

## Research Article

# A Study of Clinical Profile, Risk Factors and Outcome of the Cerebral Venous Sinus Thrombosis (CVST): An Experience at a Tertiary Care Center, INDIA

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**Background:** Cerebral venous sinus thrombosis (CVST) is an uncommon condition, with extremely diverse clinical features, predisposing factors, brain imaging findings, and outcome.

**Materials and Methods:** This study was performed as a hospital based retrospective & prospective observational study at IHBAS, Delhi, India.

**Statistical Analysis:** The different variables of the patients like the demographic profile, clinical presentations, risk, prognostic factors and outcome were compiled and analyzed using appropriate statistical methods in Statistical Package for Social Sciences (SPSS) 22.0 window software.

**Results:** A total of 71 patients of CVST were included in this retrospective and prospective observational study with age more than 14 years. 30 (42%) were males and 41 (58%) were females with  $29.3 \pm 5.8$  years and  $27.14 \pm 8.6$ , respectively. Clinical presentation was acute in 19(27%), sub-acute in 40(56%), and chronic in 12 (17%) patients. Out of 71, 60(85%) patients were presented with symptoms of headache, of total 30(42%) had vomiting and 30(42%) had blurring of vision or double vision, 41 (58%) had Seizures, 20(28%) had Fever and psychosis was observed in 4 (6%) patients. Superficial venous system was involved in 66 (93%) and deep venous system in combination of superficial system involved in 4 patients. Superior sagittal sinus (the commonest sinus involved) was involved in 58(82%) patients. In our study mean hospital stay was 14.69 days, 2(2.8%) patients were expired and 3(4.2%) loss to follow up.

**Keywords:** Cerebral Venous Sinus Thrombosis; Headache; MR Venogram; Superior Sagittal Sinuses; ICH; Seizure

**Introduction**

Cerebral venous sinus thrombosis (CVST) is an uncommon condition, with extremely diverse clinical features, predisposing factors, brain imaging findings, and outcome [1]. It is frequently unrecognized type of stroke that affects approximately 5 people per million annually and accounts for 0.5% to 1% of all strokes [2]. It is one of the common causes of young stroke in India, [3] about 20% in people aged 40 years or less [4]. Depending on the site, size, duration, and rapidity of development of thrombus, it can be present as seizure, space occupying lesion, benign intracranial hypertension, subarachnoid haemorrhage, unexplained loss of consciousness, or meningoencephalitis [5]. CVST most commonly involves superior sagittal sinus (72%) followed by lateral sinus (70%), in 30 to 40% of cases more than one sinus is involved [6]. The diagnosis of CVST requires high index of suspicion because of its varied clinical presentations. CVT forms a distinct subgroup of cerebrovascular disease in India and is a leading cause of mortality in women of reproductive age group [3]. Neuro-imaging is the cornerstone in the diagnosis of cerebral venous sinus thrombosis. Imaging modalities of choice in CVST are CT scan and MRI with MR venogram. CT scan may be normal in 15-30% cases but MRI with MRV is almost 100% diagnostic [2] after introduction of heparin in treatment of CVT

mortality has come down significantly and most of the recent studies [7] reporting mortality < 20% compared to earlier studies reporting mortality between 30-50%. Even though there is a steady decline in the mortality, recent reports still indicate a mortality of 5-30% [8]. The predictors of poor outcome include: coma, intracerebral hemorrhage (ICH), rapidly progressing clinical deficits, posterior fossa lesion and involvement of the deep venous system [8].

**Review of Literature**

The first description of thrombosis of the cerebral veins and sinuses is attributed to the French physician Ribes, who in 1825 observed thrombosis of the sagittal sinus and cerebral veins in a man who had suffered from seizures and delirium [9]. In 1957, Padmavati et al [10] for the first time from India, reported 15 cases of CVT in puerperium in an epidemiological study evaluating the causes of hemiplegia in 44 women. Bansal et al [11] and Srinivasan et al [12] in their study cerebral venous/sinus thrombosis during the puerperium has been studied. Pai et al [13] in their study of six hundred and twelve (354 men, 219 women and 39 children) consecutive patients with CVT found that the main presenting clinical manifestations included papilledema (62%), headache (62%), hemiparesis (48%), seizures (31%), and cranial nerve palsy (7%). The cerebral venous system can

