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Research Article

Prognosis and Outcome of Cerebral Sinus Venous Thrombosis—A Multicenter Cohort Study

Naaem Simaan[1,2] **Asaf Honig**[3] **Hen Hallevi**[4,5] **Estelle Seyman**[4] **Ofer Rotschild**[4] **Einor Ben Assayag**[4,5] **Andrei Filioglo**[3] **Shlomi Peretz**[6] **Rom Mendel**[6] **Rani Barnea**[6] **Eitan Auriel**[6] **Shorooq Aladdin**[7] **David Orion**[7] **Khalil Darawsha**[1,2] **Fadi Shbat**[1,2] **Ronen R. Leker**[3] **and Jeremy Molad**[4]

[1]*Department of Neurology, Ziv Medical Center, Safed, Israel*
[2]*The Azrieli Faculty of Medicine, Bar Ilan University's, Safed, Israel*
[3]*Departments of Neurology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel*
[4]*Department of Neurology & Stroke, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel*
[5]*Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel*
[6]*Department of Neurology, Rabin Medical Center, Petah Tikva, Israel*
[7]*Departments of Neurology, Sheba Medical Center, Ramat Gan, Israel*

Correspondence should be addressed to Ronen R. Leker; leker@hadassah.org.il

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Objectives. Cerebral sinus venous thrombosis (CSVT) is a rare stroke subtype and data regarding prognostic factors to predict outcomes are lacking. Thus, we aimed to identify predictors for outcome among CSVT patients. *Materials and Methods*. Prospective CSVT databases from four academic medical centers were retrospectively studied. Demographics, clinical presentations, risk factors, radiological, and outcome parameters were compared. *Results*. Out of 508 patients diagnosed with CSVT, 21 patients (4%) died, and 91 (18.6%) had unfavorable outcome (mRS ≥ 2). Age (55.0 vs. 38.5, $p < 0.001$), hypertension (26% vs. 6%, $p < 0.001$), hyperlipidemia (23% vs. 6%, $p < 0.001$), diabetes (17% vs. 4%, $p < 0.001$), malignancy (35% vs. 11%, $p < 0.001$), absence of headache (51% vs. 78%, $p < 0.001$), focal neurological deficit (54% vs. 19%, $p < 0.001$), and ICH (28% vs. 13%, $p < 0.001$) were all associated with unfavorable outcome. After multivariate analysis malignancy (OR 4.2, $p = 0.003$), the presence of focal neurological deficit (OR 5.2, $p < 0.001$) and the presence of headache upon presentation (OR 0.334, $p = 0.018$) remained significant predictors for favorable outcome. *Conclusions*. Among CSVT patients, malignancy, focal neurological deficits, and absence of headache at presentation were associated with unfavorable outcomes.

1. Introduction

Cerebral sinus venous thrombosis (CSVT) is a rare stroke subtype responsible for 0.5–1% of all stroke cases [1, 2]. In most cases, CSVT has favorable outcomes; however, previous studies report up to 5% mortality during admission [3, 4] and long-term neurological sequelae in up to 15% of patients [5–8]. Thus, early identification of high risk patients is of great importance. Previous studies reported several predictors of mortality and unfavorable outcome including age, gender, intracerebral hemorrhage (ICH), malignancy, CNS infection, and thrombus location [5–7, 9–16]. However, results were inconsistent, and most studies included only partial data regarding patients' comorbidities and underlying etiology. Therefore, we aimed to identify predictors for CSVT prognosis in a large comprehensive multicenter database.

2. Methods

Data from ongoing prospective CSVT registries from four large tertiary stroke academic centers was pulled and retrospectively analyzed. The database included consecutive patients admitted with nontraumatic and nonpostneurosurgical CSVT between the years 2010 and 2021. The study was approved by the local institutional review boards of each center.

Baseline characteristics and comorbidities including vascular risk factors, smoking, use of oral contraceptives, pregnancy, and other possible premorbid factors were documented. Data regarding the clinical presentation, neurological deficit including severity as assessed by the national institute of health stroke scale (NIHSS), and seizures was obtained from the medical records. Focal neurological deficit was defined as NIHSS > 0. Coma was defined as Glasgow Coma Scale (GCS) ≤ 8, and all patients defined as coma scored 2 on item 1a of the NIHSS. Papilledema was examined by a senior neurologist or by an ophthalmologist. Clinical follow-up was performed at the stroke outpatient clinics of the participating centers including modified Rankin scale (mRS). Favorable outcome was defined as mRS < 2 at 90 days' post CSVT diagnosis. Mortality was reported within 1 year of SVT diagnosis.

