Original Article

Clinical Characteristics, Etiology, Recanalization Rates and Neurological Outcomes in CVT: A Prospective Cohort Study

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Abstract

Background: Recanalization rates in cerebral venous thrombosis (CVT) and its effect on neurological outcome have been debated worldwide and are inadequately addressed in studies from India. Our objective was to study the clinical profile of CVT and determine recanalization rates with its predictors and its effect on outcome. **Methods:** A prospective single centre cohort study on 101 patients with radiologically confirmed acute CVT between October 2018 and June 2021 was conducted. Anticoagulation was given for 3-12 months or lifelong for thrombophilias. Recanalization status of vessels was assessed between 3-6 months and at 12 months after ictus. Outcome was defined as favorable (mRS 0-1) or unfavorable. Patients with atleast one CT/MR venogram on follow up were included. **Results:** Of the 101 enrolled patients, 83 completed study protocol. Mean age of patients was 34.2 ± 11.7 years. Clinical characteristics included headache (75.9%),seizure (66.2%), altered mentation(20.4%) with clustering of cases during summers. Transverse- sigmoid sinuses were predominantly involved (66.2 %) followed by superior sagittal sinus (SSS,65.0%).Commonest etiologies were thrombophilia (27.7%) and postpartum state (15.6%). Complete recanalization was achieved in 67.4%, partial in 26.5% and no recanalization in 6.02% at end of 12 months. Recanalization rates improved from 83.09% between 3-6 months to 93.9 % at 12 months. Median time to last follow-up was 12months and at last follow up 95.1% had favorable mRS with recurrence in two patients with raised factor VIII levels. **Conclusion:** Recanalization occurred in more than 90% of CVT patients. Isolated superior sagittal sinus thrombosis and age <50 years were predictors of complete recanalization. Most patients, except few achieved a favorable mRS.

Keywords: Cerebral venous thrombosis, outcome, recanalization, thrombophilia

Introduction

Cerebral venous thrombosis (CVT) affects 0.5–1 per 100,000 populations per year in developed countries (Europe and Australia).[1] From the available literature, CVT appears to be more common in tropical developing countries.[1,2] While the clinical characteristics of patients with CVT have been abundantly reported, only a few prospective studies have been conducted globally on recanalization rates and long-term neurological outcomes in patients with CVT. Further, the effect of recanalization on the neurological outcome is debatable with conflicting evidence from the western literature.[3-7] Puerperal CVT has been reported widely from India in the past.[2] Thrombophilia along with the use of hormonal contraceptives constitute the major risk factors for CVT cases reported from Europe.[3,8] Indeed, two recent studies from western India indicate that inherited thrombophilias may be replacing puerperal CVT as the dominant etiology in our country too.[9,10]

Recanalization rates in CVT, their effect on the neurological outcome, and etiological evaluation have been inadequately addressed in studies from India. Keeping this in mind, we conducted a prospective cohort study on patients presenting with the first episode of CVT focusing on their clinical profile, etiology, recanalization rates, and its effect on neurological outcome.

Methods

Consecutive adult patients with the first episode of acute cerebral venous thrombosis presenting to a tertiary care center of northwest India were enrolled. CVT patients admitted in the department of neurology, those referred to our department from other specialties, and patients who were admitted elsewhere with complete treatment records presenting within 1 month of ictus to our outpatient department were included. Adult patients (>18 years) with new-onset symptoms and signs suggestive of CVT of less than 1-month duration with radiological evidence of venous thrombosis on venogram were included in this study. This study was conducted from October 2018 to June 2021, and all recruited patients were meticulously followed up by monthly clinic visits or telephonic interviews. Patient demographics, the onset of symptoms to arrival at the hospital, symptoms at onset, modified Rankin scale at onset, and follow-up were systematically recorded. Routine blood work up comprising complete blood count, renal,

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hepatic function tests, lipid profile, prothrombin and activated partial thromboplastin time, and viral serology (HIV 1 and 2, hepatitis B, hepatitis C) was done for all patients. Additionally, COVID-19 nasopharyngeal swab RT PCR was done for all patients recruited after the onset of the COVID-19 pandemic from March 2020 onwards. All patients completed a minimum of 3 months of anticoagulation. Prothrombotic workup (APLA, factor VIII, protein C, protein S, antithrombin III) and homocysteine levels were done. This was performed 2–4 weeks after stopping anticoagulation. Hormonal contraceptive usage in women was defined by their current usage or use up to 3 months before CVT. This study was approved by the institute's ethics committee (No 527 MC/EC/2020). All subjects or their nearest of kin (in patients with inability to comprehend or verbalize) gave written informed consent.