**Table 1:** Clinical presentation.

Clinical presentation	Present no. (%)	Absent no. (%)
Fever	20 (28.2)	51 (71.8)
Vomiting	30 (42.3)	41 (57.7)
Psychiatry manifestation	4 (5.6)	67 (94.4)
Blurring of vision	30 (43.3)	41 (57.7)
Sign and symptoms of raised intracranial tension	30 (42.3)	41 (57.7)
Pallor	16 (22.5)	55 (77.5)
Fundus, Papilledema	31 (43.6)	40 (56.4)
Headache	60 (84.5)	11 (15.5)
Location of headache	Holocranial, 39 (54.9)	
	Lt hemicranial, 10 (14.1)	
	Rt hemicranial, 5 (7.0)	
	B/L frontal, 3 (4.2)	
	Occipital, 3 (4.2)	
Seizure	41 (57.7)	30 (42.3)
Semiology	GTCS, 22 (31)	
	Lt focal, 6 (8.5)	
	Rt focal, 12 (16.9)	
	CPS/GTCS, 1 (1.4)	
Cranial nerve impairment	19 (26.7)	52 (73.2)
	B/L six, 4 (5.6)	
	Either side seventh or B/L, 8 (11.2)	
	Either side six, 5 (7.0)	
	Multiple Cranial nerve (3,4,6,9,10), 2 [2.8]	

be divided into a superficial and a deep system. The superficial system comprises sagittal sinuses and cortical veins, which drain superficial surfaces of both cerebral hemispheres. The deep system consists of the lateral sinus, straight sinus and sigmoid sinus along with draining deeper cortical veins [14].

Two case-control studies have shown an increased risk of sinus thrombosis in women who use oral contraceptives [15,16]. Until the mid-1970s, men and women were equally affected [17]. More recently, there has been a significant female predominance among young adults with sinus thrombosis (70 to 80 percent of cases are in women of childbearing age) but not among children or elderly persons [18]. Cerebral venous thrombosis (CVT), an important cause of stroke in puerperium, is frequently observed in India [19]. CVT made up approximately half of the young strokes and 40% of strokes occurring in females, majority of them were below 25 years of age [20]. Post gestational and post puerperal CVT has been described more often from the Indian subcontinent with post puerperal occurring more commonly rather than due to use of oral contraceptive (OC) pills [38.4%] [21].

More than 100 putative causes of CVT have been described in the literature. The risk factors for venous thrombosis, in general, are linked classically to the Virchow triad of stasis of the blood, changes in the vessel wall, and changes in the composition of blood. Etiological factors are usually divided into acquired risks (e.g. surgery,

trauma, pregnancy, puerperium, antiphospholipid syndrome, cancer, exogenous hormones) and genetic risks (inherited thrombophilia). Drugs like oral contraceptives (OCs), steroids, hormone replacement therapy, and oncological treatments have been implicated in the causation of CVT. [Table: 1 (supplemental file)] lists the various etiological factors responsible for CVT [22].

Besides the classic deficiencies in antithrombin III, protein C and protein S and having the factor V Leiden or the prothrombin gene mutations, [23,24] more recent studies have emphasized the role of the elevation of plasma factor VIII levels [25] and elevation of von Willebrand factor; [25] both are also associated with an increased risk of CVT.

Hyperhomocysteinaemia is an independent and strong risk factor for CVT that is present in 27-43% of patients and in 8-10% in the community [26,27].

There are different mechanisms for the signs and symptoms in patients presenting with cerebral venous thrombosis: thrombosis of the cerebral veins, with local effects caused by venous obstruction, and thrombosis of the major sinuses, which causes intracranial hypertension [28].

Focal neurological deficits are noted in 44% of patients with cerebral venous thrombosis [29]. Focal or generalized seizures, including status epilepticus, are observed in 30% to 40% of patients with cerebral venous thrombosis [29]. Head CT is the most frequently performed imaging study for evaluation of CVT. Although non-contrast head CT may detect alternative diagnoses or demonstrate venous infarcts or hemorrhages, it has poor sensitivity and shows direct signs of cerebral venous thrombosis in only one third of patients [30]. Signs of cerebral venous thrombosis on CT include hyperdensity in the area of a sinus or cortical vein (cord sign) and filling defects, especially in the superior sagittal sinus (empty  $\Delta$  sign), in contrast-enhanced studies [30].

Magnetic resonance imaging of the head combined with MR venography is the most sensitive study for detection of cerebral venous thrombosis in the acute, subacute, and chronic phases [2]. Acutely, cerebral venous thrombosis appears isointense to brain tissue on T1-weighted images and hypointense on T2-weighted images [30]. In the sub-acute phase, thrombus appears hyper intense in both T1- and T2-weight images. In chronic stages, the thrombus can be heterogeneous with variable intensity relative to surrounding brain tissue. On T2-weighted images, thrombus may be directly visualized in cerebral veins and dural sinuses and appears as a hypo intense area. The addition of contrast-enhanced MR venography assists in distinguishing anatomic variants such as a hypoplastic sinus from cerebral venous thrombosis [30].

Good outcome was associated with an isolated intracranial hypertension presentation and a delta sign on CT (perhaps because this led to early diagnosis). Poor outcome including involvement of the cerebellar veins, uncontrolled seizures, pulmonary embolism, infectious or malignant aetiology [31].