CSVT diagnosis was based on neurovascular imaging (CT venography or MR venography) which were assessed by trained neuroradiologists. The location of the involved sinus or cortical vein was recorded, including superior sagittal sinus (SSS), transverse sinus, sigmoid sinus, cavernous sinus, cortical veins, and deep venous system (straight sinus, vein of Galen, and vein of Rosenthal). Multiple sinus involvement was defined as involvement of more than one venous sinus excluding the combination transverse and sigmoid. Presence of venous infarcts and intracerebral hemorrhage (ICH) were also recorded.

Patients underwent similar thorough etiology workup at the participating centers. Extensive laboratory workup was performed including complete blood count, routine blood biochemistry, protein C, protein S, antithrombin III, factor V Leiden, factor VIII, prothrombin, homocysteine, anticardiolipin and anti-beta-2-glycoprotein antibodies, and lupus anticoagulant were studied. Studies to detect JAK2 mutations were done if thrombocytosis or polycythemia were present or in other patients by the decision of senior neurologist or hematologist. Patients with CSVT with unknown etiology underwent further workup in order to rule out occult malignancy. All patients with suspected malignancy underwent a standardized screening that included blood workup for tumor markers such as CEA and CA, a total body CT, and clinical evaluation of the skin by a dermatologist to r/o melanoma. Males underwent clinical examination of the testes by a urologist to rule out testicular tumors and females underwent mammography or ultrasound to rule out breast tumors.

All patients were treated with anticoagulants therapy. Treatment allocation was done at the discretion of the attending physician at each centers. Most patients were started on low molecular heparin (LMWH) and were then transferred to oral anticoagulants but some remained on LMWH for >6 months.

2.1. Statistical Analysis. Statistical analysis was performed using the SPSS software (version 27.0, IBM, Chicago, IL, USA). Continuous variables were reported as a mean value (±SD), ordinal variables as median (IQR) and dichotomous variables as percentage of the total. Comparisons or distributions between categories were assessed using Student's t-test for continuous variables, chi square test for qualitative variables, and the Mann–Whitney or to compare differences between two independent groups when the dependent variable is either ordinal or continuous, but not normally distributed. Univariate logistic regression models were employed to examine the significance and univariate proportional hazard ratios for each risk factor. Variables yielding a $p < 0.05$ on the univariate analyses for mortality or unfavorable outcomes defined as mRS ≥ 2 at 90 days were entered into multivariate regression models.

3. Results

3.1. Overall Characteristics. A total of 508 CSVT patients (mean age 41.7 ± 18.7, 67% females) were included in the study. Follow-up information including mRS-90 was available for 488 patients (96%).

Within 90 days of admission, 91 (18.6%) patients had unfavorable outcome defined as mRS ≥ 2, and 21 (4%) patients died (Tables 1 and 2).

None of our patients were treated with endovascular procedures such as thrombectomy or stent placement as these procedures are done only as a last resort in comatose unresponsive patients.

On univariate analyses, unfavorable outcome and mortality were associated with older age (55.0 vs. 38.5, $p < 0.001$, 59.8 vs. 40.9, $p < 0.001$, respectively) and higher rates of hypertension (26% vs. 6%, $p < 0.001$, and 29% vs. 8%, $p = 0.006$, respectively). Unfavorable outcome was also associated with higher rates of hyperlipidemia and diabetes (23% vs. 6%, $p < 0.001$, 17% vs. 4%, $p < 0.001$, respectively).

3.2. Clinical Presentation. The presenting symptoms were variable and included headache vomiting focal signs and seizures. Only two patients presented with coma. Mortality and unfavorable outcome were associated with higher rates of focal neurological deficit at presentation (25% vs. 24%, $p = 0.029$, 54% versus 19%, $p < 0.001$, respectively), worse admission NIHSS scores (1[0-12] vs. 0[0-0], $p < 0.001$, 2[0-6] vs. 0[0], $p < 0.001$, respectively), and lower rates of headache (43% vs. 74%, $p < 0.001$, 51% vs. 78%, $p < 0.001$, respectively). Unfavorable outcome, but not mortality, was associated with higher rates of seizures (41% vs. 14%, $p < 0.001$).

