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Clinico-Radiological Characteristics and Predictors of Poor Outcome of Cerebral Venous Sinus Thrombosis

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Abstract

Background: *Cerebral venous sinus thrombosis (CVST) is an acute cerebrovascular disease diagnosed more frequently nowadays. Though most patients with CVST have independent survival in the short term, a small percentage have an unfavorable outcome and remain dependent functionally.* ***Objective:*** *This study aimed to explore the clinical profiles, radiological features, risk factors and outcomes of patients with CVST in a tertiary-level hospital in Bangladesh with a special emphasis on determining the factors influencing the clinical outcome.* ***Materials and Methods:*** *This prospective analytical study included 40 patients confirmed to have CVST clinically and radiologically. Follow-up information included the modified Rankin Scale (mRS) at discharge and 90 days of follow-up from the diagnosis.* ***Results:*** *The mean age was 33±10.7 years, and 67.5% were female. Female-specific risk factors (Oral contraceptive pill use and pregnancy) were more common in the study, followed by infections, hematological conditions, smoking, prothrombotic conditions, and malignancy. Common symptoms/signs were dull aching bilateral headache, vomiting, focal or bilateral tonic-clonic seizure, limb weakness, visual disturbance, altered mental status and papilledema. On MRI, hemorrhagic and non-hemorrhagic infarct was observed respectively, in 28 (70%) and 3 (7.5%) patients. Parenchymal lesions were found in 31 (77.5%) patients. Most patients had superficial sinus involvement, and superior sagittal sinus, transverse sinus, and sigmoid sinuses were the frequently affected sinus. Twenty-two (55%) patients had poor outcomes (mRS > 2) at discharge and 5 (12.5%) at 90 days with a mortality rate of 7.5%. Most of the patients (87.5%) had good functional outcomes at 90 days. The presence of limb weakness and multiple risk factors were related to the outcome. On multivariate analysis, the number of total risk factors (OR = 10.43; 95% CI = 1.02-12.95; p=0.048) predicted the outcome at 90 days.* ***Conclusions:*** *CVST represents a relatively benign disease. However, CVST may result in an unfavorable outcome, particularly in patients with more than one risk factor at presentation.*

Keywords: *Cerebral venous sinus thrombosis; Venous Stroke; MR venography; Stroke outcomes.*

Introduction:

Cerebral venous sinus thrombosis (CVST) is a rare venous thromboembolism due to complete or partial occlusion of the main sinus/sinuses or the feeding cortical veins, which can lead to secondary effects of vascular congestion and focal or generalized neurological deficits.1 Amongst various neurological manifestations of the coronavirus

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disease of 2019 (COVID-19), CVST has gained recent importance. Multiple reports of SARS-CoV-2 associated with CVST have come to the surface from home and abroad and continue to do so.[2-4] There are very few studies with good quality on the epidemiology of CVST in low-to-middle-income countries, where CVST incidence appears to be higher, probably reflecting high pregnancy rates and high prevalence of infections and nutritional deficits.[5]

Though literature supports a dramatic decrease in the mortality rate associated with CVST, there is considerable variation.[5-7]

The poor outcome associated with CVST is perhaps influenced by the patient's demographics and the pathological conditions leading to venous thrombosis in the cranial circulation. In an Asian series, death and dependency were observed in 12.7% of the patients with CVST.[8]

Predicting outcomes may help decision-making in acute clinical practice, which is the most important stage in determining the fate of patients suffering from CVST. CVST is an important yet under-recognized cause of intracranial hypertension and stroke in young. Clinical presentation is extremely varied, and a high index of suspicion is needed. It can present many signs and symptoms, making it difficult to distinguish from other neurological conditions. Early recognition of symptoms and treatment improves overall outcomes in these patients. CVST demands a close functioning of both clinical and radiological proficiency for prompt detection and optimizing patient care.[5]

