Original Article

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Radiology Section

Utility of Hounsfield Unit: Haematocrit Ratio in Diagnosing Acute Cerebral Venous Sinus Thrombosis on Unenhanced Computed Tomography

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ABSTRACT

Introduction: The non-invasive imaging technique of choice in diagnosing Cerebral Venous Sinus Thrombosis (CVST) is Magnetic Resonance Imaging (MRI), but it has its own set of limitations like not being available universally in the acute setting. Computed Tomography (CT) Venography (CTV) can be used as an alternative diagnostic modality with an advantage of being more readily available which can be comparable to MRI in diagnostic accuracy.

Aim: To determine the value of Hounsfield unit: haematocrit (H:H) ratio on unenhanced brain CT scans in diagnosing acute CVST and to determine an optimal cut-off value for sensitivity and specificity based on the Receiver Operating Characteristic Curve (ROC) curve.

Materials and Methods: This was a retrospective case-control study on 60 adults, divided into two groups A and B consisting of 30 each. Group A consisted of 30 healthy controls who came for unrelated complaints, in whom the imaging findings for CVST were negative, which was confirmed on contrast CTV. Group B consisted of 30 Test subjects with imaging findings of CVST confirmed on CTV. For control images, attenuation was measured in 3 random, but different, venous sinuses in plain CT images. For study group, thrombosed venous sinus was measured on three different locations in the respective sinus by using the cursor. The location and densities of the thrombus was also documented. The non-enhanced CT brain images of both the groups were assessed for the attenuation of the dural sinus. CTV was utilised only to confirm the presence or absence of dural thrombosis. The statistical software namely SPSS 22.0, and R environment ver.3.2.2 were used for the analysis of the data.

Results: The average sinus attenuation in the study group of acute CVST (M=84.5 HU, SD=6.1 HU) compared to the control group (M=65.2 HU, SD=4.3HU) demonstrated significant difference of $p<0.0001$. The average H: H ratio in the study group of acute CVST (M=2.3, SD=0.4) compared to the control group without CVST (M=1.6, SD=0.1); demonstrated significant difference of $p<0.0001$. On the basis of ROC curves, with 72 HU as cut-off value, the study determined a sensitivity of 100% and a specificity of 96.6%. The study determined a cut-off H: H ratio of 1.8 for 100% sensitivity and a specificity of 96.6%.

Conclusion: Both density measurement in the venous sinus and calculation of the H:H ratio will increase the confidence of the radiologist in a setting where CT is the only available modality. Determining the H:H ratio on a per case basis helps in clinical scenarios of such blood disorders like anemia, polycythemia, while considerably reduced the risk of a false negative or a positive diagnosis. The present study is just an attempt to equip the radiologist with another tool at his disposal in cases where he is not able to access MRV/CTV either due to logistical or patient contraindications. Although in this study H:H ratio was accurate and sensitive enough, further large multicenter studies might be needed before utilising H: H ratio parameter for acute CVST.

Keywords: Anaemia, Polycythemia, Primary health center, Superior sagittal sinus, Transverse sinus

INTRODUCTION

Unenhanced brain CT scan is often the first imaging technique used in an emergency setting and is most often the only modality available in many primary health centers. There are only few studies which have attempted to utilise the H: H ratio and the attenuation of dural sinuses to delineate between thrombosed and non-thrombosed sinuses [1,2]. This study is just another attempt of finding similar such utility in the Indian population. Due to the lack of nationwide multicentric studies or the population-based studies, it is difficult to arrive at an exact incidence of CVT in India. However, there are data from a few epidemiological studies from the western countries done for the purpose of determining the incidence of CVT. In a nationwide multicentric hospital-based study series in Portugal [3], it was reported that the incidence of CVT to be around 0.22/100,000 person-years and a similar multicentric hospital study which was conducted in the Netherlands [4] reported an overall incidence of 1.32 per 100,000 person-years.

Clinical spectrum of CVST falls broadly into one of the three categories: symptoms and signs of raised Intracranial Pressure (ICP), focal brain lesion, or both a focal brain lesion and concomitant raised ICP. Non-specific symptoms are present in the majority. At one end, it can present with relatively mild symptoms such as headache, while at the other end can present with life-threatening complications like sudden increased intracranial hypertension and haemorrhagic venous infarctions [5].