3.3. Underlying Etiology. When examining the underlying etiology, mortality and unfavorable outcome were associated with higher rates of malignancy (81% vs. 13%, $p < 0.001$, 35% vs. 11%, $p < 0.001$, respectively), lower rates of oral contraceptives (0% vs. 22%, $p = 0.013$, 11% vs. 22%, $p = 0.006$, respectively), and lower rates of any laboratory measured coagulopathy (5% vs. 40%, $p < 0.001$, 20% vs. 41%, $p < 0.001$, respectively).

Table 1: Comparison of CSVT patients, Survival and Mortality.

Characteristics	Mortality $N = 21$	Survival $N = 487$	p
Age, mean (SD)	59.8 (17.7)	40.9 (18.0)	**<0.001**
Gender male (%)	8 (38)	161 (33)	0.707
Smoking (%)	3 (14)	89 (18)	0.582
Hyperlipidemia (%)	4 (19)	13 (3)	0.219
Hypertension (%)	6 (29)	40 (8)	**0.006**
Obesity (%)	0 (0)	21 (4)	0.273
Diabetes (%)	3 (14)	27 (6)	0.178
Malignancy (%)	17 (81)	61 (13)	**<0.001**
Previous thrombotic events (%)	0 (0)	40 (8)	0.163
Oral contraceptives (%)	0 (0)	106 (22)	**0.013**
Precipitating triggers			
Dehydration (%)	0 (0)	12 (2)	0.761
Infections (%)	1 (5)	29 (6)	0.802
Clinical presentation			
Papilledema (%)	3 (14)	122 (25)	0.299
Headache (%)	9 (43)	361 (74)	**<0.001**
Vomiting (%)	2 (10)	77 (15)	0.386
Seizure (%)	3 (14)	99 (20)	0.459
Any focal neurological deficit (%)	11 (52)	121 (24)	**0.029**
NIHSS upon admission (IQR)	1 (0-12)	0 (0-0)	**<0.001**
Hematological workup			
APLA (%)	1 (5)	60 (12)	0.275
Protein C/S deficiency (%)	1 (5)	18 (4)	0.963
Factor V deficiency (%)	0 (0)	37 (8)	0.182
Factor II mutation (%)	0 (0)	9 (2)	0.522
PT 20210	0 (0)	25 (5)	0.277
Behcet's disease (%)	0 (0)	18 (4)	0.364
MTHFR (%)	0 (0)	24 (5)	0.283
JAK 2 (%)	0 (0)	33 (7)	0.223
Thrombocytosis (%)	0 (0)	25 (5)	0.200
Hyperhomocysteinemia (%)	0 (0)	9 (2)	0.526
Any coagulopathy (%)	1 (5)	193 (40)	**<0.001**
Radiological findings			
Multiple veins (%)	8 (38)	117 (24)	0.132
Cortical vein involvement (%)	2 (10)	54 (11)	0.828
Deep vein involvement (%)	3 (14)	20 (4)	**0.027**
Venous infarction (%)	6 (29)	43 (9)	**0.012**
ICH (%)	6 (29)	78 (16)	0.154
Involved sinus (%)			
Isolated SSS	10 (48)	178 (36)	0.289
Transverse sinus	11 (52)	323 (66)	0.171
Sigmoid sinus	10 (48)	312 (64)	0.116
Cavernous sinus	2 (10)	8 (2)	**0.011**

NIHSS: National Institute of Health Stroke Scale, APLA: antiphospholipid antibodies, PT 20210: prothrombin 20210, MTHFR: methylenetetrahydrofolate reductase, ICH: intracerebral hemorrhage, SSS: superior sagittal sinus.

3.4. Radiological Findings. Mortality was associated with higher rates of deep vein involvement and cavernous sinus involvement (14% vs. 4%, $p = 0.027$, 10% vs. 2%, $p = 0.011$, respectively). No additional association was found between unfavorable outcome and the involved sinus or cortical vein involvement. Unfavorable outcome was associated

Table 2: Comparison of CSVT patients, favorable outcome, and unfavorable outcome.