Other than outcome, and etiological factors, clinical and radiological characteristics of CVST vary among regions.9 Although CVST is more common in Asian countries, most of the studies are from Western countries, while the demographic and clinical characteristics of CVST in Asian countries are different from those of the West.[8,10-12] Large published multicenter studies mainly constitute patients from Western populations and particularly do not contain Bangladeshi patients.[5-7] The differences in etiological, clinical, and radiological profiles of CVST in Bangladesh, as a Southeast Asian country, may influence the outcome.This study was designed to explore the clinical profiles, radiological features, etiological factors, and outcomes of CVST in patients admitted to a tertiary care center in Bangladesh with a special emphasis on determining the factors influencing the clinical outcome. The study would help the clinicians to identify subgroups of CVST patients with potential clinical instability and the patient's need for intensified clinical observation.

Materials and Methods

This prospective observational study was conducted in the Department of Neurology, Chattogram Medical College Hospital (CMCH), Chattogram, Bangladesh, from September 2021 to August 2022. The study was conducted after approval from the Ethical Review Committee of Chittagong Medical College, and informed written consent was taken from the patient/and legal guardians.

Patients older than 18 years, admitted with a diagnosis of CVST based on clinical profiles of raised intracranial pressure, seizures, with or without focal neurological deficits and confirmed imaging diagnosis based on MRI of the brain with MRV were included in the study. Patients with arterial stroke, primary intracerebral hemorrhage, space-occupying lesions, metabolic encephalopathy, and demyelination were excluded. Those who had inconclusive neuroimaging findings and those who refused to participate in the study were not included.

Data were collected by using a structured case record from consecutive patients. Detailed history, clinical examination, and laboratory investigations were undertaken in all cases of CVST. Demographic and clinical data including the neurologic symptoms and signs were noted. All the patients underwent MRI and MRV of the brain on a 1.5 T MRI system (Symphony; Siemens; Erlangen, Germany). The scan protocol included an axial T1 film, axial Fluid Attenuated Inversion Recovery (FLAIR), axial and coronal T2W film, T1 3D sagittal image, diffusion-weighted at B value of 0.500 and 1000 s/Sq mm with the generation of Apparent Diffusion Coefficient (ADC) map, axial gradient sequence. This was followed by contrast

MRV after injecting 20 ml of gadolinium (Magnevist; Bayer Zydus) using a pressure injector at a rate of 4 ml/s and acquiring a repeated, continuous image of the brain. A 3D MR venogram was obtained after post-processing the base images using dedicated software on a workstation.

All patients were treated with standard institutional protocols of anticoagulation (5–7 days) of Low Molecular Weight Heparin (LMWH) followed by 3–5 days overlap with oral anticoagulants (warfarin) to achieve an International normalized ratio (INR) in the range 2–3. Anti-epileptics, osmotic diuretics, and other supportive therapy were used wherever required. All patients were followed up for 90 days monthly to assess their response to therapy and clinical outcomes. Death or disability on discharge and at 90 days from the time of diagnosis was evaluated according to mRS, which runs from 0 (complete recovery) to 6 (death).[13] The outcome was evaluated by the "simple questions"14 score and modified Rankin Scale (mRS) at the time of discharge and three months from the time of diagnosis. mRS score of 0-2 was considered a favorable outcome, and a score of 3 and above was poor.

Data were recorded and fed into SPSS version 23 for processing and analysis. Continuous data were expressed as mean ±standard deviation (SD) or median (interquartile range), and categorical variables were presented as frequency and percentages. Based on the 90-day functional outcome, the study population was divided into two groups: patients with good and poor outcomes. Between these groups, continuous data were compared by independent sample t-test and categorical data were compared by either the Chi-square test or Fisher's exact test as appropriate. Finally, factors having a significant association with poor outcomes in univariate analysis were included in a binary logistic regression analysis to determine the independent predictors of poor outcomes. The results were expressed as an odds ratio with a 95% confidence interval for the odds ratio. $P < 0.05$ was considered statistically significant.