The gold standard diagnostic method for diagnosing CVST is CTV and MRV, although in the past Digital Subtraction cerebral Angiography (DSA) was used, which has fallen out of favour. In the acute emergent clinical scenarios, non-enhanced CT plays an important role, due to non-availability of MRI universally at all levels of health care system, even though MRI is considered more sensitive and the technique of choice [6] in diagnosing CVST. Non-enhanced CTV can be used as an alternative diagnostic modality with an advantage of being more readily available which can be comparable to MRI in diagnostic accuracy. Increase in attenuation of the occluded sinus has a sensitivity and specificity of 64.6% and 97.2% [7,8], respectively in detecting acute CVST. A linear relationship exists between the attenuation of blood and haemoglobin and Haematocrit (HCT) causing false-positive interpretation of CVST in polycythemia vera and false negative interpretation in anaemia.

By using patient's HCT as an internal control, the study can attempt to normalise measured sinus HU attenuation which can improve the detection of CVST on unenhanced CT scans. There are only few studies which have attempted to utilise the H:H ratio and the attenuation of dural sinuses to delineate between thrombosed and nonthrombosed sinuses [1,2]. Hence, the present study was conducted with an aim to determine the value of H:H ratio on unenhanced brain CT scans in diagnosing acute CVST and to determine an optimal cut-off value for sensitivity and specificity based on the ROC curve.

MATERIALS AND METHODS

A retrospective case control study was conducted in Mysore Medical College and Research Institute from January to September 2019. The Institutional Ethics committee approval was obtained with ref number ECR/134/Inst/KA/2018/RR-16. For an outcome variable on Average sinus attenuation (HU) with minimum difference of 4.7 HU, and common standard deviation of 7.95, derived from previous literature [4] in a case-control study with 90% statistical power and 5% level of significance (Type I error), the sample size of 60 (30 in cases and 30 in controls) was determined adequate for the study. Systematic random sampling was used.

Data was compiled retrospectively from 60 patients with CVST who were divided into Group A, consisted of 30 Healthy controls who came for unrelated complaints, in whom the imaging findings for CVST were negative, which was confirmed on contrast CTV. Group B consisted of 30 Test subjects with imaging findings of CVST confirmed on CTV.

Inclusion criteria: Patients with diagnosed acute CVST based on CTV were included for this study if they had undergone non-contrast CT 24 hours before or after CTV.

Exclusion criteria: Patients were excluded from this study if they was a difference of more than 24 hours between the diagnosis of CVST on plain and contrast brain scan, Presence of symptoms older than seven days before the CT scan, Presence of old thrombus or hypoplastic venous sinuses or presence of blood in extra-axial space.

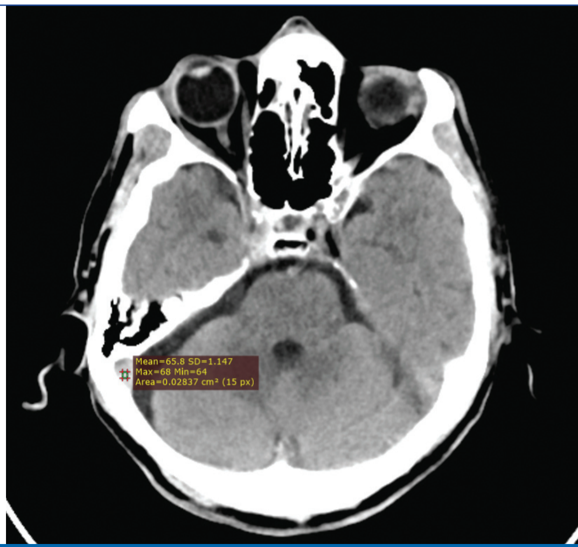
All CT images were acquired on Siemens 128 slice CT scanner SOMATOM DEFINITION EDGE TM using CT parameters of 120 kV; section thickness, 5 mm; 320 -380 mA. An Region of Interest (ROI) was drawn by using a cursor within the sinuses, careful to not include the margins of the sinuses to eliminate partial volume averaging [Table/Fig-1a-c]. For control images, attenuation was measured in three random, but different, venous sinuses [Table/Fig-2]. For study group, thrombosed venous sinus was measured on three different locations in the respective sinus by using the cursor. The location and densities of the thrombus were documented [Table/Fig-3].

