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# Case Study of Pediatric Cerebral Sinus Venous Thrombosis Center of a Low Middle-Income Country

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**Abstract**

Pediatric cerebral venous sinus thrombosis (CVST) is rare but a potentially fatal disease requiring its understanding in local setting. In this study, we observed the clinical course, management, and outcome of pediatric patients with sinus thrombosis in a tertiary care center at Pakistan. Patients between age 0 to 18 years of both genders diagnosed with sinus thrombosis during 2011 to 2020 were included. Data was collected through in-house computerized system and SPSS version 19 was used for analysis. Of 143492 pediatric admissions, 32 (21 males and 11 females) patients with a median (IQR) age of 4.5 years (0-16) had CVST. This is equivalent to 18.5 CVST events per million pediatric admissions. Adolescents were mostly affected, and the overall mortality was 7%. Primary underlying disorders were infections (59%), hematological neoplasms (12.5%), thrombotic thrombocytopenic purpura (3%) and antiphospholipid syndrome (3%). Activated protein C resistance (44%) was the most common inherited thrombophilia. Twenty-one (66%) patients were anemic with a mean ($\pm$SD) hemoglobin of 9.0 g/dL ($\pm$2.3). Regression analysis showed a positive association of anemia with multiple sinus involvement (*P*-value 0.009) but not with duration of symptoms (*P*-value 0.344), hospital stay (*P*-value 0.466), age (*P*-value 0.863) or gender (*P*-value 0.542) of the patients. SARS-COV2 was negative in patients during 2020. Adolescents were primarily affected by sinus thrombosis and infections was the predominant risk factor for all age groups, with a low all-cause mortality. A high index of clinical suspicion is required for prompt diagnosis and intervention.

**Keywords**

pediatric thrombosis, cerebral vein thrombosis, infection, neonates

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## Introduction

Cerebral venous sinus thrombosis is the thrombotic obstruction of the dural venous sinuses draining the brain with the subsequent risk of cerebral ischemia and/or hemorrhage. The estimated annual incidence is 3 to 4 cases per 1 million population and up to 7 cases per 1 million among children.[1] Risk factors contributing to pediatric CVST include infections, trauma, recent intracranial surgery and prothrombotic disorders. Predominant presenting symptoms were headache, vomiting, visual disturbances such as papilledema and sixth nerve palsy in 21 children diagnosed with CVST in a study.[2] Otitis media was observed in 62% of children in this study and despite anticoagulation, 48% of patients had adverse outcomes such as death, chronic intracranial hypertension, residual hemiparesis or sixth nerve palsy.[2] Although pediatric CVST is rare, the current literature reports that neonates are more commonly affected.[3] There are also differences in the clinical manifestations between neonates and non-neonates. For example, neonates frequently present with seizures while focal and generalized neurological signs are more commonly observed in non-neonates.[4] Similarly acute systemic illness (dehydration, bacterial sepsis and perinatal complications) are the predominant risk factors for neonatal CVST while head/neck infections, chronic systemic diseases and

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prothrombotic conditions are more prevalent in non-neonates.[4] The diagnosis of CVST is primarily made using neuroimaging. Unenhanced CT scan as the first-line imaging technique[3] is limited by its low sensitivity of 30%,[3,5] and decreased specificity in neonates because of their slower blood flow, high hematocrit levels, and the relative low density of the surrounding non-myelinated brain tissue also increased risk of radiation exposure.[6] Contrast-CT may show the classic "empty delta" sign of CVST which may be delayed for several days after the onset of symptoms.[3,7] A combination of MRI and MRV is now being accepted as the "gold standard" for diagnosis of CVST[5] while transfontanellar Doppler ultrasound which is a readily available and non-invasive modality is another choice for diagnosis in neonates especially in the low middle income (LMIC) country setting.[3]

Pakistan is a low middle-income country (LMIC) of South Asia and is the sixth most populous country in the world. Although the healthcare system is improving, it still lacks national registries for various diseases including venous thromboembolism. We previously shared our experience with pediatric thromboembolism[8] and searched the literature for rare thrombotic events in pediatric patients like CVST in LMICs. Except for a few case reports,[9,10] one cross-sectional study[11] from Pakistan and few cases from India[12-14] not much is known about pediatric CVST in developing countries. Moreover, neonatal CVST has not been reported in any comprehensive way from any LMIC. This study aimed at describing the clinical course, management, and outcome of pediatric CVST with special focus on neonates in Southern Pakistan.

