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RESEARCH ARTICLE

A STUDY OF PROGNOSTIC SCORES TO PREDICT THE OUTCOME IN CEREBRAL VENOUS THROMBOSIS

Dr. Anusha Challa[1], Dr Arunakumari Upputuri[2], Dr. Butchi Raju Garuda[3], Dr. Gopi Seepana[4] and Dr. Sateeshkumar Talabhaktula[5]

1. Postgraduate student, Department of Neurology, King George Hospital, Andhra Medical College, Visakhapatnam, Andhra Pradesh, India.
2. Assistant Professor, Department of Neurology, King George Hospital, Andhra Medical College, Visakhapatnam, Andhra Pradesh, India.
3. Professor and HOD, Department of Neurology, King George Hospital, Andhra Medical College, Visakhapatnam, Andhra Pradesh, India.
4. Associate Professor, Department of Neurology, King George Hospital, Andhra Medical College, Visakhapatnam, Andhra Pradesh, India
5. Assistant Professor, Department of Neurology, King George Hospital, Andhra Medical College, Visakhapatnam, Andhra Pradesh, India.

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Abstract

Background: Cerebral Venous Thrombosis (CVT) is a multifactorial condition with wide clinical presentation. They have favourable prognosis but 15% die or become dependent. Hence, there is need for "user friendly risk scoring system" which helps in clinical decision making and predicting prognosis.

Methods: The present study was a prospective observational study of CVT patients from April, 2018 to February, 2019 at Department of Neurology, King George Hospital, Andhra Medical College, Visakhapatnam, and followed up for three months. Patients with confirmed diagnosis of CVT based on history and radiological findings were studied. All the patients were assessed for CVT Grading Scale, CVST Scoring and CVT Risk Score.

Results: Sixty-six CVT patients were enrolled with mean age of 32.4years. CVT Risk score can predict poor outcome if cut off score is above 3 with sensitivity of 92 % and specificity of 20 %. Prediction of prognosis and brain lesions by CVT risk score analysed by Fischer exact test is highly significant (p= 0.00). CVT Risk Score and CVT Grade Scale had high sensitivity in predicting prognosis at one and three months. CVT grading scale with mild scores had good outcome and those with severe grading had poor outcome.

Conclusion: Prognostic Scores in Indian population was a novel study in CVT patients. Despite low specificity, it can be used to avoid unnecessary or dangerous intervention in low-risk patients and identifies high-risk patients with poor prognosis, who require intensive interventions, such as local IV thrombolysis and decompressive surgery.

Corresponding Author:- Dr. Arunakumari Upputuri
Address:- Assistant Professor, Department of Neurology, King George Hospital, Andhra Medical College, Visakhapatnam, Andhra Pradesh, India.

Introduction:-

Cerebral venous thrombosis (CVT) is caused by thrombosis of cortical veins and cerebral dural venous sinuses[1]. Cases of CVT are many times less often than arterial strokes[2]. Traditionally, young adult women are more often affected than men[3,4], but according to recent series men are more affected.

Initial Indian Study[6] reported 50 cases of severe CVT among 1000 deliveries conducted per year. There was a higher prevalence rate in developing countries, and an Indian Study published by Panagariya A, et al[7] in 1997 reported that CVT constituted 50 % of young strokes.
Modern neuroimaging techniques in India helped in early recognition and timely management. This led to a favourable prognosis in more than 80% of CVT patients and a low mortality rate. The study by Srinivasan et al.[6], reported a change in the trend of mortality and observed a decrease from 50.6% to 10% in the last three decades.

CVT was a multifactorial condition with good prognosis but 15% die or become dependent even with recent advances in treatment [8]. Hence, there was need for user-friendly risk scoring system which helps in clinical decision making and predicting prognosis. It would be of interest to study the predictor variables for outcome in CVT patients.