To normalise them with respect to HCT, the study calculated the H:H ratio for all 60 patients. Patient details like sex, age, haemoglobin, HCT, serum urea nitrogen and creatinine levels one day before or after the CT examination were noted for both, case and control groups.

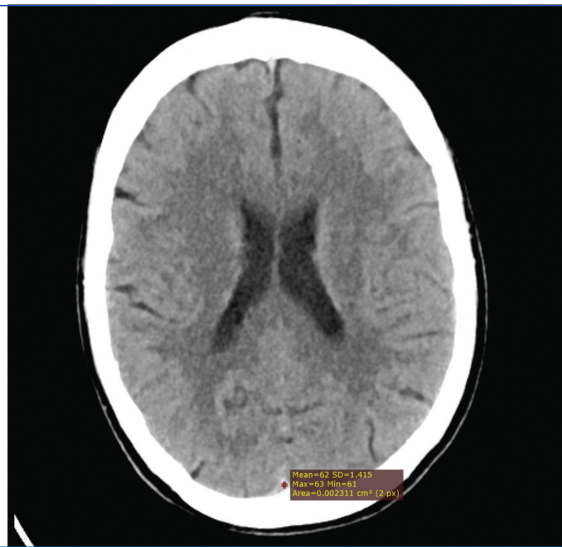
STATISTICAL ANALYSIS

Descriptive statistics has been done in the present study. Results on categorical measurements are represented in number, whereas outcomes on continuous measurements are represented in the form of Mean±SD. Significance is assessed at 5% confidence interval.

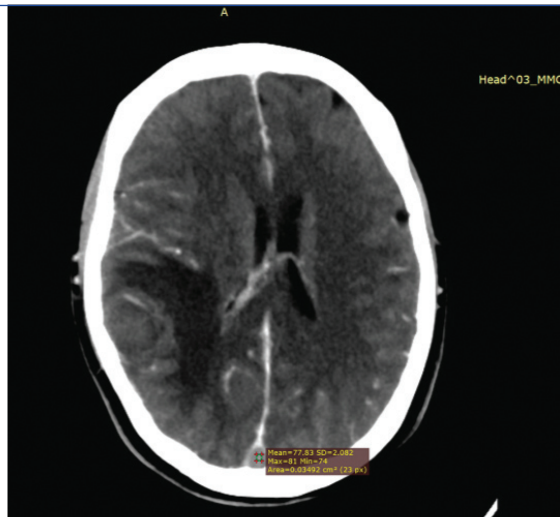
Chi-square and Fisher-Exact test is used to find the significance of study parameters. ROC curve analysis is performed to find the predictability of study variables for predicting the outcome.



[Table/Fig-1a]: Axial brain plain CT scan in a control subject with a cursor in the right transverse sinus.



[Table/Fig-1b]: Axial brain plain CT scan in a control subject with a cursor in the superior sagittal sinus.



[Table/Fig-1c]: Axial brain contrast CT scan in a study subject with a cursor in the venous confluence measuring the thrombus.

Diagnostic values based on area under curve

0.9-1.0-Excellent test

0.8-0.9-Good test

0.7-0.8-Fair test

0.6-0.7-Poor test

0.5-0.6-Fail

Laboratory values						
S. No.	Age in years	Sex	Haemoglobin	Haematocrit	Serum urea	Serum creatitine
1	66	F	14.3	40.3	63.8	1.48
2	36	M	15.1	43.2	22.6	0.65
3	38	M	16.7	44.9	35.6	0.88
4	30	M	14	37.6	24.3	0.96
5	65	M	12.5	38.8	28.9	0.79
6	65	M	16.4	45.6	28.5	1.09
7	32	M	15.7	42.1	32.1	0.56
8	65	M	14.3	40.1	17.3	0.69
9	65	M	10.2	29.2	41.7	0.78
10	96	F	12.3	35.8	15.8	0.46
11	26	M	16.4	45.6	25.7	0.87
12	58	M	17	47.5	21.5	1
13	24	M	14	38.8	36.8	0.92
14	29	F	15	39.3	11.7	0.57
15	31	M	18.5	51	20.9	10.4
16	60	F	14.9	40	31.3	0.56
17	56	M	14.6	43.3	54.3	1.56
18	50	M	15.3	44	11.8	0.67
19	56	F	14.9	44.6	31.1	0.83
20	30	F	14.7	44	16.7	0.58
21	62	M	11	30.2	19.9	0.53
22	35	F	16.3	45.1	29.7	0.72
23	80	M	14.5	40.9	31	1.02
24	70	F	11	31	59	1.5
25	83	M	13	36.9	50.2	1
26	40	F	13.3	41	36.3	0.4
27	45	F	14.1	40.9	21.5	0.86
28	60	M	11.4	30.8	34.7	0.78
29	33	F	13	36.6	19.9	1.09
30	38	M	15.7	45.3	36.5	1.21