## Materials and Methods

This study was performed as a hospital based 40 patients in retrospective and 31 in prospective observational study at IHBAS,

**Table 2:** Etiological and predisposing factors in CVST patients.

<b>Pregnancy, abortion and puerperium</b>	<b>29</b>
Oral contraceptives	07 (2 had abortion)
Drugs (Androgen, danazol, lithium, vitamin A, IV immunoglobulin, ecstasy/antipsychotic)	03 Male (1 had history of intake anabolic steroid, 2 male were on trifluoperazine and risperidone)
Cancer related, Antineoplastic drugs (tamoxifen, L-asparaginase)	01 female on L-asparaginase for carcinoma breast
Diarrhea and fasting	02 (2 Male, 1 Female)
Infection ,Parameningeal infections (ear, sinus, mouth, face, and neck)	4 female had retained product of conception, 6 female and 5 male had mastoiditis and sinusitis.
Microcytic hypochromic anemia	27 (25 Female+2 Male)
Megaloblastic anemia	2 (Male)
Dimorphic anemia	5 (4 Female, 1 Male)
Normocytic normochromic	9 (5 female, 4 male)
HB>16.5	9 (Male)
Paroxysmal nocturnal hemoglobinuria	0
CRP (QUALITATIVE)	33 (47%) 26/41 (female), 7/30 (male)
Rheumatoid arthritis and connective tissue disease	5 [2 SLE, 1 Wegener's, 2 only RA]
Fatty liver in USG abdomen	16 had fatty liver and 3 had both hepatomegaly with fatty liver
Lipid profile	21 (30%) patients had abnormal lipid profile increased cholesterol, triglyceride, low density lipoprotein and decreased HDL single or in combination
Thyroid disease	01 (Female)
Sarcoidosis	0
Wegener's granulomatosis	01 (Male)
Hyperhomocysteinemia: 40(56%)	24 (9 Female, 15 Male) [6 post-partum female, 1 had MTHFR Mutation, 2 female had megaloblastic anemia], [9 (3 had MTHFR Mutation) male had vitamin B12 deficiency, 3 had protein C deficiency and 1 had protein S deficiency] 2 male had exclusively.
Antiphospholipid, $\beta$ -2 Glycoprotein and anticardiolipin antibodies	01 (female)
Resistance to activated protein C, Factor V Leiden and Antithrombin III deficiency	Not done
MTHFR Mutation	04 (3 male, 1 female)
Prothrombin GMutation G20210A	02 (Male)
Von Willebrand factor (VWF)	8 [3 female & 5 male]
D-Dimer: 32(45%)	28 (88%) had >500ng/mL and 4 (12%) had <500ng/ml.
No provoked factor identified	4

Delhi, India from Dec 2008 to May 2015

**Inclusion Criteria:** (1) All confirmed cases of cerebral venous sinus thrombosis (CVST) were included. (2) Patients with age range between 14 – 60 years were taken. (3) Patients who gave consent for the prospective study were included.

**Exclusion criteria:** (4) Patients who were initially diagnosed as CVST but MRV/angiogram was normal (2 Patients) were excluded. (5) Age below 14 years (1 patient). (6) Patients or guardian who did not give consent in prospective enrolment (None).

**Study Tool:** (7) Semi Structured Proforma: Relevant Information was collected. The evaluation was done by taking the detailed clinical history, general and neurological examination. (8) Lab investigations: Laboratory investigations directed towards the evaluation of the risk factors was done. Neuroimaging (MRI Brain and MR Venography, CT Head), was done in all patients. (9) Outcome

a. mRS - Functional status was recorded on the basis of Modified Rankin Scale.

b. (mRS) at admission, discharge and follow-up (1, 3, 6 months) (good 0-2, 3-6 poor).

c. Glasgow Coma Scale – at admission and follow-up (1, 3, 6 months).

### Statistical methods

The different variables of the patients like the demographic profile, clinical presentations, risk, prognostic factors and outcome were compiled and analyzed using appropriate statistical methods in Statistical Package for Social Sciences (SPSS) 22.0 window software. All tests were two sided and P value equal to or less than 0.05 was considered statistically significant.

### Observations and Results (Table no 1 & 2 in Manuscripts)

A total of 71 patients of CVST were included in this retrospective and prospective observational study with age more than 14 years. Of the total 71 patients with CVST 42% were males and 58% were females with  $29.3 \pm 5.8$  years and  $27.14 \pm 8.6$ , respectively. Presentation was

acute in 27%, sub-acute in 56%, and chronic in 17% patients.

Table one showed that 85% patients were presented with symptoms of headache, out of which 55% had holo-cranial, 14% had unilateral, 4% had bilateral frontal and 4% had sub occipital headache. 42% had vomiting, 42% had blurring of vision or double vision, 58% had Seizures out of which 31% had GTCS, 17% had right focal, 9% had left focal, 1% had complex partial seizure, 28% had fever and presentation as psychosis was observed in 6% patients. 23% patients had bilateral papilledema, 14% patients had bilateral disc margin blurring and 7% had unilateral papilledema with disc margin blurring on funds examination.

At time of presentation 23% had pallor. A total of 10% were unconscious, 7% were aphasic, 3% had dysarthria, 80% had normal speech, 15% had 6th cranial nerve palsy, 11% had 7th cranial nerve palsy and 3% had multiple cranial nerve palsies. Stroke like presentation was observed in 30%, presentation as unilateral weakness either left or right in 21%, 5.6% had bilateral weakness and 3% had Para paresis.