Aims and Objectives of the Study:-

1. To study the clinical and radiological features in CVT patients
2. To assess the Prognostic Scores (CVT GRADING SCALE, CVST SCORING SYSTEM, CVT RISK SCORE) in predicting the outcome in a single-centre cohort [9,10, 11].
3. Primary Outcome (death or dependency) was analysed by using Modified Rankin Scale (mRS) and Barthel Index.

Patients and Methods:-

This was a prospective observational study conducted from April 2018 to December 2019 in the Department of Neurology, King George Hospital, Visakhapatnam, with approval from the Institutional Ethics Committee. Informed consent was obtained from all patients. Sixty-six patients who fulfilled clinical and radiological inclusion criteria were recruited. Patients with age less than eighteen years were excluded.

MRI brain imaging was done and looked for the presence of haemorrhagic infarcts, supratentorial /infratentorial lesions, midline shift and other features. Findings on MR Venogram were noted for cerebral sinuses and veins involved, deep veins, cortical veins or cavernous sinus were noted during the study.

All the confirmed cases of CVT were investigated with complete hemogram, relevant biochemical studies, prothrombin time, HIV, and serum homocysteine levels. Genetic mutations of thrombophilia and thrombotic profile were not evaluated due to financial constraints. Components of CVT risk score, CVT Grading scale, and CVST score were noted, and scores were calculated bedside at the time of admission[9, 10, 11].

Patients were grouped into poor outcomes (mRS = 0 to 2) and good outcome (mRS = 3 to 6). Patients were stratified into those with independent, partially dependent, and dependent on Activities of Daily Living by Barthel Index. Outcome measures were noted at the time of admission, one month, and three months of follow up.

The statistical analysis was done using Chi-square test statistics for categorical observations and ROC for defining the cut off values for prognostic scores. Chi-square test was used to test the significance of differences in two groups. *P* value < 0.05 was considered significant.

Results:-

Sixty-six CVT patients were enrolled with mean age of 32.4 years. The age distribution was given in Table-1. There were 46 men and 20 women were enrolled with mean age of 32.46 years and 32.19 years respectively. Majority of patients had subacute presentation (72.7%). Least common presentation was chronic CVT (4.5%). Most frequent risk factor was Hyper-homocysteinemia (65%) followed by alcoholism (54.4%) as shown in Fig-1. Elevated levels of Serum Homocysteine in Alcoholics was highly significant (p=0.000) compared to non–alcoholics. None of the female CVT patients had exposed to oral contraceptive pills. Most common presentation of CVT patients was headache (98.5%) followed by seizures (68.2%). Least common presentation was stupor/coma. Focal neurological

deficits were noted in 59.1% patients. Stroke like presentation (34.8%) was the frequently reported focal neurological deficit. Least common presentation was cranial nerve palsies and aphasia (3%). Visual impairment was seen in 12.1% of CVT patients.