Results

A total of 40 patients with CVST were included in the final analysis. Female-specific risk factors were more common in the study, followed by infections, hematological conditions, smoking, prothrombotic conditions, and malignancy (Table I). The in-hospital and 90-day mortality rate was 2.5% and 7.5%, respectively. Most of the patients (87.5%) had good functional outcomes at 90 days (Table II).

Table-I

Risk factors profile of the patients (n=40)

Risk factors	Frequency
Any risk factor	30 (75.0)
Prothrombotic condition	
Protein C & S deficiency	1 (2.5)
Female specific	
Oral contraceptive pill	19 (47.5)
Pregnancy	2 (5.0)
Infections	
Systemic infection	10 (25.0)
COVID-19	2 (5.0)
CNS infection	1 (2.5)
Hematological	
Anemia	5 (12.5)
Polycythemia	1 (2.5)
Idiopathic thrombocytopenic purpura	1 (2.5)
Malignancy	1 (2.5)
Inflammatory diseases/systemic disease	1 (2.5)
Smoking	
Ex-smoker	1 (2.5)
Current smoker	3 (7.5)

Table-II

Treatment approach and outcome of the patients (n=40)

Outcomes	Frequency
In-hospital mortality	1 (2.5)
mRS at discharge	
1 (no significant disability)	1 (2.5)
2 (slight disability)	17 (42.5)
3 (moderate disability)	10 (25.0)
4 (moderate severe disability)	11 (27.5)
6 (death)	1 (2.5)
mRS at 90-days	
0 (no symptom)	8 (20.0)
1 (no significant disability)	16 (40.0)
2 (slight disability)	11 (27.5)
3 (moderate disability)	2 (5.0)
6 (death)	3 (7.5)
90-days outcome	
Good outcome (mRS≤2)	35 (87.5)
Poor outcome (mRS >2)	5 (12.5)

The association of demographic and clinical characteristics with final outcome is shown in Table III. The common presenting symptoms/signs were bilateral headache (dull aching mainly), vomiting, focal to bilateral tonic-clonic seizure, visual disturbance, limb weakness, altered mental status and papilledema. The mean age was similar in patients with good and poor outcomes. Higher proportion of female patients, patients with any risk factor for CVST, bilateral headache, seizure, altered level of consciousness, hemiparesis, dysarthria, visual disturbance, focal neurological deficit, and papilledema at presentation had poor outcomes than their counterparts. However, from these variables only the association between the presence of multiple risk factors and focal neurological deficit and poor outcome reached statistical significance (p=0.043).

On MRI, hemorrhagic infarct was observed in 28 (70%) and non-hemorrhagic infarct was observed in 3 (7.5%) patients.Parenchymal lesions were found in 31 (77.5%) patients. Most of the patients had superficial sinus involvement and superior sagittal sinus, transverse sinus, and sigmoid sinuses were the frequently affected sinus. Table IV shows that all of the patients with poor outcomes had parenchymal lesions on MRI and on MRV, superficial sinus involvement (Superior sagittal sinus involvement, and Transverse sinus), but none of them were found to have a significant association with 90-day outcome.

All the patients in the present study received anticoagulant therapy (100%), and 42.5% of the patients received antiepileptic therapy. The higher proportion of patients with poor outcomes received mannitol, and antiepileptic therapy than the patients with good outcomes. However, none of the treatment approaches had a significant association with outcome (Table V). On multivariable analysis, a poor outcome was predicted by the number of total risk factors, for an increase in one additional risk factor odds of having a poor outcome increased by 10.43 times (OR = 10.43; 95% CI = 1.02-12.95; p=0.048).