## Materials and Methods

### Setting

A retrospective study was conducted at the Pediatric Unit of Aga Khan University Hospital (AKUH), Pakistan. AKUH is an academic care center with advanced facilities for diagnosis and management of patients. AKUH was JCIA-accredited in 2006 and its associated clinical laboratories received CAP accreditation in 2016. Hospital related details for pediatric admissions were as described previously.[8] Briefly, AKUH neonatal ICU is 24 bedded with approximately 1200 new admissions annually. Of these 1200 admissions, 80% (around 950) are from the metropolis of Karachi having a population of 18 million (unofficial figures). The remaining 20% (around 250) admissions are from the rest of the country (with 208.57 million residents). As per institutional practice, CT scan was performed in patients with neurological symptoms admitted to the ER while MRI-MRV was the first-line neuroimaging in admitted patients with new onset of neurological signs and in the neonates to minimize radiation exposure.

### Data Collection

During the period of 10 years from 2011 to September 2020, ICD coding 9 was used to identify patients with CVST between age 0-18 years irrespective of gender. Patients were classified as neonates (0-1 month), infants (>1 month-2 years), children (3-11 years), and adolescents (12-18 years). In-house computerized system was used to collect clinical details, diagnostics, treatment received, and outcome of sinus thromboses.

**Table 1.** Age-Wise Burden of Pediatric Cerebral Sinus Venous Thrombosis During 2011-2020.

| Age-group | Total pediatric admissions, n | Pediatric CVST, n | Annual event rate per million admissions |
|---|---|---|---|
| Neonates | 59048 | 8 | 11 |
| Infants | 29950 | 7 | 19 |
| Children | 37884 | 2 | 4 |
| Adolescents | 16610 | 15 | 75 |
| All | 143492 | 32 | 18.5 |

### Ethical Concerns

The study was conducted after approval from ethical review committee of AKUH (#2019-1893-4949**).**

### Statistical Analysis

IBM SPSS (Statistical Package for Social Sciences) was used for all statistical analysis. Normality of data was checked through Shapiro-Wilk test. The descriptive data was reported as mean $\pm$ SD for normal and median (IQR) for skewed data, while frequency was given in percentages. Continuous and nominal variables were compared between neonates and non-neonates using Mann-Whitney and independent T test. Regression analysis was used to determine the association of disease severity with any clinical or laboratory parameters. Threshold of significance was a $P$-value of $<0.05$.

## Results

### Demographics and Epidemiology

During the study period, 40 pediatric patients were identified for CVST from 143492 pediatric admissions. However, 8 patients (with diagnosis of mumps, AV malformation, sepsis, acute leukemia with retropharyngeal abscess, meningitis, encephalopathy, gliomatosis cerebri and metabolic disorder) were not considered for further evaluation because sinus thrombosis was not confirmed on neuroimaging. Only 32 unique patients were confirmed with the diagnosis of sinus thromboses on radiological imaging including 21 males (66%) and 11 females (34%) with a median (IQR) age of 4.5 years (0-16). There were 8 neonates (25%), 7 infants (22%), 2 children (6%) and 15 adolescents (47%) with an overall annual CVST rate of 18.5 events per million pediatric admissions in the hospital. Table 1 shows that the highest annual event rate of CVST was 75 per million admissions in adolescents while that of neonates was low at 11. The demographics of the patients are shown in Table 2. This shows that median (IQR) duration of symptoms was 4 days[2-7] prior to hospital visit with 24/32 patients (75%) of patients presenting within 10 days of onset of symptoms. Predominant risk factors were head and neck infection (12/32, 37.5%), sepsis (5/32, 15.6%) and cancer (4/32, 12.5%)