Imaging protocol

All patients underwent baseline computed tomography (CT)/magnetic resonance imaging (MRI) brain and contrast CT/MR venogram of the brain. MRI brain was obtained on a 3.0-T Philips Ingenia (Netherlands) scanner using an identical protocol in all patients. A complete MRI brain study consisted of T2-weighted imaging, T1-weighted imaging before and after application of contrast agent and diffusion-weighted imaging. All studies were performed with cardiac gating without using gradient-moment nulling technique.

Contrast-enhanced venography techniques are sensitive in the detection of venous thrombosis.[11] The accuracy of CT venogram (CTV) vs MR venogram (MRV) in the detection of cerebral venous thrombosis is comparable.[12] Faster image acquisition and reduced motion-related artifacts are advantages of CT venography over MR venography. Contrast-enhanced MRV is more robust in the detection of venous thrombosis than TOF MRV. However, the higher cost involved in performing a contrast-enhanced MRV at our institution was a limitation faced by us and hence CTV or MRV-TOF was preferred for initial and follow-up imaging. Women in the reproductive age group were recommended to undergo MRV-TOF. Noncontrast CT head and CT venogram were performed on Philips Ingenity (Netherlands) scanner with the following parameters: 128 slices; slice thickness/gap = 0.9 mm/0.45 mm; pitch rotation time: 0.5 s. Ninety mL of nonionic contrast (iohexol 300 mg/100 mL) mixed with 30 mL of normal saline was injected at 4.3–4.5 mL/s. Reconstruction and bony subtraction were done automatically with workstation software developed by Philips.

Treatment and follow up protocol

Patients with CVT were treated acutely with low molecular weight heparin (enoxaparin) and maintained on oral anticoagulant (nicoumalone or dabigatran). Except in patients with antiphospholipid antibody syndrome, where controversy exists on the use of novel oral anticoagulants, all patients were offered either of the oral anticoagulants. The dose of nicoumalone was titrated to achieve a therapeutic range INR (2–2.5) by biweekly monitoring initially followed by monthly monitoring. Follow-up CT or MR venogram was recommended for all patients 36 months after the ictus in accordance with the 2011 AHA/ASA stroke guidelines to assess for recanalization.[12] Due to the ongoing COVID-19 pandemic, a delay in performing the first follow-up venogram was accepted by us. All patients with at least one follow-up venogram done between 3 and 6 months or at 12 months after the ictus were included. In patients with partial or no recanalization detected at the first follow-up scan, a repeat venogram was done at 12 months. A minimum of 6 months of the clinic or telephonic follow-up and a minimum of one radiological follow-up (CT/MR venogram) within the first year of ictus was mandatory for inclusion in this study. A clinic or telephonic follow-up was continued until completion of the study for most patients. Recanalization status of the vessel was classified using the scheme proposed by Stolz *et al.*[4] Complete recanalization was defined as uninterrupted blood flow of a previously affected sinus (luminal narrowing of <50%), partial recanalization as luminal narrowing of ≥50% of affected sinus, and no recanalization when the flow was interrupted. When all involved sinuses met the criteria for uninterrupted blood flow, it was considered as complete recanalization; if only one of the affected sinuses showed full recanalization, it was termed partial recanalization; and when no sinuses showed recanalization it was called no recanalization.

Oral anticoagulation was given for 3–12 months to all patients and lifelong for patients with thrombophilia. Oral anticoagulation was given for a maximum of 12 months or until any (partial or complete) recanalization was observed, whichever occurred earlier. The clinical outcome measured using an mRS was classified as favorable (mRS 0 and 1) or unfavorable (mRS 2–5). If severe thrombophilia (protein C, protein S, antithrombin III deficiency, APLA syndrome) was identified, oral anticoagulation was considered lifelong. Patients who failed to continue clinic or telephonic follow-up and those who expired were excluded from the study.