Characteristics	Favorable outcome $N = 397$	Unfavorable outcome $N = 91$	p
Age, mean (SD)	38.5 (16.3)	55.0 (20.5)	**<0.001**
Gender, male (%)	136 (34)	29 (31)	0.653
Dehydration (%)	10 (3)	1 (1)	0.632
Infections (%)	24 (6)	6 (7)	0.684
Smoking (%)	78 (19)	14 (15)	0.339
Hyperlipidemia (%)	27 (6)	21 (23)	**<0.001**
Hypertension (%)	23 (6)	24 (26)	**<0.001**
Obesity (%)	20 (5)	1 (1)	0.088
Diabetes (%)	15 (4)	16 (17)	**<0.001**
Malignancy (%)	44 (11)	32 (35)	**<0.001**
Previous thrombotic events (%)	34 (9)	6 (7)	0.525
Oral contraceptives (%)	95 (24)	10 (11)	**0.006**
Clinical presentation			
Papilledema (%)	108 (27)	17 (19)	0.141
Headache (%)	325 (82)	46 (51)	**<0.001**
Vomiting (%)	71 (18)	8 (9)	0.064
Seizure (%)	60 (15)	38 (41)	**<0.001**
Any focal neurological deficit (%)	81 (20)	49 (54)	**<0.001**
NIHSS upon admission, mean (SD)	0 (0-0)	2 (0-6)	**<0.001**
Hematological workup			
APLA (%)	55 (14)	6 (7)	0.06
Protein C/S deficiency (%)	17 (4)	3 (3)	0.849
Factor V deficiency (%)	32 (8)	4 (4)	0.244
Factor II mutation (%)	9 (2)	0 (0)	0.153
PT 20210	18 (5)	7 (8)	0.181
Behcet's disease (%)	18 (5)	0 (0)	**0.042**
MTHFR (%)	20 (5)	1 (1)	0.101
JAK 2 (%)	29 (7)	4 (4)	0.435
Thrombocytosis (%)	22 (6)	2 (2)	0.196
Hyperhomocysteinemia (%)	8 (2)	0 (0)	0.181
Any coagulopathy (%)	174 (44)	18 (20)	**<0.001**
Radiological findings			
Multiple veins (%)	89 (22)	35 (38)	**0.002**
Cortical (%)	38 (10)	15 (16)	0.059
Deep (%)	16 (4)	7 (8)	0.141
Venous infarction (%)	25 (6)	24 (26)	**<0.001**
ICH (%)	57 (14)	26 (28)	**<0.001**
Involved sinus (%)			
Superior sagittal sinus (%)	140 (25)	46 (51)	0.008
Transverse sinus (%)	272 (69)	59 (64)	0.525
Sigmoid sinus (%)	267 (67)	54 (59)	0.124
Cavernous sinus (%)	7 (2)	3 (3)	0.357
MRS 90 (IQR)	0 (0-0)	3 (2-5)	**<0.001**

NIHSS: National Institute of Health Stroke Scale, APLA: antiphospholipid antibodies, PT 20210: prothrombin 20210, MTHFR: methylenetetrahydrofolate reductase, ICH: intracerebral hemorrhage, SSS: superior sagittal sinus, MRS: modified Rankin scale, IQR: interquartile range.

with multiple veins involvement (38% vs. 21%, $p = 0.002$). Mortality and unfavorable outcome were associated with venous infarction (29% vs. 9%, $p = 0.012$, 26% vs. 6%, $p < 0.001$, respectively). Unfavorable outcome was also associated with ICH (28% vs. 13%, $p < 0.001$). 25 patients in our cohort had both ICH and venous infarct. These

patients had higher mortality rates (12.5% versus 3.7%, $p = 0.038$) and lower rates of favorable outcome (54.2% versus 84.5%, $p < 0.001$).

3.5. Multivariate Analysis. A multivariate logistic regression model controlling for age, hypertension, malignancy, headache, any coagulopathy, focal neurological deficit, oral contraceptives, deep vein involvement, and venous infarction was used to assess for predictors of survival among CSVT patients (Table 3). Malignancy (OR 89.78, $p < 0.001$) remained as positive predictor and headache at presentation remained a negative predictor (OR 0.07, $p = 0.008$) for mortality.

A multivariate logistic regression model controlling for age, gender, hypertension, hyperlipidemia, diabetes, malignancy, any coagulopathy, use of oral contraceptives, headache, focal neurological deficit, seizures, ICH, multiple vein involvement, and venous infarction was used to assess for predictors of unfavorable outcomes (Table 4). Malignancy (OR 4.176, $p = 0.003$) and the presence of focal neurological deficits (OR 5.167, $p < 0.001$) were found to be positive predictors of unfavorable outcome whereas headache at presentation (OR 0.334, $p = 0.018$) was identified as a negative predictor of unfavorable outcomes. Other variables did not influence the chances of unfavorable outcome.