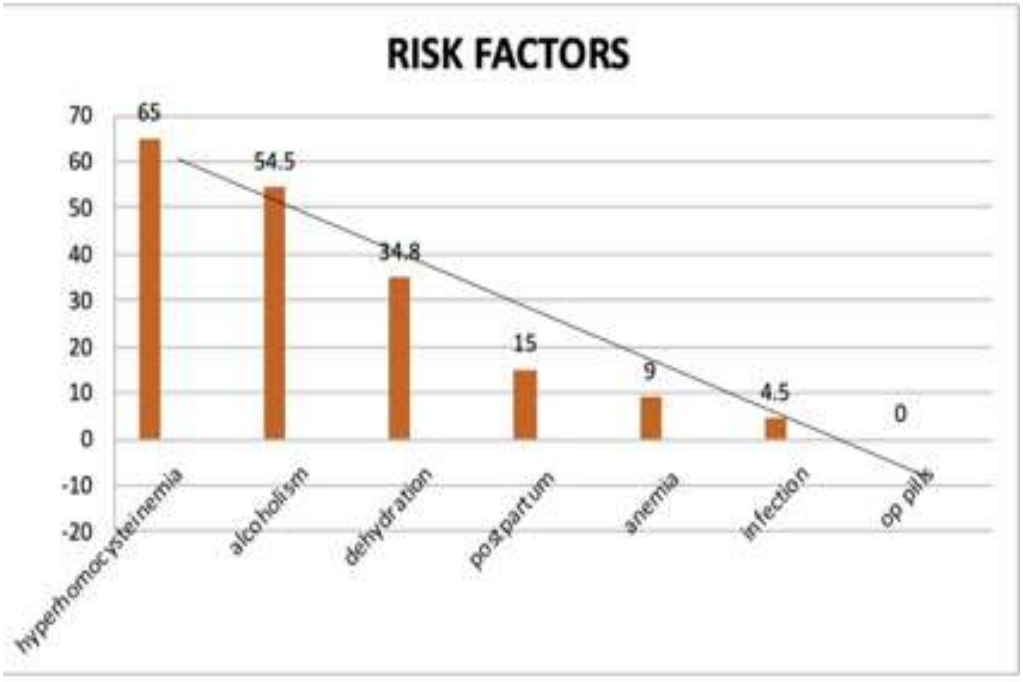
Table 1:- Age wise distribution of CVT patients.

AGE	N	Percentage %
20 and below	6	9.1
21 - 30	29	43.9
31 - 40	20	30.3
41 - 50	6	9.1
Above 50	5	7.6
Total	66	100.0

Haemorrhagic infarcts (42.4 %) were more frequently noted on imaging. Non-haemorrhagic infarcts constituted 28.8% and normal imaging findings were noted in 28.8 % of the patients. Superior sagittal sinuses (72.7 %) are most frequently affected followed by transverse sinus (66.7 %) and sigmoid sinus (51.5 %). Majority of the patients in the study had involvement of multiple cerebral venous sinuses (75.7 %).

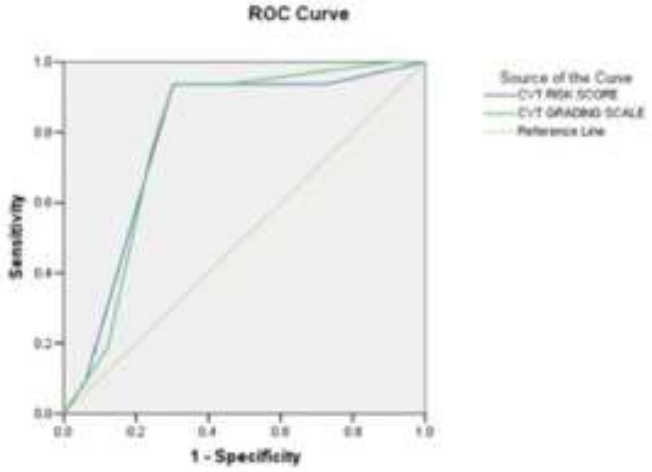
All the CVT patients were managed with medical treatment, which include Low Molecular Weight Heparin during acute phase followed by oral anticoagulants [8].

Fig 1:- Risk factors for development of CVT.