Statistical analysis

Data analysis was performed using Graphpad Prism version 9.0 and SPSS V.21 (IBM Corp; Armonk, New York, USA). Categorical variables were expressed as percentages and continuous variables as mean and standard deviation or as median. Data of patients with partial or no recanalization was compared with complete recanalization patients using Chi square or Fisher's exact test for categorical variables between groups and student's unpaired *t*-test for continuous variables. Predictors of complete recanalization were obtained using binary multivariate logistic regression analysis by entering the significant parameters from univariate analysis. Two-tailed tests were used, and a *P* value of <0.05 was considered statistically significant.

Results

Of the hundred and one patients enrolled, eighty-three patients completed the requisite clinical and radiological follow-up.

Seven patients expired in the first 2 weeks after the ictus and eleven patients failed to complete the required study protocol.

The mean age was 34.2 ± 11.7 years (range 19–62), 15.6% of the patients were older than 50 years, and males outnumbered females (47:36 respectively). The baseline clinical parameters are summarized [Table 1]. Most patients presented with headache (75.9%) followed by seizure (66.2%) and altered sensorium (20.4%). In this part of the country, during the peak summer months from April to June, the day temperature hovers around 38–46°C. Clustering of CVT cases was observed in the summer season (77.10%). CVT was diagnosed with CT venogram in 43 patients (51.8%) and with MR venogram in 40 patients (48.1%). The mean time from symptom onset to presentation was 4.0 ± 2.1 days, and the median hospital stay was 8 days. The median mRS at discharge was 1 (1–5), at 3 months was 0 (0–3), and at 6 months 0 (0–2) [Table 2]. Thrombosis affecting transverse and sigmoid sinus was considered together. The most commonly affected sinus was transverse-sigmoid (66.2%) followed by superior sagittal sinus (65.0%). In 28 patients (33.7%), isolated superior sagittal sinus thrombosis occurred. Multiple sinuses were thrombosed in 33.17% and deep venous system comprising inferior sagittal sinus, straight sinus, vein of Galen, internal cerebral vein, and basal vein of Rosenthal was affected in 8.4% [Table 2]. Hemorrhagic venous infarct was noted in 33 patients (39.7%) and venous infarct without hemorrhage in 15 patients (18%). The commonest risk factors were thrombophilia (25.3%) followed by postpartum state (15.6%) and hyperhomocysteinemia (14.4%). Infective CVT [systemic and central nervous system (CNS) infection] was observed in 9 patients (10.8%) and dehydration following gastroenteritis in 7 patients (8.0%). The first follow-up venogram was done in 71 patients (85.5%) between 3 and 6 months. More than 50% (36/71) had complete recanalization by 6 months. Complete recanalization was achieved in 67.4% (56/83), partial recanalization in 26.5% (22/83), and no recanalization (5/83) in 6.02% at the end of 12 months [Table 3, Figure 1]. Univariate analysis of demographics, clinical characteristics, risk factors, thrombosed sinuses, and outcome between patients with and without complete recanalization was done [Table 4]. Age <50 years ($P = 0.002$) and isolated superior sagittal sinus (SSS) thrombosis ($P = 0.023$) were predictors of complete recanalization [Table 5].

The median time to last follow-up was 12 months (6-22 months) and at last follow-up, 95.1% had favorable mRS. Recurrence occurred in two patients. Both patients had elevated factor VIII levels. One patient had CVT recurrence in the third week of discontinuation of oral anticoagulant after a year and 2 months of regular intake. The second patient developed recurrence in the second week of discontinuation after good compliance for 1 and 1/2 years. Residual episodic headache without features of raised intracranial pressure was observed in 20 patients (24.0%). The frequency of headache days varied from one to a maximum of three headache days per month with prompt improvement on taking nonsteroidal anti-inflammatory drugs during the attack (single tablet of diclofenac 50 mg). All these patients had normal MRI brain and magnetic resonance angiography. Only one patient complained of persistent headache 10 months after the ictus. Reinvestigation with MRI brain showed features of intracranial hypertension with normal angiography of the brain and partial recanalization of the previously thrombosed transverse sinus. A lumbar puncture was done, and a raised intracranial opening pressure was recorded (CSF opening pressure:280 mm of water) with normal cerebrospinal fluid analysis. Patient's headache improved with acetazolamide. Decompressive hemicraniectomy was done in one patient and optic nerve fenestration surgery in one patient with grade 4 papilledema and severe visual loss.

