e372, https://doi.org/10.1097/MPH.0000000000001149.
[5] S. Grunt, K. Wingeier, E. Wehrli, Cerebral sinus venous thrombosis in Swiss children, Dev. Med. Child Neurol. 52 (12) (2010) 1145–1150, https://doi.org/10.1111/j.1469-8749.2010.03722.x.
[6] G. Sébire, B. Tabarki, D.E. Saunders, Cerebral venous sinus thrombosis in children: risk factors, presentation, diagnosis and outcome, Brain 128 (3) (2005) 477–489, https://doi.org/10.1093/brain/awh412.
[7] M. Wasay, A.I. Dai, M. Ansari, Cerebral venous sinus thrombosis in children: a multicenter cohort from the United States, J. Child Neurol. 23 (1) (2008) 26–31, https://doi.org/10.1177/0883073807307976.
[8] L.P. Cornelius, N. Elango, V.K. Jeyaram, Clinico-etiological factors, neuroimaging characteristics and outcome in pediatric cerebral venous sinus thrombosis, Ann. Indian Acad. Neurol. 24 (6) (2021) 901–907, https://doi.org/10.4103/aian.AIAN_221_21.
[9] R.N. Ichord, S.L. Benedict, A.K. Chan, International Paediatric Stroke Study Group. Paediatric cerebral sinovenous thrombosis: findings of the International Paediatric Stroke Study, Arch. Dis. Child 100 (2) (2015) 174–179, https://doi.org/10.1136/archdischild-2014-306382.
[10] A. Mineyko, A. Kirton, L. Billinghurst, Seizures and outcome one year after neonatal and childhood cerebral sinovenous thrombosis, Pedia Neurol. 105 (2020) 21–26, https://doi.org/10.1016/j.pediatrneurol.2019.08.012.
[11] A.R. Karlin, N.K. Kumar, A. Vossough, Pediatric cerebral sinovenous thrombosis and risk for epilepsy, Pedia Neurol. 146 (2023) 85–94, https://doi.org/10.1016/j.pediatrneurol.2023.05.014.
[12] E. Lindgren, S.M. Silvis, S. Hiltunen, Acute symptomatic seizures in cerebral venous thrombosis [published correction appears in Neurology. 96 (13) (2021) 639. doi: 10.1212/WNL.0000000000011322.
[13] D.M. Ferriero, H.J. Fullerton, T.J. Bernard, Management of stroke in neonates and children: a scientific statement from the american heart association/american stroke association, e51-e96, Stroke 50 (3) (2019), https://doi.org/10.1161/STR.0000000000000183.
[14] J.M. Ferro, M.,G. Bousser, P. Canhão, European Stroke Organization guideline for the diagnosis and treatment of cerebral venous thrombosis - endorsed by the European Academy of Neurology, Eur. J. Neurol. 24 (10) (2017) 1203–1213, https://doi.org/10.1111/ene.13381.
[15] G. Saposnik, F. Barinagarrementeria, R.D.Jr Brown, RD, Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association, Stroke 42 (4) (2011) 1158–1192, https://doi.org/10.1161/STR.0b013e31820a8364.
[16] R.S. Fisher, J.H. Cross, J.A. French, Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology, Epilepsia 58 (4) (2017) 522–530, https://doi.org/10.1111/epi.13670.
[17] D.J. Thurman, E. Beghi, C.E. Begley, Standards for epidemiologic studies and surveillance of epilepsy, Epilepsia 52 (7) (2011) 2–26, https://doi.org/10.1111/j.1528-1167.2011.03121.x.
[18] E. Beghi, A. Carpio, L. Forsgren, Recommendation for a definition of acute symptomatic seizure, Epilepsia 51 (4) (2010) 671–675, https://doi.org/10.1111/j.1528-1167.2009.02285.x.