Table 3: Multivariate analysis for predictors of mortality.

	OR	95% CI		p
Age	1.023	0.974	1.075	0.358
Gender (male)	0.243	0.031	1.913	0.179
Hypertension	2.599	0.285	23.700	0.397
Any malignancy	**89.784**	**7.571**	**1064.770**	**≤0.001**
Any coagulopathy	0.000	0.000		0.994
Oral contraceptives	0.000	0.000		0.998
Headache	**0.070**	**0.010**	**0.497**	**0.008**
Focal neurological deficit	0.744	0.151	3.659	0.716
Deep sinus	2.583	0.220	30.391	0.451
Cavernous sinus	8.741	0.530	144.092	0.129
Venous infarct	3.086	0.522	18.248	0.214

OR: odds ratio, CI: confident interval.

4. Discussion

In the current study, we examined numerous clinical and radiological factors for identification of prognostic factors in patients with CSVT. We found that the presence of malignancy and focal neurological deficit at presentation were associated with higher risks of unfavorable outcomes, while headache at presentation was associated with lower risks of unfavorable outcome among patients with CSVT.

Prior studies examining CSVT prognosis had shown conflicting results or focused on specific factors and presented only limited data [4–17]. None of these studies examined the interrelation between CSVT and cardiovascular risk factors. Previous large cohort studies [5, 14] demonstrated conflicting results regarding the association between prognosis and age, ICH, thrombus location, and clinical presentation. Another study by Dentali et al. [16] included 706 patients and examined long-term survival and recurrence risk, but not neurological or functional outcomes.

Malignancy was the strongest predictive factor for poor prognosis in our cohort. This finding was also reported in other studies [5, 7, 14]. Malignancy is a well-described predisposing factor for venous thrombotic events and is associated with poor outcomes and higher recurrence rates. These findings suggest that clinicians should have a high index of suspicion for malignancy-associated CSVT and should initiate early diagnostic measures for its detection if no other causes are apparent. Indeed, in the current study, malignancies were identified in 15% of patients. Unfortunately, we did not assess the time to diagnosis of malignancy or the specific types of malignancy in the current work, and these should be studied more carefully in future studies.

In line with previous studies, patients who presented with headache had lower rates of unfavorable outcomes and lower mortality rates [14, 17]. Such patients presumably seek medical consultation earlier and are diagnosed closer to CSVT occurrence, allowing early treatment thus avoiding complications including development of focal neurological deficits or seizures. In our cohort, headache was associated with younger age. This may be due to higher rates of brain atrophy in older patients, allowing milder elevation of the intracranial pressure, and indeed, patients without headaches had lower rates of papilledema. Another plausible explanation may relate to lower rates of headache among patients with impaired glucose metabolism [18].

Patients with focal neurological deficit had higher rates of unfavorable outcomes and mortality on univariate analysis. However, the presence of focal deficits did not remain a significant modifier of mortality after adjustments in the multivariate analysis although it did remain significantly associated with a higher risk of unfavorable outcome. Similarly, in accordance with previous studies, we found no association between cortical vein involvement and outcomes. This could be somewhat surprising, as cortical vein thrombosis is associated with higher rates of focal neurological deficits and seizures [19]. However, in line with previous studies, seizures were not associated with unfavorable outcomes in the current analysis [5, 8, 14, 17].

Surprisingly, we found no association between the involved sinus or the presence of multiple vein or sinus involvement and outcomes. In the VENOST study, superior sagittal sinus involvement was associated with poor outcomes, while transverse sinus involvement was associated with higher rates of favorable outcomes [14]. In the ISCVT study, only involvement of the deep cerebral veins was associated with prognosis [5]. Of note, we also found associations between deep vein thrombosis and mortality in the univariate analysis, but significance was lost in the adjusted multivariable analysis. The reasons for these discordant results across studies are not entirely clear.

Unlike most previous studies, which have reported male gender to be associated with unfavorable outcome [5, 14], we could not detect such an association. However, we did not

Table 4: Multivariate analysis for predictors of unfavorable outcome.