**Table 2.** Demographics of Patients With Cerebral Venous Sinus Thrombosis During 2011-Sep 2020 (n = 32).

| Primary diagnosis | N (%) | Age, years, Mean ± SD | M/F | Duration of symptoms (days) before presentation, median (IQR) | No. of patients with dehydration, N (%) | Length of stay (days), median (IQR) |
|---|---|---|---|---|---|---|
| Head and neck infections | 12 (37.5) | 9.7 ± 7.6 | 9/3 | 4.5 (3-13) | 5 (41.7) | 8 (5-12.7) |
| Sepsis | 5 (15.6) | 4.2 ± 7.7 | 3/2 | 1.5 (1-8.7) | 4 (80) | 13 (5-32.5) |
| Cancer | 4 (12.5) | 12.2 ± 6.4 | 3/1 | 4.0 (0.25-7) | 0 | 6.5 (3.5-13.2) |
| Idiopathic | 9 (28.1) | 4.9 ± 7.7 | 5/4 | 2 (1-7) | 2 (22) | 9 (8-15.5) |
| Miscellaneous | 2 (6.1) | 17 ± 1.4 | 1/1 | 135 (–120) | 0 | 5 (–2) |
| All | 32 (100) | 8.1 ± 7.6 | 22/11 | 4 (2-7) | 11 (33.3) | 8 (5-14.5) |

**Table 3.** Summary of Patients With Unknown Diagnosis in 7 Patients With Cerebral Sinus Venous Thrombosis.

| Patient# | Age | Gender | Underlying systemic disorder | Inherited thrombophilia* |
|---|---|---|---|---|
| 1 | 0 day | F | Hypoxic brain injury, Anemia | Not tested |
| 2 | 3 days | M | Nil | Positive |
| 3 | 15 days | M | Dehydration | Positive |
| 4 | 1 month | M | Hypertrophic cardiomyopathy | Positive |
| 5 | 3 months | F | Anemia | Positive |
| 6 | 14 years | F | Nil | Positive |
| 7 | 17 years | M | Anemia | Negative |

*Tests done during acute event.

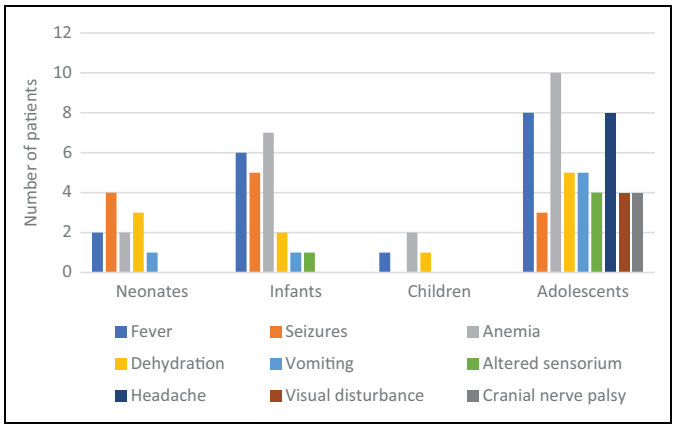


**Figure 1.** Age-wise distribution of clinical presentation in pediatric patients having cerebral sinus venous thrombosis (n = 32).

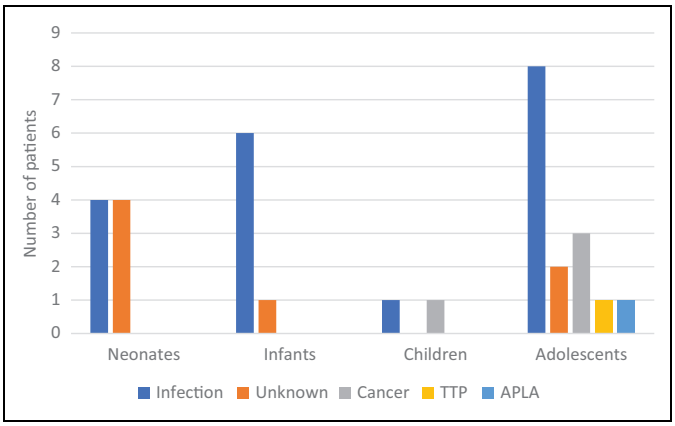


**Figure 2.** Risk factors as per age group in 32 patients with pediatric sinus thromboses.

(Figure 1). Patients with acute lymphoblastic leukemia (3/32) were receiving asparaginase and intrathecal methotrexate while 1 patient had polycythemia rubra vera. One patient with acute leukemia was simultaneously diagnosed with pulmonary embolism. Rare or less common risk factors were thrombotic thrombocytopenic purpura or TTP (1/32, 3%) and antiphospholipid syndrome or APLA (1/32, 3%). Inherited thrombophilia screening was positive in 5/7 patients (71%) with no identified cause for CVST (Table 3).