Discussion

Males were affected more (56.6%) than females (43.3%, male: female = 1.3) in this study with clustering in summer months, akin to another large Indian study on CVT.[13] This is in contrast to studies from Mexico and Europe that have noted women's preponderance in CVT, with most cases being ascribed to the use of hormonal contraceptives (37.5% and 46.9%,

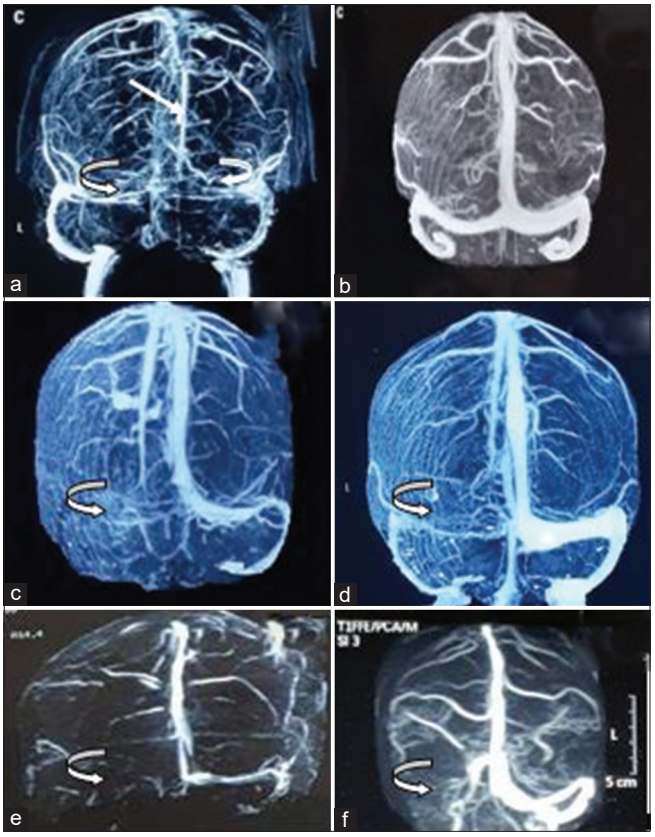

Figure 1: a CT venogram: Superior sagittal sinus thrombosis (straight arrow) with bilateral transverse sinus thrombosis (curved arrow) and right sigmoid sinus thrombosis, b: Complete recanalization of all thrombosed sinuses, c: CT venogram: Left transverse and sigmoid sinus thrombosis (curved arrow), d: Partial recanalization of thrombosed sinuses, e: MR venogram: Right transverse and sigmoid sinus thrombosis (curved arrow), f: No recanalization of sinuses

Table 1: Baseline clinical characteristics and risk factors

Demographic/clinical features	*n*=83 (%)
Age (years) Mean±S.D	34.2±11.7
Gender (Male: Female)	47:36
Headache	63 (75.9)
Seizure	55 (66.2)
Visual complaints (Diminution of vision or diplopia)	25 (30.1)
Altered mentation	17 (20.4)
Focal neurological deficit	
Papilledema	33 (39.2)
Speech deficit	17 (20.4)
Hemiparesis	13 (15.6)
Risk factors	
Thrombophilia (Factor8, Protein C, Protein S, Antithrombin 3 deficiency and polycythaemia, APLA)	23 (27.7)
Postpartum	13 (15.6)
Hyperhomocysteinemia	12 (14.4)
Dehydration	7 (8.4)
Anemia	7 (8.4)
Systemic infection (Malaria, pulmonary TB, Hepatitis B, HIV)	6 (7.2)
Normal etiological work up	5 (6.0)
Incomplete etiological work up	4 (4.8)
Head and neck infections (Meningitis, CSOM)	3 (3.6)
Hormonal contraception	2 (2.4)
Inflammatory (Sarcoidosis)	1 (1.2)