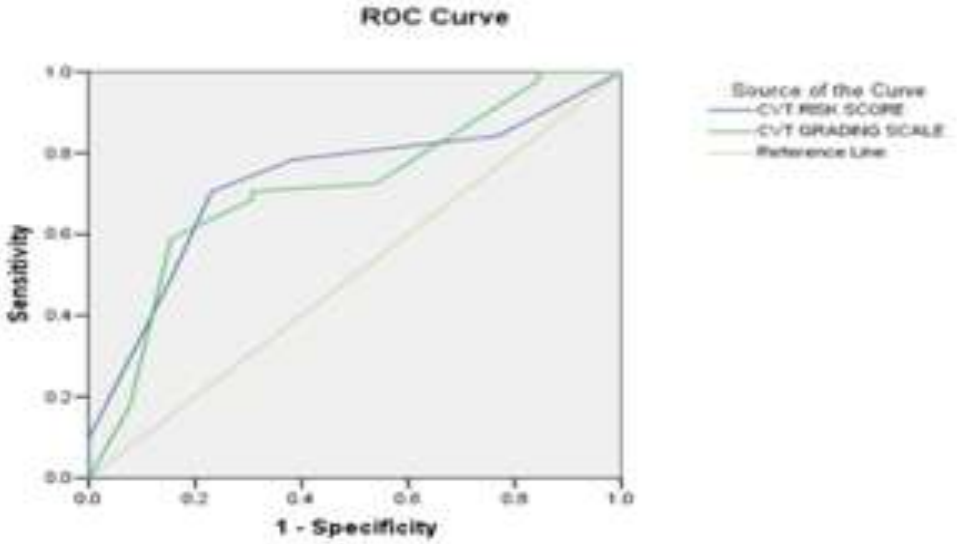
CVT Risk Score and CVT Grading Scale had high sensitivity in predicting prognosis at one and three months as seen in the Fig: 2&3.

Fig 2:- Cut off for CVT risk score and CVT grading scale for predicting prognosis at 1 month of follow up.



PROGNOSTIC SCORES	CUT OFF SCORE	Sensitivity	Specificity
CVT RISK SCORE	3	93.8	69.7
CVT GRADING SCALE	3	93.8	69.7

Fig-3:- Cut off for CVT risk score and CVT grading scale for predicting prognosis at 3 months of follow up



Prognostic scores	CUT OFF SCORE	Sensitivity	Specificity
CVT RISK SCORE	3	70.6	69.5
CVT GRADING SCALE	5	70.6	69.2

Modified Rankin Score (mRS) suggestive of poor prognosis at admission, one month and three months of follow up were 47%, 13%, 7% respectively. mRS scores suggestive of good prognosis at admission, one

month and three months of follow up were 53%, 87%, 93% respectively. Only two patients expired during the study suggesting good prognosis.

During follow up Barthel index showed dependency in 34 % of patients at admission and 1.5 % at three months follow up. Independent in ADL were reported in 49% of patients at admission and in 88% at three months of follow up.

CVT patients with haemorrhagic infarcts had short term poor outcome at admission and was statistically significant (p= 0.00) compared to non-haemorrhagic infarcts. Lower amount of alcohol intake (0-200 ml) had mild score (0-3) on CVT grading scale and high amount of alcohol intake (201-500 ml) had moderate score (4-6) & severe score (7-9). This relation had high statistical significance with p value=0.000. Patients with exposure to binge alcohol had higher CVT Risk Score at admission, than those with lower score values with p-value of 0 .032. CVT risk score > 3 predicts poor outcome at admission and <3 predicts good outcome (Fig-4). CVT grading scale with mild scores had good outcome and those with severe grading had poor outcome (Fig-5).

Fig 4:- Prediction of prognosis by CVT RISK SCORE.