## *Clinical Presentation*

Figure 2 shows the greater frequency of seizures in the neonates (4/8, 50%) and infants (5/7, 71%) compared to non-neonates (children 0, adolescents 3/15, 20%); however this difference in frequency of seizures between neonates and non-neonates did not reach a statistical significance (*P*-value 0.415). In contrast, visual problems (neonates 0 vs. 4/24 in non-neonates, 17%; *P*-value 0.043) headache (neonates 0 vs. 8/24 in non-neonates, 33%; *P*-value 0.003) and altered mental status (neonates 0 vs. 5/24 in non-neonates, 021%; *P* 0.022) were more prevalent in non-neonates in comparison to neonates.

## *Laboratory Diagnosis*

Laboratory details are summarized in Table 4. Low hemoglobin and leukocytosis were the significant lab findings and were observed in 21/32 (66%) and 15/32 (47%) patients, respectively. Anemia was observed in 19/24 of non-neonates (79%) in contrast to only 2/8 of neonates (25%). Low MCV was

**Table 4.** Laboratory Details of 32 Patients With Respect to Age; All Values Are Median (Interquartile Range).

| | Neonates, N = 8 | Non-neonates, N = 24 | *P*-value |
|---|---|---|---|
| Hemoglobin | 16.3 (10.6-18.5) | 9.6 (7.6-12.1) | 0.008* |
| White cell count | 17.4 (12.4-19.6) | 10.9 (9.2-16.2) | 0.037* |
| Platelet count | 152 (26-215) | 427 (294-587) | 0.001* |
| PT | 15.9 (13.9-17.5) | 11.6 (11-12.8) | 0.000* |
| APTT | 31.2 (25.2.4-38.0) | 25.5 (21.8-29.8) | 0.060 |
| Protein C** | 50.0 (26.5-61.2) | 78.4 (60.5-89.7) | 0.005* |
| Protein S** | 47.5 (31.2-68.0) | 74.5 (60-102.9) | 0.018* |
| Antithrombin III** | 67.0 (48.5-101.2) | 91.5 (82.5-96.7) | 0.102 |
| APCR** | 0.81 (0.69-0.89) | 0.93 (0.82-1.02) | 0.083 |

Abbreviations: PT, prothrombin time; APTT, activated partial thromboplastin time; APCR, activated protein C resistance.
*P-value < 0.5.
**Thrombophilia screening results were available for 6/8 neonates (75%) and 12/24 non-neonates (50%).

observed in 11/24 non-neonates (46%) which may be reflective of iron deficiency anemia though serum ferritin was not checked in any patient. Regression analysis showed a positive association of anemia with multiple sinus involvement (*P*-value 0.009) but not with duration of symptoms (*P*-value 0.344), hospital stay (*P*-value 0.466), age (*P*-value 0.863) or gender (*P*-value 0.542) of the patients. Prolonged PT was observed in 8/31 patients (25%) while 4/31 patients (12%) had prolonged APTT on presentation. A significant finding was shortened APTT in 10/31 patients (31%). Table 4 showed that PT was significantly prolonged in neonates compared to non-neonates (*P*-value 0.000). Overall, thrombophilia screening was done in 18/32 patients (56%) during acute thrombotic event. Activated protein C resistance, protein S, protein C and anti-thrombin III deficiency was seen in 8/18 (25%), 6/18 (19%), 6/18 (19%) and 2/18 (6%) patients respectively. However, they were not labeled as having inherited thrombophilia as the tests were done during acute events and were not repeated to confirm the consistency in the results. Table 4 showed that neonates had significantly low protein C (*P*-value 0.005) and protein S (*P*-value 0.018) compared to non-neonates.