Table 2: Imaging characteristics and follow up outcome at 0, 3, and 6 months

	n=83 (%)
Hemorrhagic venous infarct	33 (39.7)
Venous infarct	15 (18.0)
Intracerebral hemorrhage	4 (4.8)
Subarachnoid hemorrhage	3 (3.6)
Leptomeningeal enhancement	2 (2.4)
Pachymeningeal enhancement	1 (1.2)
Thrombosed sinus/es on venogram	
Transverse and/or sigmoid	114 (66.2)
Superior sagittal sinus	54 (65.0)
Isolated superior sagittal sinus	28 (33.7)
Deep veins	7 (18.4)
Internal Jugular Vein	15 (18.0)
Multiple sinuses	28 (33.7)
Favourable mRS (0 and 1)	
At discharge	43 (51.8)
At 3 months follow up	73 (87.9)
At 6 months follow up	77 (2.7)

respectively).[3,6] Hormonal contraceptive usage associated with CVT was much lower (2.4%) in our study, a reflection of the preference for permanent sterilization here.[14] Improved postpartum care with a higher incidence of smoking-associated hyperhomocysteinemia in men is also the likely reason for this gender shift.[2] Headache, seizure, altered mentation, focal neurological deficit were the most commonly reported initial symptoms, similar to the existing literature.[3,6,7,15]

Putaala *et al.*[7] found increasing age to be associated with no recanalization, and Arauz *et al.*[6] found age less than 50 years to be a predictor of complete recanalization. Dichotimising the age at 50 years similar to Arauz *et al.* we also found age to be associated with CVT. Isolated SSS thrombosis also was a predictor of complete recanalization in our study, similar to previous studies.[12,16] A meta-analysis by Dentali *et al.*[17] showed no difference in recanalization rates at 3 and 12 months after ictus (84% vs 85%). They suggested that recanalization occurred early and did not improve with time. Our recanalization rates showed improvement from 83.09% between 3 and 6 months to 93.9% at 12 months. These results are in agreement with two large recent studies.[3,6] Arauz *et al.*[6] found recanalization to be a dynamic process with rates increasing from 71% at 3 months to 94% by 9 months. Herweh *et al.*[3] in another study from Europe also concluded similarly, complete recanalization rates improved from 13.8% at 3 months to 89.7% at 12 months.[7]

Although puerperal CVT cases were widely reported from India previously, the trend appears to be changing.[2] In the last decade, studies from the south and west India reported fewer cases of puerperal CVT (9.8% and 8.1%, respectively).[9,15] Both these studies reported genetic thrombophilia to be more common (12.3% and 18%, respectively) than puerperal CVT. In this cohort also, thrombophilia was the commonest etiology and constituted one-fourth of the cases (25.3%) followed by puerperal CVT (15.6%). Similar to Anadure *et al.*,[10] we found elevated factor VIII to be an important genetic thrombophilia causing CVT. In fact, both our male patients with CVT recurrence had highly elevated factor VIII levels {218% and 357% (normal factor VIII:60%–150%)}. In 2011, American Heart Association and (AHA)/American Stroke Association (ASA) guidelines on CVT elevated factor VIII was classified as a mild thrombophilia state with low recurrence risk.[12] However, in a case-control study by Vecht *et al.*,[18] raised factor VIII levels were associated with a fifteen-fold higher risk of CVT with a stronger risk association in men. Elevated factor VIII is thus an emerging under-recognized strong risk factor and requires to be actively worked up in the prothrombotic screen.

Table 3: Recanalization scan time line

Months from ictus	Number of follow up scans		Number of scans showing category of recanalization		
	First follow up	Second follow up	Complete	Partial	No
3-6 months	71		36	23	12
12 months	12		8	1	3
		35	12	21	2
At the end of 12 months (Overall, *n*=83)			56	22	5

Table 4: Univariate analysis of clinical characteristics, risk factors, thrombosed sinuses, and outcome between patients with and without complete recanalization

	Complete recanalization *n*=56 (%)	Partial and No recanalization *n*=27 (%)	*P*
Demographic & clinical characteristics			
Males	28 (50.0)	19 (70.3)	0.10
Age <50 years	53 (94.6)	17 (62.9)	0.0005*
Headache	42 (75.0)	21 (77.7)	0.78
Seizure	35 (62.5)	19 (70.3)	0.48
Visual symptoms	15 (26.7)	10 (37.0)	0.34
Altered Mentation	12 (21.4)	5 (18.5)	0.75
Papilledema	23 (41.0)	10 (37.0)	0.72
Speech deficit	10 (17.8)	6 (22.2)	0.63
Hemiparesis	9 (16.0)	5 (18.5)	0.78
Etiology			
Thrombophilia	15 (26.7)	8 (29.6)	0.68
Postpartum state	11 (19.6)	2 (8.3)	0.20
Hyperhomocysteinemia	8 (14.2)	4 (14.8)	0.99
Imaging			
Hemorrhagic infarct	22 (39.2)	11 (40.7)	0.89
Infarct	10 (17.8)	5 (18.5)	0.94
Thrombosed sinuses	*n*=116 (%)	*n*=84 (%)	
Transverse and sigmoid	66 (56.8)	48 (57.1)	0.97
Superior sagittal sinus	38 (32.7)	16 (19.0)	0.03*
Isolated SSS	24 (20.6)	4 (4.7)	0.001*
IJV	10 (8.6)	5 (5.9)	0.47
Deep veins	2 (1.7)	3 (3.5)	0.10
Multiple sinuses	20 (17.2)	8 (9.5)	0.12
NOAC	5 (8.9)	3 (3.5)	0.71
Favourable mRS			
At discharge	29 (51.7)	14 (51.8)	0.99
3 months	53 (94.6)	22 (81.4)	0.10
6 months	53 (94.6)	24 (88.8)	0.38