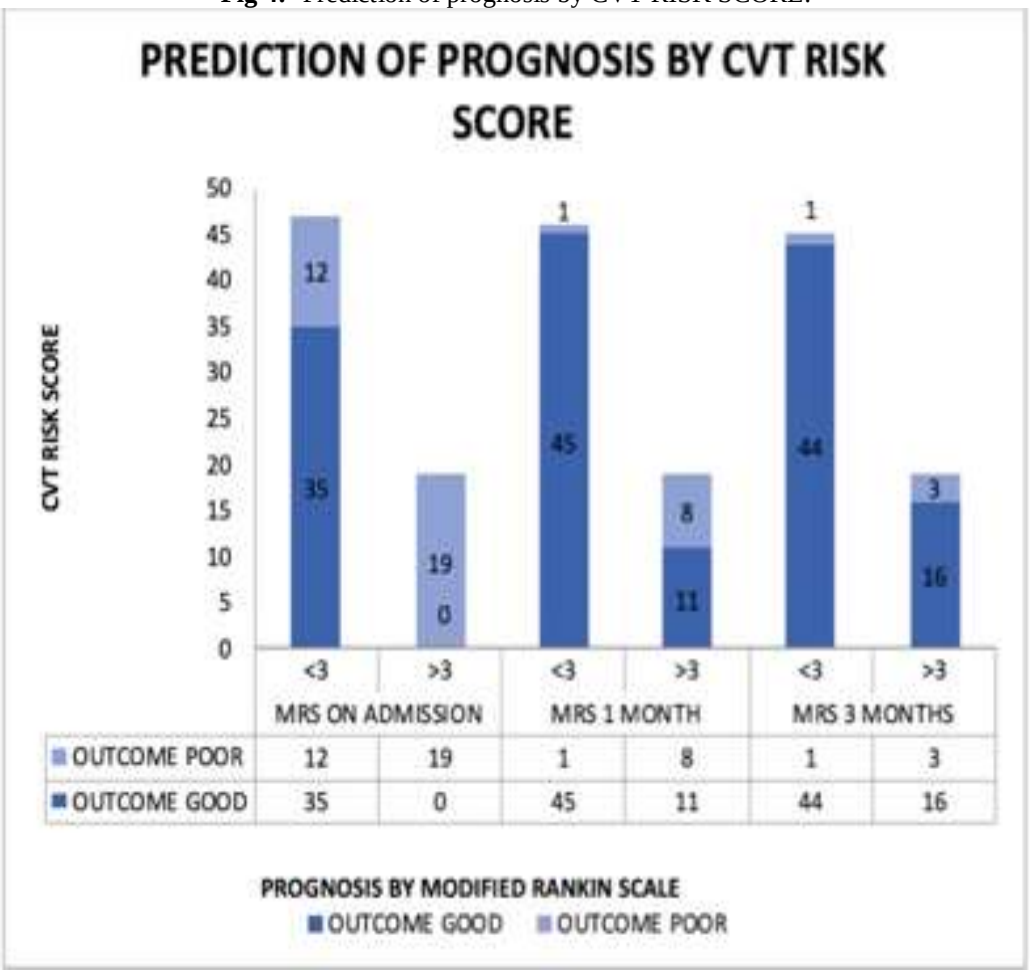
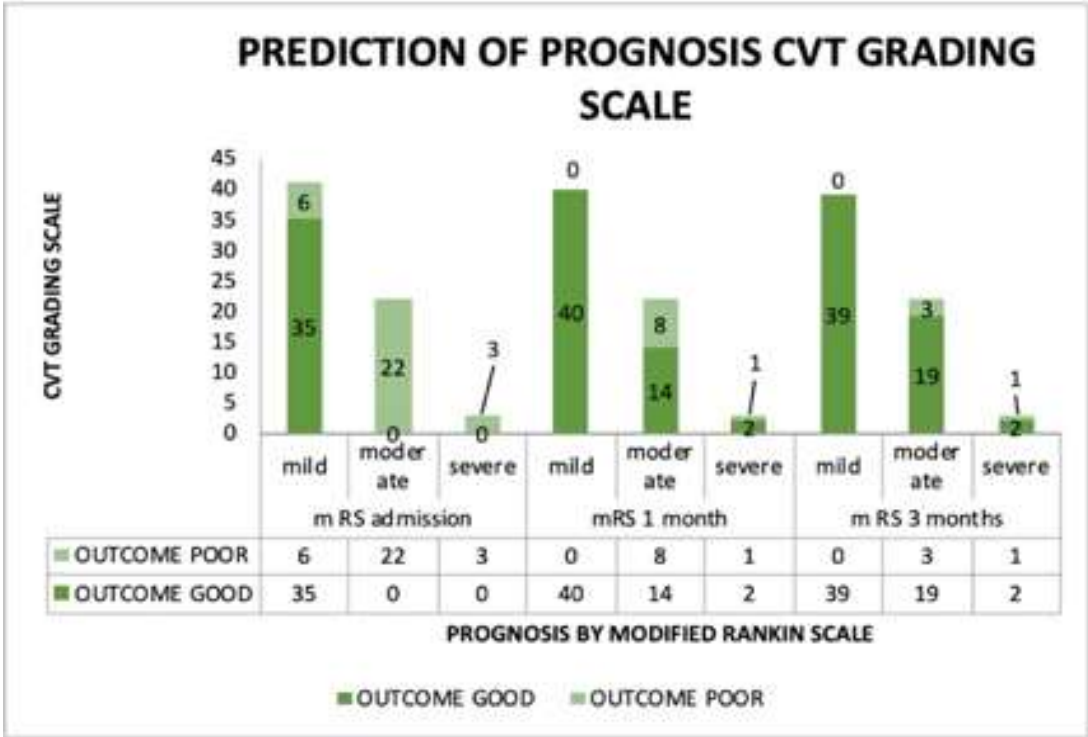