Table 2 showed that out of 71 CVST cohorts 59% were non-pregnancy or non-abortion related, out of 41 females 42% were pregnancy related and out of those one pregnant, twenty-six were postpartum and 2 were abortion related. 17% had history of oral contraceptive (OCP) in last two months and one on chemotherapy (L-asparagines). None of the womens were smoker or alcoholic. 27% males were chronic alcoholics and smokers both, 10% only alcoholic, 3% were chronic smokers. Two males and one female had history of fasting. Two males were diagnosed case of schizophrenia and on Risperidone, Trifluoperazine, one had history of HTN, one was diagnosed case of Wegener granulomatosis and one had history of intake an anabolic steroid.

Table 2 showed that 61% were anemic, among those 83% were women. Most common type of anemia in women was microcytic hypochromic (25/41), four had dimorphic anemia, five had normocytic normochromic and none had macrocytic anemia. In nine anemic males four were normocytic, two macrocytic, two microcytic and one had dimorphic anemia. Nine males were with  $HB \geq 16.5$  and 2 had macrocytic peripheral smear without anemia. CRP (QUALITATIVE) was positive in 47%, out of those 63% and 23% were female and male respectively. Rheumatoid factor (qualitative) was positive in 7%, out of them two had ANA/anti ds-DNA, one had C-ANCA and one had Anti RO/LA positive.

D-dimer was done in 32(45%) who were admitted with acute to sub-acute symptoms and 88% had  $>500\text{ng/ml}$  and 12% had  $<500\text{ng/ml}$ . In total studied population 30% had low vitamin B12 ( $\leq 200\text{pg/ml}$ ), out of which 14 and 7 were males and females respectively.

Out of total population 56% were evaluated for serum homocysteine and 60% had  $>15\text{mg}/100\text{ml}$  and a total of hyperhomocysteinemic population 62.5% were males. Lipid profile was normal in 70% patients and 30% patients had abnormal lipid profile as increased cholesterol, triglyceride, low density lipoprotein and decreased HDL single or in combination.

Table 2 also showed that out of CVST cohort, test for prothrombotic state protein C and protein S deficiency which was done in 24 patients, out of which 25% patients had protein-C

deficiency and 4% had protein-S deficiency. Antiphospholipid antibodies, Anti Cardiolipin antibodies and  $\beta$ -2 Glycoprotein antibodies was done in forty patients out of which only one was positive for these antibodies.

677TT methylene tetra hydro folate reductase genotyping was done in sixteen patients out of which three had heterozygous mutation and one had homozygous mutation. Polymorphism for prothrombin G20210A Mutation was done in twelve male patients out of them two had polymorphism. In our study VWF level was done in twenty-eight patients out of which eight had increased level greater than normal range. Antithrombin III, Resistance to activated protein C, factor V Leiden gene mutation were not done due to economic issue. Table 2 showed that patients had more than one etiological and predisposing factors.

### Neuroimaging

NCCT head was normal in 27.6% patients and remaining 72.2% had findings included edema, and/or hemorrhage and hemorrhagic Infarction. Infarction was present in 73% out of those 82.69% had hemorrhagic infarction and 17.3% patients had non-haemorrhagic infarction. According to the site, forty-eight patients had cortical infarction while four patients had evidence of both cortical and deep infarction.

Our study showed that in direct or primary sign of CVST, total involvement of sinuses was seen in twenty-six patients with various combinations of other sinuses or isolated. Superior sagittal sinus was involved in fourteen patients (the commonest sinus) and isolated SSS in eight patients. Isolated transverse sinus either right or left was involved in three patients. Five patients had superior sinus with left transverse sinus involvement.

MRI brain was done in 68 patients out of them 22.05% had normal MRI brain, in remaining 77.9% abnormal findings included edema, and/or hemorrhage, hemorrhagic Infarction and with or without subarachnoid haemorrhage. Haemorrhagic Infarction was present in 68% out of them 58% had haemorrhagic infarction and 10% Patients had non-haemorrhagic infarction. According to the site, forty-five patients had cortical infarction while three patients had evidence of both cortical and deep infarction out of them one patient had corpus callosum involvement. Most common site of cortical involvement was frontal followed by fronto-parietal region.

Four patients had normal MRI brain with suggestive of idiopathic intracranial hypertension (IIH) either "empty sella" sign, posterior globe flattening, widening of the optic nerve, increased tortuosity and enhancement of the optic nerve was present.