Blood culture was performed in all patients at the time of admission and only 8/32 patients (40%) had culture-proven bacterial infection. CSF examination was performed in 18/32 (56%) patients and low glucose, high proteins and elevated chloride were observed in 8/18 (44%), 4/18 (22%) and 3/18 (16%) patients respectively. In the sub-group analysis of 12 patients with head and neck infection, CSF was performed in 8/12 patients (67%) and pyogenic meningitis was seen in 2/8 patients (25%) only. SARS-Cov2 was tested in 2 patients in 2020 but was not detected in them.

## *Neuroimaging*

CT scans with and without contrast were performed in 10/32 and 19/32 patients (31% and 59%) respectively while combined MRI / MRV was performed in 28/32 patients (87%). Non-contrast and contrast CT scan were positive in 8/19 and 8/10 patients (42% and 80%) respectively. Overall, multiple sinus involvement was seen in 19/32 patients (59%), while single sinus involvement was more frequent in neonates (5/8, 62%) than in non-neonates (8/24, 33%). Superficial venous system like superior sagittal sinus (SSS) (41%) was less frequently involved compared to deep sinuses like transverse sinus (72%), sigmoidal (47%), straight (19%) cavernous sinus (6%), and internal jugular vein (19%). Figure 3 shows the location of thrombosis was mainly SSS in neonates. Overall, both infarction and hemorrhage were observed in 6/32 patients (19%), while 7/32 patients (22%) had infarcts only and CVST-associated isolated hemorrhage was less common and occurred in 2/32 patients (6%). A relatively higher frequency of brain infarction was observed in neonates (5/8, 62%) as compared to non-neonates (8/24 or 33%) without reaching the statistical significance (*P*-value 0.155). However, the frequency of hemorrhage was equivocal among neonates (2/8, 25%) and non-neonates (6/24, 25%).

## *Complications, Management, and Outcome*

Neonatal CVST was complicated with hypoxic brain encephalopathy in 4/8 (50%) at the time of presentation. Neurological defects in non-neonates were hemiplegia (n = 1/24, 4%), aphasia (n = 1/24, 4%), visual disturbances (n = 1/24, 4%), and cranial nerve palsy (n = 4/24, 16%). The long-term neurological deficits remained unknown because of lost to follow-up.

Anticoagulation was received by 6/8 neonates (75%) and 19/24 non-neonates (79%). Overall, 25/32 patients (78%) were anticoagulated using low-molecular-weight heparin (5 neonates and 17 non-neonates), unfractionated heparin (1 neonate and 1 non-neonate), and rivaroxaban (1 non-neonate). Besides anticoagulation, clopidogrel was also given to an 18-year-boy with polycythemia rubra vera, while thrombectomy was performed in a 17-year-patient with extensive sinus thromboses. Seven patients (2 neonates and 5 non-neonates) were not anticoagulated because of active/high risk of bleeding (n = 1 neonate and 3 non-neonate), thrombocytopenia (n = 1 neonate), lost to follow-up (n = 1 non-neonate), and early death (n = 1 non-neonate). However, the difference in outcome of patients with and without anticoagulation was not studied.

Median hospital stay was 8 days (range 2-60 days) and 27/32 (84%) patients were discharged alive, 3/32 (9%) left against medical advice and 2/32 (6%) died during hospital admission. One patient having a fatal outcome was a 13-month-infant having epidermolysis bullosa and vancomycin-resistant enterococcal infection with candidiasis. The other patient was a 14-day-neonate who was admitted with sepsis having infection with Acinetobacter and candidiasis.