Fig 5:- Prediction of prognosis by CVT GRADING SCALE.



Discussion:-

Sixty-six patients of cerebral venous thrombosis were included in the study with men were predominantly affected (69.7%) when compared to women (30.3 %). These results were similar to Indian studies by Parikh et al.[11], Bose P et al. [12], Pai et al.[13], and Narayan D, et al [14]. Some recent studies like NISVR study[14], reported 57.3 %, and Bose P et al.[12] showed a 60% higher incidence of CVT among men. This change in trends of gender over the last two decades could be due to the improvement in obstetric care and change in risk factors and life style.

In contrast to the Indian studies, four Western studies described below had a higher incidence of CVT in young women. ISCVT study by Ferro JM et al.[15], Diana Aguiar de Sousa et al.[16], Koopman et al. [17]and Jonathan M Coutinho et al[18] reported higher preponderance of CVT in women, which can be explained by differences in the risk factors like usage of OC pills, smoking and clinical profile among the Western population.

The most common age group affected by CVT in the study belongs to 21-30 years (43.9%), followed by 31- 40 years (30.3%). The oldest age of the patient affected with CVT was 75 years. The mean age of presentation was 32.4 years, which were similar to two Indian studies conducted by Subash Kaul et al [14] and Pai et al.[13].

72.2 % of CVT patients in the present study had a subacute presentation. This observations were similar to recent Indian studies by Bose P et al.[12] and Sharma K K et al.[19], and in two western studies by Ferro JM et al [15] Stolz et al [20.] The average duration of hospital stay was 14.4 days.

Hyper-homocysteinemia, alcoholism, dehydration, infections like HIV, tuberculosis, puerperal period, and anemia were the risk factors (Fig-1). Majority of the patients had hyper-homocysteinemia (65%) followed by alcoholism (54.5%) which were comparable to the Indian studies by NISVR[14] and Shubakaran et al [19]. Unlike the current study, ISCVT study[15] reported usage of OCP and Hereditary Thrombophilia as the most common risk factors. The present study was similar to those by Ida Martinelli et al.[22] and meta-analysis study by Dentalli et al[23] who reported a four-fold increase of cerebral venous thrombosis in patients with Hyperhomocysteinemia. A more substantial number (88%) of men with raised homocysteine levels were effected and was comparable to the studies by Kulkarni et al. [24], Manasi Harale[25] and Pillai et al. [26].

Men with CVT (78.2%) had exposure to alcohol compared to those without exposure (21.8%). This study had a higher number of men with alcohol consumption than those observed in two recent South Indian studies by Aneesh T et al., [27] and Rath et al[28]. Heavy alcohol intake was a chief factor for the development of CVT which may be due to dehydration, hyper viscosity, and reactive thrombocytosis.