Table-III

Demographic, clinical characteristics, and outcomes of the patients

Variables	Total (n=40)	Good outcome (n = 35)	Poor outcome (n = 5)	P value
Age, years, mean ±SD	33.0±10.7	33.5±10.7	29.4±11.6	0.433†
Sex				
Female	27 (67.5)	23 (65.7)	4 (80.0)	1.0*
Male	13 (32.5)	12 (34.3)	1 (20.0)	
Risk factor				
No risk factor	10 (25.0)	10 (28.6)	0 (0)	
Single risk factor	20 (50.0)	19 (54.3)	1 (20.0)	0.009**
Multiple risk factor	10 (25.0)	6 (17.1)	4 (80.0)	
Presenting features				
Unilateral headache	12 (30.0)	11 (31.4)	1 (20.0)	0.609*
Bilateral headache	26 (65.0)	22 (62.9)	4 (80.0)	0.452*
Seizure	23 (57.5	13 (37.1)	4 (80.0)	0.144*
Vomiting	25 (62.5)	21 (60.0)	4 (60.0)	0.633*
Altered consciousness	9 (22.5)	7 (20.0)	2 (40.0)	0.311*
Hemiparesis	11 (27.5)	8 (22.9)	3 (60.0)	0.117*
Dysarthria	7 (17.5)	5 (14.3)	2 (40.0)	0.204*
Visual disturbance	17 (42.5)	13 (34.1)	4 (80.0)	0.144*
Focal deficit	14(35.0)	10 (28.6)	4 (80.0)	0.043*
Papilledema	26 (65.0)	21 (60.0)	5 (100.0)	0.143*

†Independent sample t test; **Chi-square test; *Fisher's exact test

Boldface text indicates statistically significant values

Table-IV

Association between imaging findings and outcome of the patients (n=40)

Parameters	Total (n=40)	Good outcome (n =35)	Poor outcome (n = 5)	Pvalue*
MRI findings				
Normal	2 (5.0)	2 (5.7)	0 (0)	0.583
Hemorrhagic infarct	28 (70.0)	24(68.6)	4 (80.0)	0.615
Non-hemorrhagic infarct	3 (7.5)	2(5.7)	1 (10.0)	0.615
Empty delta sign	24 (60.0)	21 (60)	3(60.0)	0.994
Parenchymal lesion	31 (77.5)	26 (74.3)	5 (100.0)	0.197
Type of sinus involved				
Superficial	35 (87.5)	30 (85.7)	5 (100.0)	1.0
Mixed	5 (12.5)	5 (14.3)	0 (0)	
Sinus involved				
Superior sagittal sinus	33 (82.5)	28 (80.0)	5 (100.0)	0.565
Transverse sinus	33 (82.5)	28 (80.0)	5 (100.0)	0.565
Sigmoid sinus	20 (50.0)	17 (48.6)	3 (60.0)	1.0
Cortical vein	11 (27.5)	9 (25.7)	1 (20.0)	1.0
Stright sinus	5(12.5.0)	4 (11.4)	1 (20.0)	1.0
Internal jugular vein	4 (10.0)	4 (11.4)	0 (0)	1.0

*Fisher's exact test

Table-V

Association between treatment approach and outcome of the patients (n=40)

Parameters	Total (n=40)	Good outcome (n = 35)	Poor outcome (n = 5)	P value*
Anticoagulant therapy	40(100)	35 (100)	5 (100.0)	NA
Steroid	6 (15.0)	6 (17.1)	0 (0)	1.0
Mannitol	7 (17.5)	5 (14.3)	2 (40.0)	0.244
Antiepileptic therapy	17 (42.5)	13 (37.1)	4 (80.0)	0.144

Table VI

Multivariable binary logistic regression analysis to determine the independent predictor of poor outcome

Variables	Odds ratio (95% CI for OR)	P value*
Presence of limb weakness	5.86 (0.48-15.2)	0.167
Total number of risk factors	10.43 (1.02-12.95)	0.048

Discussion

The results of the present study showed that 87.5% of the patients had an overall good outcome after 90 days. None of the evaluated risk factors could be used individually to predict poor outcomes but the number of risk factors correlated with poor outcomes. Although the sample size of the present study was small, it had similarities to the previously reported series. The common features include onset in young adulthood, a female predominance, a low mortality rate, and good improvement among most survivors.[5,15]

The mean age of patients was consistent with other similar studies conducted in India[16], Pakistan[17] and multicenter of Asia.[8] Female preponderance in the current study was also supported by another study conducted in CVST patients from different Asian countries.[8] A study of CVST patients from Europe and USA showed mean age of 38 years and a female preponderance (60%).[18] These findings suggest that CVST in Asian countries occurs at a younger age as compared to Europe and the USA with similar female predominance.