MRV Brain was done in 69 patients, superficial venous system was involved in 93% and deep venous system in combination of superficial system was involved in three patients. Superior sagittal sinus was involved in 82% patients (the commonest sinus) and Isolated SSS in 30% patients. Isolated left transverse sinus was involved in eight patients and right transverse involved in three patients. Thirty-four patients had superior sinus thrombosis with other sinus in combination involvement. Nine patients had thrombosis with collaterals which suggestive of chronic CVST, three had cortical vein thrombosis with other sinus involvement and one had only cortical vein thrombosis, while deep venous system was involved in three

**Table 3:**

Variable	Narayan et al <sup>37</sup> (2012)	Pai et al <sup>13</sup> (2013)	Halesha et al <sup>44</sup>	Present study (2015)
No of patients	428	612	50	71
Study design	Prospective case series	Prospective case series	Prospective case series	Prospective and retrospective case series
Mean age	31.3	31.9	29.06	27.74
Male: Female	1.16:1	3.2	10:40	30:41:00
Onset symptom to admission	16.1 days	na	na	14.82
Headache	88.30%	61.90%	90%	85%
Vomiting	74.10%	na	na	42%
fever	5.40%	na	na	28%
Papilledema	63.40%	62.40%	40%	42.70%
Aphasia	na	na	20%	7% (Aphasic)
				3% (dysarthria)
				10% (unconscious)
Seizure	39.90%	31.20%	44%	58%
Motor impairment	25.3% (hemi paresis)	47.7 (hemi paresis)	48% (focal deficit)	21% (hemiparesis)
	.9% (paraparesis)			5.6% (B/L weakness)
	1.4% (quadriparesis)			3% (paraparesis)
Mental disorder	14.50%	na	na	6%
Coma	10.40%	na	14%	10%
Pregnancy, puerperium, abortion	9.80%	2.40%	50%	40.80%
Oral contraceptive	11.40%	na	6%	9.80%
Genetic thrombophilia	26.50%	18%	na	18.30%

patients.

Out of total CVST cohort 57.7% patients had seizure twenty-eight patients had control of seizure with single antiepileptic, whereas seven patients required two antiepileptic and five patients required three AEDS. 16% patients had seizure at 6 month or last maximum follow up, out of which 4 had remote seizure (>2 weeks after diagnosis).

Ventriculo-peritoneal shunt was done in only one (1.4%) patients as treatment of visual loss in idiopathic intracranial hypertension (IIH) that expired due to complication of LMWH associated subarachnoid haemorrhage.

#### Follow up

Follow-up was ranging from 6 months to 36 months was available for 66 patients. 30% had minor memory complain as most common complaint on follow-up followed by headache which was presented in 18% patients, out of which five patient had thrombosis with collaterals. Chronic intracranial hypertension was in 1 (1.4%) and recurrence of deep venous thrombosis in lower limbs was present in 1 (1.4%) female.

#### Outcome

Our study showed that 84.5% patients became normal (mRS: 0-1), 4.2% patients became functionally independent (mRS = 2), and 5.7% remained dependent (mRS 3-5) at the end of 6months and one female had deep venous thrombosis in right leg but no recurrence of CVST was observed.

In our study mean hospital stay was 14.69 days, 2.8% patients

were expired and 4.2% lost to follow up.

Death in one patient was caused due to raised intracranial pressure leading to cerebral herniation and respiratory depression. Other one patient expired due to complication of LMWH and anticoagulants.

Variables for unfavorable out come at three months were: aphasia and dysarthria at admission (P= 0.005 (odds ratio (OR) 13.7, 95% confidence interval (CI) 1.002 - 173), pallor (P= .049, OR 12.9,95% confidence interval (CI) 2.05-80.83),unconsciousness(P=.003,OR 5.1, 95% confidence interval (CI) 3.3-8.4) presence of hemorrhagic infarction (P= 0.012, OR 24.7, 95% CI 2.05 - 29.8), and diffuse cerebral edema (P= 0.004, OR 13.5, 95% CI 2.18- 86.4).

### Discussion (Table no 3 & 4 in Manuscript)

Cerebral venous sinus thrombosis (CVST) is an uncommon condition, with extremely diverse clinical features ranging from an isolated headache to focal deficits to encephalopathy to psychiatric manifestation to coma, predisposing factors, brain imaging findings, and outcome [2].

Comparison of the etiological factors and clinical presentation of CVT of previously published Indian series [Table 3 in manuscript], western series [Table 4 in manuscript] and current study.

In this retrospective and prospective observational study case series of 71 (CVST) patients seen at our institution, the female to male ratio was 41:30, the mean age was 28.07 ± 7.6 years, the mean age of females was 27.14 ± 8.6 years which was lower than the mean age of males which was 29.3 ± 5.8 years. Majority of females were below 25

**Table 4:** Comparison of Clinical features and etiological factors of published western study and present study.

	Ferro et al <sup>38</sup>	Ferro et al <sup>22</sup>	Wasay et al <sup>39</sup>	Present study
Year published	2001	2004	2008	2015
No. of patients	142	624	182	71
Age	38	39.1	38	28
Female%	71.10%	74.50%	60%	57.70%
Onset of symptoms to admission, days	5days	4 days	na	14.8
Headache	92%	88.80%	71%	85%
Fever	na	na	14%	20%
Papilledema	45%	28.30%	32%	42.70%
Aphasia	18%	19.10%	5%	7%
Sensory symptoms	11%	5.40%	na	na
Seizures	37%	39.30%	32%	57.70%
Paresis	42%	37.20%	41%	30%
Mental status disorder	na	22%	30%	6%
Coma	na	13.90%	20%	10%
Oral contraceptives	55%	54.50%	5%	9.80%
Pregnancy or puerperium	11%	20.10%	7%	40.80%
Genetic thrombophilia	14%	22.40%	10%	Not done in all pts (18.3% out of investigated pts)
Infection	17%	12.30%	3/182	21.12%
Malignancy	1%	7.40%	7%	1.40%

yr of age, in our cohort 71% of the females were in the postpartum or pregnancy related. This was comparable to that reported in previous Indian studies by Bansal et al [11], Srinivasan et al [12], Nagaraja D et al [19,13].