Non-puerperal CVT patients in women had a higher incidence (85%) compared to puerperal CVT (15%) in the present study. Improved obstetric and postpartum care resulted in a declining trend of puerperal CVT. Septic CVT was the least common in the present study, which constituted HIV infection (4.5%) and tuberculosis (1.5%). Lower incidence of Septic CVT was comparable to Suhana et al. [29] and western studies like ISCVT study.

Headache (98.5%) was the most frequent symptom followed by seizures (68%) in the present study. These results were similar to studies conducted by NIVSR [14], ISCVT [15], Sajad Tak et al [30] Patil CV et al.[31], Bose P et [12], Halesha BR et al[32], and Rajasekhar VK et al.[33]. There was a higher incidence of seizures in the current study in comparison to Srinivasan K et al. [6] and Kalita J et al.[34]. Papilledema was observed in 45.5 % patients and was comparable with Valerie AP et al. study[35]. 59.1 % of CVT patients had focal neurological deficits, which were similar to Bose P et al. [12] study, and deficits were higher compared to (27.6%) NISVR[14], (49.5%) ISCVT [15] reviews.

75.7 % of patients had involvement of multiple cerebral venous sinuses, and only 24.2% had isolated venous sinuses in the current study. Superior sagittal sinus thrombosis (72.7%) was the most common followed by transverse sinus thrombosis (66.7%). These findings were similar to studies of Saposnik G et al. [8], Halesha BR[32], Rajasekhar et al.[32]and Bose P et al [12].

98.5 % of patients had frequent involvement of superficial cerebral venous system, and 1.5 % had effected with deep venous system, similar to Narayan et al[14]. Cortical veins were involved in 13.6% of patients. Three patients with cortical vein thrombosis had multiple hemorrhagic infarcts. Unlike the present study, the ISCVT study showed a higher frequency of involvement of transverse sinus, followed by superior sagittal sinus.

The current study had normal MRI Brain in 28.8% of patients, which was similar to Bousser et [4], Narayan et al [14]. 42.4 % had haemorrhagic infarcts, and 28.8 % had non-haemorrhagic infarcts in CVT patients.

Medical management with anticoagulants was the mainstay of treatment in the present study. Protocol for management of CVT cases includes parenteral administration of Low Molecular Weight Heparin as bridging therapy followed by oral anticoagulants. Treatment with supportive measures like antiepileptic drugs and anti-edema measures were given as per the case basis.

There was low mortality due to CVT (3%) was attributed to timely management withanticoagulation therapy. Similar results of low mortality were reported in studies by Pai et al.[13], RENEMEVASC registry[35], NIVSR registry [14] (7.7%), Suhana et al. (7%), ISCVT [15](8.3%).

Outcome measures were reported using the modified Rankin scale and Barthel index. Modified Rankin scale was classified as good prognosis (mRS = 0 – 2), and poor prognosis (mRS:3-6) as per ISCVT and VENOPORT studies[9]. Barthel index was classified based on activities of daily living. These results were similar to RENEMEVASC registry[35], and NISVR registry[14] . Unlike the present study, Narayan et al.[14] study reported 7.7% deaths during the hospital stay due to cerebral herniation and septicaemia.

CVT Grading Scale had shown statistical significance to predict the prognosis at admission, one month, and three months (Fig-3 & 4) follow up by using mRS and at admission by Barthel index.

A new observation was made between prognostic scores and the amount of alcohol consumed. The severity of clinical features categorized by the CVT grading scale had statistical significance with amount of alcohol intake but not with duration of alcohol exposure. Similar findings were observed in 2018 by Barboza et al[36] study in predicting prognosis by using the CVT grading scale.