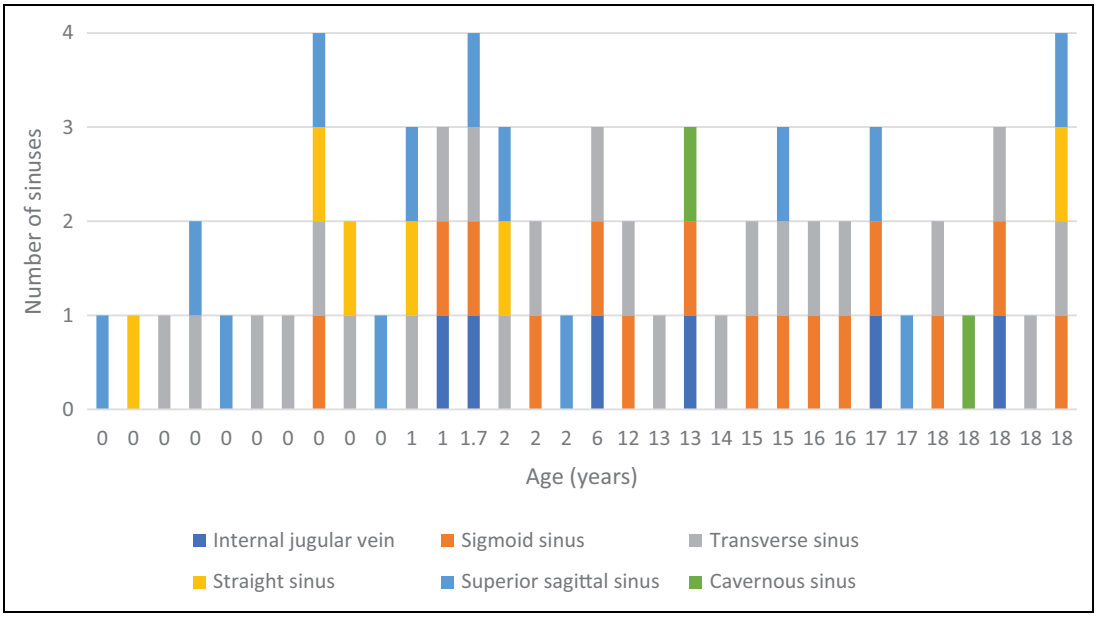


**Figure 3.** Sinus involvement by thrombosis in 32 pediatric patients with respect to their age.

## Discussion

This study described the clinical course and outcome of 32 pediatric patients having CVST. There were some striking differences in this study compared to published data from western countries. For example, the study showed that the most frequently affected age group was adolescents (9.0 per 10000 admissions) followed by infants (2.3 per 10000 admissions). In contrast, several reports have shown a preponderance of neonatal CVST. Heller et al in 2003 reported CVST in 40 neonates (27%) from a total of 149 pediatric patients[15] equivalent to an annual incidence rate of 2.6 per 100 000 neonates.[15] Similarly de Veber et al in 2001 reported 69 neonates having CVST (43%) in a registry of 160 pediatric patients.[4] A lower incidence of neonatal CVST in this study was parallel to our previously published findings for pediatric VTE (8) where only 3 patients were neonates from a total of 77 having DVT/PE. A possible explanation for this age-discrepancy could be that being the largest NICU in the country, the admitted patients are complex with majority having sepsis and multiple complications. It is possible that due to the severity of the illness some of these did not undergo MRI and only head ultrasounds were performed as screening tests. Moreover, being a rare disease, it is difficult to recognize CVST clinically and requires a high index of suspicion for diagnosis. Our study showed a male predilection though there is no significant association of CVST with sex in the pediatric population due to a lack of sex-specific risk factors.[3]

Clinical manifestations in CVST are usually nonspecific and diverse making the diagnosis very difficult unless there is a high index of clinical suspicion. The most predominant symptoms were fever, headaches, vomiting and seizures in this study. Many studies have reported similar findings along with visual impairment due to an increase in intracranial pressure.[5,16] Generalized neurological deficits are reported to be more common in children while seizures are frequent in neonates.[3,15,17] We also found altered sensorium (27%), visual disturbances (27%) and cranial nerve palsies (13%) primarily in adolescents while seizures were more common in neonates in this study.

We found local (mastoiditis/meningitis) and systemic infection as the highest risk factor for pediatric CVST (59%), and this was true for each individual age-group as well. These findings were agreeable with many researchers reporting otitis media and mastoiditis as the most common causal factors[3,18] ranging from 55% to 57%.[17,19] This study showed that 47% of patients who were infected were dehydrated as well at the time of presentation. Dehydration which is often associated with infections in pediatric patients is also a risk factor for CVST.[5,20] Reports have shown that 23% to 30% of patients with pediatric CVST are dehydrated.[4,5,11]

A review described inherited thrombophilia (protein C, S, anti-thrombin III deficiencies, factor V Leiden mutation) in 20% to 62% and anti-phospholipid syndrome in 17% of patients having pediatric CVST.[3] Other common risk factors include chronic diseases that lead to a prothrombotic state such as systemic lupus erythematosus, nephrotic syndrome, nephritis, head trauma and malignancies.[3,5,15,18,20] In our study, 12/18 patients (66%) were positive for thrombophilia screening. However, these labs were done during acute event and were not repeated later to observe the consistency of the results, therefore patients were not labeled with IT.