This was also comparable with the study of Allroggen et al [40] and Azin et al [41].

Patil et al [42] in their study of the 50 patients with CVST had 21 (42%) males and 29 (58%) females with the mean age  $39 \pm 10$  years and  $29 \pm 7$  years, respectively. In other study Kalita et al [48] reported that CVST more often occurs during pregnancy, multiparity, and infection. In their study of 33 patients with CVST, mean age was 37.5 years (range 16-76) and 23 were female which also comparable to our study.

In our study, symptom onset was acute in 27%, sub-acute in 56%, and chronic in 17% patients. 70% males were presented with sub-acute symptoms, which is comparable to Ferro et al<sup>22</sup> study which reported the mode of onset as acute in 232 patients 37.2%, subacute in 346 (55.5%), and chronic in 45 (7.2%). In other study by Crassardi et al [45] the onset of cerebral venous thrombosis was subacute in 50% of cases (between 2 and 30 days), acute in 30% of cases (<2 days), and chronic in 20% of cases. Acute presentation was more common in puerperal cases than in non-puerperal patients.

In our study mean duration of symptoms before admission was 14.82 days which was similar to the NIVSR cohort [37] in which mean duration of symptoms before admission was 16.1 days.

In our study headache was presenting symptom in 85% of patients. Headache was significantly more common in women compared with men (91% versus 82%). Similarly, in study of Ferro et

al [22] headache was the presenting symptom in 70–90% of cases and was more common in females. Similarly, Pfefferkorn et al [46] studied 32 patients with CVST with headache (81%) being most common presenting symptom. In majority of previous studies headache was the most common presenting symptom [15,16,22-30,37-44]. Similar to our study Mehndiratta et al [36] reported that headache (80%) is the most frequent symptom in patients with CVT with 75% being female population.

In our study 2<sup>nd</sup> most common presenting complaint was seizure in 58% patients, which is comparable to Nagarajan et al [19], a study of total 25 patients with CVST in which 47% presented with convulsions (47%) Kalita et al, [49] studied 90 patients of CVST out of which 42 (47%) patients presented with seizures which is also comparable to our study.

In our cohort 30 (42%) had vomiting which was comparable to Appenzeller et al [50] as they reported vomiting in (33%).

In our study 42% had complaint of transient blurring of vision or double vision, and 44% had papilledema which is comparable to other study of NIVSR [37] cohort in which 29.3% had diplopia, 22.1% had blurring of vision and 63.4% patients had papilledema.

Kuehnen et al [51] reported that, five patients who were initially evaluated for etiologies of single/multiple cranial nerve palsies finally turning out to be the cases of thrombosis of the ipsilateral transverse and sigmoid sinus on evaluation. Cranial nerve palsy as an isolated manifestation of CVT has been attributed to the elevated intracranial pressure, extension of thrombosis to venous channels, or direct pressure from the clot itself [51]

In our cohort of CVST stroke like presentation was observed

in 30%, which was unilateral either left or right in 21%, asymmetric bilateral weakness in 5.6% and paraparesis in 3%. This was similar to Appenzeller et al [50] (29.5%) and Narayan, et al [37] (25.3%).

Narayan et al [37] reported in their study alcoholism as risk factors in 67 (15.6%), oral contraceptive pill (OCP) intake in 49 (11.4%), postpartum state in 42 (9.8%). Narayan et al [37] stated that alcohol contributes to thrombosis by dehydration, hypercoagulability, and reactive thrombocytosis. Whereas Prabhakar et al [52] in their study of two hundred and six consecutive CVT patients found that patients did not differ significantly from controls with respect to smoking (13.3% vs. 14.6%,  $P = 0.77$ ) and alcohol consumption (11.2% vs. 12.2%,  $P = 0.76$ ). Similar results were reported by Elisabeth et al [57] in The MEGA study of total of 4,423 patients and 5,235 controls.

Similarly, a study by Khealani et al, [7] of 109 patients of CVT from Pakistan and the Middle East, Eighteen of 58 (31%) females were in postpartum period, and 12 of these 18 (66%) presented within 2 weeks of their delivery. Seven (12%) women were using oral contraceptive pills (data were available for only 46 women). Twenty (18%) had an infectious process. Three patients had underlying acute lymphocytic leukemia (2 of these received L-asparaginase), 3 had ulcerative colitis, and 1 each had non-Hodgkin lymphoma, myelodysplastic syndrome, glomus jugulare tumor, and Bechet disease. Thirteen patients had hypercoagulopathy, and 1 had systemic lupus erythematosus. As in our study two male was on antipsychotic, similarly Andole et al [53] reported a 41-year-old man known case of schizophrenia and was on zuclopenthixol on weekly basis had cortical vein thrombosis.