Table 5: Multivariate logistic regression analysis for predictors of complete recanalization

Parameter	B	Odds ratio	Lower CI	Upper CI	*P*
Age <50	2.436	11.423	2.518	51.829	0.002
SSS	0.241	1.273	0.405	3.999	0.680
Isolated SSS+	1.618	5.042	1.250	20.333	0.023

Favorable outcome (mRS 0 and 1) improved with time and at the last follow up, 95.1% had achieved a favorable outcome. This outcome was better than the International Study on Cerebral Vein and Dural Sinus Thrombosis study CVT cohort (79% had mRS 0 or 1 at median follow up of 16 months) and comparable to the recently published studies by Arauz, Putaala, and Herweh.[3,6-8] The influence of recanalization on clinical outcome is debatable with conflicting evidence from studies. Arauz *et al.* and Putaala *et al.* found recanalization to influence outcome, whereas in studies by Stolz *et al.*, Strupp *et al.*, and Hereh *et al.* no significant association of recanalization on outcome was found.[3-7] Our study is in line with these latter studies, we found no significant association of complete recanalization on the outcome.

The RE-SPECT CVT trial in 2019 suggested dabigatran and warfarin to be equally effective in CVT.[19] In this study, eight (9.03%) patients were put on dabigatran after initial anticoagulation with LMWH for 5–7 days. There was no difference in recanalization rates or outcome between patients on dabigatran and nicoumalone. One patient on dabigatran developed malena necessitating its discontinuation in the second month. He was continued on nicoumalone thereafter and had no adverse effects. No major hemorrhagic complications were reported in the nicoumalone group. Our study indicates that dabigatran is largely safe and effective in patients with CVT. The duration of anticoagulation is yet another grey area in the management of CVT patients. Wide variability in the duration of anticoagulant usage has been reported. An ongoing cluster-randomized trial aims to provide answers in this regard {short (3–6 months) vs long (6–12 months) anticoagulation to prevent CVT recurrence}.[20]

Seven patients (8.4%) expired in the first 2 weeks after symptom onset. Three males and four females expired. One female patient was 7 months pregnant multipara with deep venous thrombosis and extensive bilateral thalamic and basal ganglia infarcts. All patients had poor Glasgow Coma

Scale (GCS) at admission (GCS:5-7), bilateral extensor plantar, and large parenchymal lesions (six patients had hemorrhagic infarct and one had bilateral infarcts without hemorrhagic transformation) with midline shift and succumbed to cerebral herniation and sepsis.

Our limitations include the inability to perform follow-up neuroimaging at fixed intervals and nonuniformity of the scanners employed. With the COVID-19 pandemic ravaging during the study duration, this shortcoming was accepted by us. Secondly, a complete thrombophilia workup could not be done for all patients due to the economic constraints of a developing nation. Also, testing for factor V Leiden mutation, a common thrombhophilia predisposing to CVT, was not available at our institute. Nonetheless, this prospective cohort study on patients with cerebral venous thrombosis brought out several facts.

Seasonal clustering in summers, elevated factor VIII levels as an important cause of thrombophilia, high recanalization rates, and improvement in recanalization with the passage of time were brought out in this study. Further, age less than 50 years and isolated SSSthrombosis were found to be predictors of complete recanalization. The majority of the patients achieved favorable outcomes and usage of dabigatran (though used in a small number due to the higher cost) was largely safe in CVT. To the best of our knowledge, this is the first prospective study from Asia on recanalization rates in CVT.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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