Prothrombotic conditions are the most common risk factor identified for unprovoked CVST in published literature throughout the world. In the International Study on Cerebral Venous Thrombosis (ISCVT) cohort,[19] 34% patients had prothrombotic conditions, and 22% had underlying genetic prothrombotic states. On the contrary, only one patient (2.5%) in the present study had a predisposing thrombophilic condition. A complete and exhaustive pro-thrombotic workup was not possible in the present study due to financial constraints and the ineligibility of patients to do thrombophilia screening during the first three months. However, the majority of cases of CVST as recorded in published literature, have multifactorial etiology.[5] In the present study, female-specific risk factors like OCP use and pregnancy were more common, followed by infections, hematological conditions, smoking, prothrombotic conditions, and malignancy. In the present study, it was not possible to find any cause in one-fourth of the CVST patients. Few previous studies also were unable to find any cause in 13% of their CVST patients even after procoagulant workup.[20]

Headache was the most common presenting symptom, as identified in previous studies.[8,18,21,22] Following the headache, the most frequent sign was papilledema present in 65% of patients. Very high frequency of papilledema may reflect more parenchymal involvement and a longer duration of thrombosis. Seizures are far more frequently seen in CVST than in arterial stroke. At times seizures are heralding symptoms in CVST and should arouse the suspicion of the diagnosis. In the present study, 42.5% of cases had seizures which was comparable with most other previous studies.[16,18,20] Focal neurological deficit was another common presenting feature present in 35.5% of the CVST patients in the present study. A young patient especially a woman with headache, papilledema, and seizure or focal neurological deficit should prompt any physician to consider CVST.23 Public and physicians' awareness may play a key role in the early identification and treatment of these patients.

The recent ISCVT study, performed in the era of modern neuroimaging, LMWH and other oral anticoagulant administration and endovascular intervention reported much lower mortality rates (3%–15%) and significantly better outcomes.18,19 The overall outcomes of our study are favorable with 45% of patients being independent (mRS≤2) at discharge and 87.5% of patients reporting independence at the end of follow-up. The mortality rate was 7.5%, which is near the bottom of the previously reported range. However, the outcome of patients with CVST varied widely in recent studies with small sample sizes from single centers like the present study. A higher rate of poor outcomes than the present study was reported in a recent study from India. At the time of discharge, 44.3% of patients had poor outcomes, with 27.3% having dependent morbidity and 16% of mortality.24 On the other hand, in another series; a mRS score of 0–1 was achieved in 96% of patients at the end of 6 months follow-up with no mortality.[20]

Due to limited sample size and with very few patients (12.5%) with poor outcomes, it was not possible to do a robust analysis to determine the predictive factors in the present study. Previous studies have identified various risk factors associated with poor outcomes.18,25-28 In the present study, a higher proportion of female patients, patients with any risk factor for CVST, bilateral headache, seizure, altered level of consciousness, hemiparesis, dysarthria, visual disturbance, focal neurological deficit, and papilledema at presentation had poor outcome than their counterpart. However, from these variables only the association between the presence of multiple risk factors, limb weakness and poor

outcome reached statistical significance in the univariate analysis. Finally, on multivariate analysis, poor outcome was predicted by the number of total risk factors, for an increase in one additional risk factor odds of having a poor outcome were increased by 10.43 times in the present study. Theincreased number of risk factors may increase the risk of developing CVST as well as they may increase the clinical severity.

Conclusion

In conclusion, CVST represents a potentially treatable disease that primarily affects young female individuals. However, CVST may result in an unfavorable outcome, particularly in patients with more than one risk factor at presentation. Awareness of diverse clinical and radiological presentations of CVST is essential to avoid misdiagnosis and treatment delay.

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