In our study 61% were anemic; among them 83% were women and 13% were men. Similarly, Narayan et al [37] found anemia as risk factor in 79 (18.4%) patients.

In study by Jonathan et al, [56] in 152 cases and 2916 control, Anemia was more frequent in cases (27.0%) than in controls (6.5%;  $P < 0.001$ ). But in our study anemia had stronger association with female specifically in postpartum or pregnancy related.

Similarly, Stolz et al, [55] in their prospective study of 121 patients of cerebral venous thrombosis suggest a significant association of severe anemia ( $Hb < 90$  g/L), and hypercholesterinemia which was similar to our study.

Cantu et al [26] in their study of 45 patients found that there was a higher frequency of MTHFR mutation in patients with CVST (22%) with high plasma concentrations of homocysteine, and low plasma folate levels were associated with an increased risk of CVST. Similarly, in our study 24% patients had hyperhomocysteinemia ( $29.5 \pm 6.3$   $\mu$ mol/L). In another study Martinelli et al [15] found that the hyperhomocysteinemia is associated with a 4-fold increased risk of CVT. Similarly, Pillai et al [21] in their study with CVST stated that eleven out of 15 patients tested for homocysteine levels had increased levels, of which 14 were males.

In our cohort D-dimer was done only in 45%, among them 88% had  $> 500$  ng/ml and in those level was  $< 500$  ng/ml had sub-acute to chronic symptoms which comparable to Misra et al [51].

Dentali et al [54] reviewed that the D-dimer accuracy was good, with a resulting weighted mean sensitivity of 93.9% and weighted mean specificity of 89.7%, which was similar to our study.

In our study 28.57% of 28 patients had increased for von Willebrand factor (vWF) levels, which was comparable to case control study of cerebral venous thrombosis and plasma concentrations of factor VIII and von by Bugnicourt et al [25].

In our study NCCT head was normal in 27.6%, remaining 72.3% had parenchymal lesions. Bousser et al [2] reported that due to anatomic variability of the venous sinuses makes CT diagnosis of CVT insensitive, with results on a plain CT being abnormal only in 30% of CVT cases.

In our study 36.6% had primary sign of CVT in NCCT in form of dense triangle sign. Superior sagittal sinus was the most common sinus involved in 53.84% patients. Isolated superior sagittal sinus (SSS) was in 38% followed by isolated transverse sinus either right or left was present in 14.28% patients and 23.8% patients had superior sagittal sinus with left transverse sinus in combination, which is comparable with other previous study [6,28,30,37,38]

In our study out of 68 patients, 15 (22.05%) had normal MRI brain which similar to Bousser et al [2]. Superior sagittal sinus was the commonest as involved in 41.1% patients and isolated SSS was involved in 22% followed by Isolated either left or right transverse sinus was involved in 22% patients, which is comparable to other previous studies [2,28,26,30,38,39,43,44]

In study of Narayan et al [37] MRI was done in 392 patients and CSVT diagnosis was made by hemorrhagic infarct in 179 (45.6%), hyperdense sinuses in 145 (36.9%), empty delta sign in 80 (20.4%), and cord sign in 13 (3.3%) patients. MRI can even be normal in up to 30% of patients which is comparable to our study. Similarly, this Khealani et al [7] reported in their study of seventy-two (66%) had infarctions and out of them 37 (34%) had hemorrhagic. Three patients had focal subarachnoid hemorrhage. In 54 (50%) patients, only 1 sinus was involved. Superior sagittal sinus was most commonly involved sinus, followed by transverse and sigmoid sinus which was also comparable to our study.

MRV to be the most effective noninvasive technique to confirm the diagnosis [2,5,6,30,37,38] similar observation was made in our study as all 69 patients had finding suggestive diagnosis of CVST. In our study on MRV brain superficial venous system was involved in 93% and deep venous system in combination of superficial system involved in 7% patients. Superior sagittal sinus was the most common sinus in 82% patients, isolated superior sagittal sinus in 30% patients followed by isolated left transverse sinus involved in 11.6% and right transverse sinus was involved in 4.3% patients which are also comparable other previous study [7,37].

Halesha et al [44] reported in their study that superior sagittal sinus was most common sinus involved in 82%, left lateral sinus 36%, right lateral sinus 32%, straight sinus 16% and deep venous system was involved in 10% patients this was similar to our study. In our study four patients had only sign and symptoms of raised intracranial tension, without any risk factors. All four patients had elevated CSF opening pressure and on MRV two patients had superior sagittal sinus thrombosis, one had isolated left transverse sinus thrombosis and one had superior sagittal sinus with transverse sinus thrombosis which was comparable with Ridha et al [58] Ameri et al [1] reported that Up to 40% of patients with CVT present with isolated intracranial

hypertension.