CVT risk score consists of six variables noted at the time of admission to the hospital. These six components were chosen as predictors of unfavourable outcome in the ISCVT [30] study. The CVT Risk score was assessed in the current study and cut off score for predicting good outcome at one month of follow up was 3 with a sensitivity of

93.8%, specificity of 69.7%. The cut off of 3 with a high sensitivity of 96.1% was similar to the original study by Jose M. Ferro, which validated the score in patients of ISCVT and VENOPORT studies. Hence, the CVT risk score was better in predicting prognosis in CVT patients at admission even for poor outcomes compared to ISCVT study[9].

CVT RISK SCORE and CVT GRADING SCALE had similar specificity and sensitivity to predict prognosis at one month and three months of follow up. Therefore, these prognostic scales could be used bedside to stratify the CVT patients and provide necessary lines of management.

CVST score [11] was a radiological score that quantifies the extent of the clot in the Dural sinuses. The score was calculated using the following components:

1. Occlusion of internal cerebral vein and vein of Galen: 1 point per each vein
2. Superior sagittal sinus was divided into thirds: 1 point was assigned to each third.
3. Each sinus involved with thrombosis: 1 point for each sinus affected with thrombosis.

CVST radiological score was not significantly related to the presence of brain parenchymal lesions in MRI Imaging (p=0.14) (Table-2) and outcome measures (p=0.52). Similar findings were reported in 2019 by Kalita et al[38], and the CVST scores were not correlated with brain parenchymal lesions and outcome measures at three months. In contrast to the present study on CVST score, Alexander Y. Zubkov et al. [11] reported that CVST score was correlated with parenchymal lesions outcome measures. CVST score of 1.9 in patients without brain lesions and 3.1 in patients with brain lesions.

Table 2:- Prediction of brain parenchymal lesions by CVST SCORE.

CVST score	**MRI Brain**		**Total**
	Abnormal	**NORMAL**	
1	1	4	5
2	17	7	24
3	10	2	12
4	9	4	13
5	9	2	11
6	1	0	1
Total	47	19	66

Retrospective study done by Poungvarin et al [38] had proposed Thai venous stroke prognostic score (TV-SPSS) in 2009. Thai venous stroke prognostic score had a high sensitivity of 93 % and a low specificity of 33%. CVT risk score and CVT grading scale had a similar sensitivity and a higher specificity (69%) than Thai venous stroke prognostic score (33%). A retrospective study conducted by Bushnaq S.A. et al [39] developed a predictive CVT score consisting of clinical, radiological and laboratory parameters. Comparable to CVT risk score in present study, CVT score by Bushnaq et al[39] had a lower sensitivity of 71.4% and higher specificity of 76.2% . Higher specificity of CVT Score helps to better predict patients with poor outcome than CVT risk score.

Highlights of the Study:-

The present study was the first Indian study to assess prognostic scores among CVT patients with the following bedside scores - CVT Risk score, CVT grading scale and CVST scores. CVT Risk score and CVT grading scale had similar sensitivity of 93.8% and specificity of 69.7% in predicting prognosis at admission and one month of follow up.

Limitations:-

The small sample size of the study prevents for generalization of the scores in the Indian population.Complete workup for hyper-coagulable states including genetic mutations for thrombophilia, autoimmune profile were not evaluated in view of limitation of available resources.

Summary & Conclusions:-

The study showed a change in the profile of risk factors in CVT patients with increase in novel risk factors like hyper-homocysteinemia and intake of alcohol were predominant like in other Indian studies.There was a decrease in conventional risk factors like puerperal states, oral contraceptive pills especially in India.

CVT Risk Scores and CVT Grading Scale are simple, bedside scores for predicting the prognosis of the patients. CVT Risk Scores and CVT Grading Scale had similar sensitivity and specificity in predicting the prognostic outcome. There was a dire need for validating the prognostic scores in large scale, multi-center studies in India as there are emerging differences in the aspects of clinical features, etiology, and management compared to Western countries.

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