[19] R.S. Fisher, C. Acevedo, A. Arzimanoglou, ILAE official report: a practical clinical definition of epilepsy, Epilepsia 55 (4) (2014) 475–482, https://doi.org/10.1111/epi.12550.
[20] E. Trinka, H. Cock, D. Hesdorffer, A definition and classification of status epilepticus–Report of the ILAE task force on classification of status epilepticus, Epilepsia 56 (10) (2015) 1515–1523, https://doi.org/10.1111/epi.13121.
[21] L. Kitchen, R. Westmacott, S. Friefeld, The pediatric stroke outcome measure: a validation and reliability study, Stroke 43 (6) (2012) 1602–1608, https://doi.org/10.1161/STROKEAHA.111.639583.
[22] N.S. Graham, S. Crichton, M. Koutroumanidis, Incidence and associations of poststroke epilepsy: the prospective South London Stroke Register, Stroke 44 (3) (2013) 605–611, https://doi.org/10.1161/STROKEAHA.111.000220.
[23] J.M. Ferro, P. Canhão, J. Stam, M.G. Bousser, Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT), Stroke 35 (3) (2004) 664–670, https://doi.org/10.1161/01.STR.0000117571.76197.26.
[24] J.M. Ferro, M. Correia, M.J. Rosas, Cerebral venous thrombosis portuguese collaborative study group[Venoport]. Seizures in cerebral vein and dural sinus thrombosis, Cereb. Dis. 15 (1-2) (2003) 78–83, https://doi.org/10.1159/000067133.
[25] D. Soni, A.K. Pannu, A. Saroch, The utility of quantitative D-dimer assay as a biomarker in the diagnosis and exclusion of cerebral venous sinus thrombosis, Indian J. Hematol. Blood Transfus. 40 (1) (2024) 122–129, https://doi.org/10.1007/s12288-023-01677-8.
[26] I. Domitrz, A. Sadowski, W. Domitrz, Cerebral venous and sinus thrombosis diagnosis: preliminary study of clinical picture and D-dimer concentration correlation, Neurol. Neurochir. Pol. 54 (1) (2020) 66–72, https://doi.org/10.5603/PJNNS.a2020.0006.
[27] H.F. Wang, C.Q. Pu, X. Yin, D-dimers (DD) in CVST, Int. J. Neurosci. 127 (6) (2017) 524–530, https://doi.org/10.1080/00207454.2016.1207172.
[28] G. deVeber, M. Andrew, C. Adams, Cerebral sinovenous thrombosis in children, N. Engl. J. Med 345 (6) (2001) 417–423, https://doi.org/10.1056/NEJM200108093450604.
[29] M.D. Moharir, M. Shroff, A.M. Pontigon, A prospective outcome study of neonatal cerebral sinovenous thrombosis, J. Child Neurol. 26 (9) (2011) 1137–1144, https://doi.org/10.1177/0883073811408094).
[30] A.R. Hart, V. Ganesan, K.S. Pysden, Variations in the management of children with cerebral venous sinus thrombosis in the UK and Ireland, Dev. Med Child Neurol. 54 (8) (2012) 770–771, https://doi.org/10.1111/j.1469-8749.2011.04137.x.
[31] S.E. Smith, G. Vargas, A.J. Cucchiara, Hemiparesis and epilepsy are associated with worse reported health status following unilateral stroke in children, Pedia Neurol. 52 (4) (2015) 428–434, https://doi.org/10.1016/j.pediatrneurol.2014.11.016.
[32] N. Carney, A.M. Totten, C. O'Reilly, Guidelines for the management of severe traumatic brain injury, fourth edition, Neurosurgery 80 (1) (2017) 6–15, https://doi.org/10.1227/NEU.0000000000001432.
[33] J.M. Ferro, P. Canhão, Acute treatment of cerebral venous and dural sinus thrombosis, Curr. Treat. Options Neurol. 10 (2) (2008) 126–137, https://doi.org/10.1007/s11940-008-0014-0.