Anemia was considered as a risk factor for CVST and stroke in pediatric patients in some case reports [11,17,21-23] secondary to sickle cell disease, thalassemia or iron deficiency anemia.[20,24] In our study 66% of patients were anemic and half of them had microcytic anemia though they were not evaluated for iron

deficiency anemia. We also observed that anemic patients had multiple sinus involvement, but infection, cancer and dehydration were the confounders in all cases. As anemia is frequently observed in sick children therefore case-control studies are needed to define the contributory role of anemia, if any, in pediatric CVST. Besides neonatal causes, maternal factors such as obstetrical trauma and inherited thrombophilia in mothers may be contributory to neonatal thrombosis.[3,18] However, we did not evaluate maternal factors as the risk factors in neonatal CVST.

Neuroimaging showed that 19 patients (60%) had thrombosis in more than 1 sinus and overall thrombosis was located mainly in deep compared to superficial sinuses (70% vs. 30%). However, neonates showed a predilection toward superior sagittal sinus (SSS) in this study. Several reports have reported SSS as the most commonly involved sinus[4,5,15] which may be because of neck flexion and compression of SSS by occipital bone in neonates.[20]

The guidance of treating pediatric CVST is derived from the experiences of managing adult CVST. Anticoagulant therapy is required to prevent thrombus extension, facilitating recanalization and preventing long term neurological deficits.[7] LMWH is usually the drug of choice[5] but requires laboratory monitoring through anti-xa assay.[5] In our study, 69% of our patients were treated with enoxaparin while 1 patient received rivaroxaban. Both American Heart Association (AHA) Scientific Statement[7] and the American College of Chest Physicians (ACCP)[25] suggested full anticoagulation of pediatric CVST for 6 weeks to 3 months. Outcome studies with treatment showed improvement even in the presence of ICH. Moreover, a study reported propagation of thrombosis in 1/4th of neonates and 1/3rd of children who were not anticoagulated.[26] AHA suggested anticoagulation in neonatal CVST with those having propagation of thrombus or with inherited thrombophilia[7] while ACCP suggest anticoagulation even with ICH.[25]

Neurological complications were observed in 22% of the patients in this study while the long-term sequelae of patients having brain infarcts and hypoxic ischemic encephalopathy remained unknown because of the loss of follow-ups. A review described moderate or severe disability (modified Rankin Scale 3 or 4) in 5%-10% of survivors of acute phase and 34% of those having massive CVST.[3]

The all-cause mortality was low at 7% in this study. Pediatric CVST is now no longer considered a highly fatal disease as mortality stands low at 6%-10%.[11,20,27] The possible reasons may be increase clinical awareness, advances in neuroimaging and perhaps effective use of antibiotics[28] as pediatric CVST is mostly associated with infections.

### *Strengths and Limitations*

The study helped in defining the clinical course of pediatric CVST with special focus on neonates in LMIC. It undermined the need of a high clinical suspicion for CVST in young patients having local or systemic infections. However, the study was limited by its retrospective nature, single-center data, lack of standardization in first-line neuroimaging technique/thrombophilia screening, missing data on maternal risk factors and a long term-follow-up.

## Conclusion

Adolescents were primarily affected by sinus thrombosis and infections was the predominant risk factor for all age groups, with a low all-cause mortality. A significant proportion of patients was anemic requiring case-control studies for evaluating the role of hemoglobin as an additional biomarker for pediatric sinus thrombosis.

### Authors' Note

Data can be provided by corresponding author on request. The study was designed and supervised by BM. Data were collected by MWS, RDU, AA, and IA. Initial draft was written by BM, MWS, RDU, AA, and IA and critically reviewed by SA. All authors approved the final version of the manuscript.

### Declaration of Conflicting Interests

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