	OR	95% CI		p
Age	1.015	0.989	1.042	0.267
Gender (male)	0.612	0.257	1.456	0.267
Hypertension	1.097	0.287	4.189	0.893
Hyperlipidemia	3.313	0.906	12.116	0.07
Diabetes	3.308	0.836	13.098	0.088
Malignancy	**4.176**	**1.628**	**10.713**	**0.003**
Any coagulopathy	0.389	0.148	1.024	0.065
Oral contraceptives	1.156	0.323	4.137	0.823
Headache	**0.334**	**0.135**	**0.825**	**0.018**
Focal neurological deficit	**5.167**	**2.219**	**12.036**	**≤0.001**
Seizure	1.561	0.630	3.870	0.336
ICH	1.025	0.385	2.729	0.960
Multiple veins	1.479	0.636	3.441	0.364
Venous infarction	1.316	0.862	2.011	0.204

OR: odds ratio, CI: confident interval, ICH: intracerebral hemorrhage.

perform analysis of gender-specific risk factors on the resulting outcome other than the use of oral contraceptives. Future studies should further investigate the effect of gender-specific factors on outcome and divide the patient population by gender to see if these have particular effects in specific populations [20].

Additionally, in our cohort, older age was not independently associated with unfavorable outcome on multivariate analysis. Age was associated with prognosis in one large previous cohort [5, 14] but not in others [8, 16, 17]. It should be noted that the average age of patients in the current study was similar to those reported in previous studies. We report that higher rates of cardiovascular risk factors were found among patients with unfavorable outcome. As the rates of cardiovascular risk factors increase with age, this may explain the previous association reported between age and outcome among CSVT patients. Hypertension is related to increased blood-brain barrier breakdown and elevated cerebral blood flow and, therefore, may be associated with higher rates of ICH. However, in our cohort, hypertensive patients had similar rates of ICH and venous infarct compared to patients without hypertension.

Interestingly, hyperlipidemia was associated with unfavorable outcomes in the current study. However, this association was only seen in the univariate analysis and did not remain significant after adjustments in the multivariate analysis. Some studies described elevated risk for systemic venous thrombotic events (VTE) among patients with dyslipidemia [21–23]. Several possible mechanisms were suggested including a prothrombotic effect and endothelium altering properties of circulating lipids, as well as an association between triglycerides and various coagulopathy factors [21, 23]. Another possible mechanism includes a dose-dependent association found between VTE risk and decreased levels of apolipoproteins B and A1, possibly due to anticoagulant properties [22]. Moreover, it was previously suggested that statins may reduce the risk for VTE [21, 24, 25]. Future studies should further examine the association between CSVT and hyperlipidemia, as well as the influence of statins on CSVT occurrence and outcome.

The strengths of our study include the relatively large multicenter cohort of CSVT patients and the vast clinical and radiological factors examined. Study limitations include the retrospective design which makes it prone to different types of bias, lack of follow-up imaging including recanalization parameters, lack of data on infarcts volume and location, and lack of data regarding days past from clinical presentation to diagnosis. Furthermore, we had insufficient data regarding the exact date and cause of death in patients who died after discharge. Moreover, our regression analyses included a relatively large number of variables relative to the low number of outcomes, which may limit the reliability of these analyses. This occurred despite a relatively rigorous methodology that only included variables that yielded a p value of <0.05. Last, none of our patients were treated with endovascular techniques which are reserved as a last resort in patients with increased intracranial pressure and no response to conservative treatments. Therefore, we cannot exclude the possibility that this may have skewed mortality rates, as the exact cause and timing of death were not collected.

5. Conclusions

Among CSVT patients, we found that malignancy and presence of focal neurological deficit at presentation appear to be associated with unfavorable outcomes, while headache at presentation was associated with favorable outcome.

Data Availability

Full data are available following a formal request and in compliance with state regulations.

Conflicts of Interest

None of the authors have any financial disclosures or conflicts of interests.

Authors' Contributions

Simaan N and Molad J conceived and designed the work including data acquisition, analysis, and drafting of the manuscript. A. H, H. H, E. S, O. R, E. B, a. F, S. P, R. M, R. B, E. A, S. A, D. O, K. D, F. D, and R.R.L took part in manuscript revision and further analysis.

Supplementary Materials

Flow chart detailing patient recruitment. *(Supplementary Materials)*

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