In our study 70 patient received LMWH for 5 to 10 days with target INR 2-3 with warfarin initiation. Only one patient had complication of anticoagulation and she expired in hospital after 35days hospitalization. In a study conducted by Misra et al [59] 32 patients were randomized to the UFH arm and 34 to the LMWH arm. In-hospital mortality was significantly lower in the LMWH group (0% vs. 19%). On the basis of data from randomized, controlled trials and observational studies, anticoagulation is recommended as safe and effective for treatment of cerebral venous thrombosis with or without intracranial hemorrhage on presentation [30].

In our study successful recanalization with improvement of symptoms was achieved in seventeen patients and with collaterals in eight patients which is comparable to the studies done by Stolz et al [55] and Baugmatner et al [35].

On follow up in our study, depressed mood with minor memory complaints was present in 30%, followed by headache in 18% and 16% had seizure. One patient had developed progressive bilateral painless vision loss and one patient (protein C deficiency, low vitamin B 12, and hyperhomocysteinemia) had developed deep venous thrombosis in right lower limb on anticoagulation. But in NIVSR [37] study chronic headache was seen on follow up in 4.2%, other were recurrent seizure in 1.1%, chronic intracranial hypertension in 0.9%, deep venous thrombosis in 0.4%, and arterial thrombosis in 0.7% patients.

A study by Khealani et al, [7] of 109 patients of CVT from Pakistan and the Middle East in which follow-up was available for 72 patients. Sixty-one (85%) had no disability on follow-up which is comparable to our study.

Wasay et al [39] in that 10-year period study of 182 patients, one year follow up was available for 96 patients (53%). Of these, 26 (27%) were healthy, 43 (45%) were ambulatory with assistance, and 27 (28%) were still bedridden.

Predictors associated with a poor outcome at 3 months in the multivariate analysis were aphasia, dysarthria, pallor, unconsciousness, presence of hemorrhagic infarction and diffuse cerebral edema at admission which was comparable to other studies [2,5,6,8,22,40,41,44,45].

In the NIVSR [37] cohort the independent predictors of poor outcome were fever, deep venous thrombosis, seizures, focal neurological deficit, and unconsciousness.

In Ferro et al [22] study at the end of follow-up (median 16 months), 356 patients (57.1%) had no symptom or signs (mRS=0), 137 (22%) had minor residual symptoms (mRS=1), and 47 (7.5%) had mild impairments (mRS=2). Eighteen (2.9%) were moderately impaired (mRS=3), 14 (2.2%) were severely handicapped (mRS=4 or 5), and 52 (8.3%) had died. Predictors of death or dependence were age >37 years, male sex, coma, mental status disorder, hemorrhage on admission CT scan, thrombosis of the deep cerebral venous system, central nervous system infection, and cancer.

## Limitations

- The major limitation of our study is that it is an observational study.

- Our study is limited in term of number of patients and being partially retrospective.

- Lack of uniform evaluation in term of work-up for hypercoagulopathy.

## Summary

Total 40 patients in prospective study and 31 patients in retrospective study were enrolled.

- Females were 58% of total affected population.
- Most of females had CVST in their peripartum period. Peripartum period is vulnerable for development of CVST due to the presence of infection, microcytic anemia and hyperhomocysteinemia.
- Majority of our patients had sub-acute onset of symptoms i.e. symptom duration (48hour -30 days).
- In our study CVST presents with a wide spectrum of symptoms and signs headache, seizures and blurring of vision were the three major clinical features.
- Alcoholism, smoking, hyperhomocysteinemia, dyslipidemia and vitamin B12 deficiency were the significant risk factors in males.
- 5 males had past history of deep venous thrombosis and 2 were on antipsychotics (Risperidone, Trifluoperazine).
- Majority of women had microcytic hypo-chromic anemia and males had vitamin B12 deficiency.
- 9(30%) males had Hemoglobin  $\geq$ 16.5.
- MRI Brain was normal in 22% patients but MRV Brain was abnormal in all patients.
- Haemorrhagic infarction was the most common abnormality noted on neuroimaging and in (94%) majority of patient's superficial venous system was involved.

- On CEMRV, Superior sagittal sinus was the commonest sinus involved followed by transverse sinus was the next most common sinus.

- In our study prognosis of patients is predominantly determined by base line mRS, unconsciousness, aphasia or dysarthria, pallor, hemorrhagic infarction and diffuse cerebral edema.

- Most of the patients who were followed up had re-canalization of the occluded sinus and veins.

## Conclusions

- From above study we conclude that CVST is a multifactorial disease that resulting from a combination of various prothrombotic risk factors and underlying clinical condition.

- We should keep a high index of suspicion of CVST in every postpartum woman with new onset neurological sign and symptoms.

- Because there are important etiologic, clinical, and therapeutic differences in developing countries as compared to western countries, there is a requirement of well-conducted, large, multicenter, multinational, cohort studies among developing countries.

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