[Table/Fig-2]: Table showing the control group demographics and CT attenuation of venous sinuses.
M: Male; F: Female

CT findings					
S. No.	Age in years	Sex	Location of sinus thrombus	HU of thrombus	HU: Haematocrit ratio
1	40	F	SAG, STS, RTR	88	2.55
2	26	F	LTR, RTR	84	2.66
3	40	M	SAG, RTR	88	1.98
4	56	M	SAG, LTR, RTR	82	3.07
5	31	M	SAG, LTR with bleed	86	2.66
6	35	F	SAG, LTR, RTR	88	2.77
7	51	M	STS, SAG, RTR, LTR	90	1.61
8	30	M	SAG, RTR, LTR	84	2.09
9	70	F	SAG, RTR with bleed	84	1.82
10	48	M	SAG, LTR, RTR	86	1.86
11	70	M	SAG with bleed	86	2.11
12	35	M	STS with bleed	82	2.9
13	37	M	STS, LTR	84	2.18
14	23	F	LTR, LSS	91	2.9
15	48	M	LTR, LSS	82	2.11
16	28	M	SAG with bleed	90	1.99
17	22	M	SAG, LTR, RTR	82	1.86
18	60	F	SAG	83	2.8
19	18	F	SAG	84	3.5
20	18	F	SAG, STS, LTR	88	2.37
21	64	M	RTR	86	2.5
22	50	F	SAG	82	2.17
23	22	F	STS, LTR	77	2
24	32	F	RTR, RSS	79	2.4
25	20	F	RTR, RSS	83	2.42
26	30	M	SAG with bleed	84	1.99
27	75	M	RTR,LTR	95	2.46
28	30	M	RTR, LTR, LSS	83	2.09
29	23	F	STS, RTR, RSS	82	2.19
30	18	M	LTR, LSS	72	1.91

[Table/Fig-3]: Table showing the study group demographics and CT findings of sinus thrombosis.
SAG: Superior Sagittal sinus; STS: Straight sinus; RTR LTR: Right and left transverse sinus; RSS LSS: Right and left sigmoid sinus; M: Male; F: Female; HU: Hounsfield unit; CT: Computed tomography

Significant figures

+Suggestive significance (p-value: 0.05<p<0.10)

*Moderately significant (p-value: 0.01<p<0.05)

**Strongly significant (p-value: p<0.01)

Statistical software: The Statistical software namely Statistical Package for the Social Sciences (SPSS) 22.0, and R environment ver.3.2.2 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

RESULTS

Out of the 30 subjects in the control group, 19 were males (63%), 11 were females (37%) and out of the 30 subjects in the test group, 17 were males (57%), 13 were females (43%). With a p-value of 0.598, there was no significant difference between genders in either groups [Table/Fig-4].

Age: In this study, 24 years was the minimum age reported in the control group and 18 years was minimum in the test group, whereas 96 years was the maximum age in control group and 75 years was the maximum in the study group.

Mean age was 50.8 years (SD=18.9) in the control group and 38.3 (SD=17) years in the study group. Median age was 53 years in the control group and 33.5 years in the test group [Table/Fig-4,5].

Parameter		Control	Case	
Mean age (years)		M=50.8, SD=18.9	M=38.3, SD=17	p-value#
Sex	Male	19 (63%)	17 (57%)	0.598
	Female	11 (37%)	13 (43%)	
Mean haematocrit		M=40.4, SD=5.3	M=37.2, SD=6.7	
Mean attenuation value of sinus		M=65.2, SD=4.3	M=84.5, SD=6.1	0.0001**
Hounsfield unit-to-haematocrit ratio		M=1.6, SD=0.1	M=2.3, SD=0.4	0.0001**

[Table/Fig-4]: Table demonstrating the variables studied in the two groups.
#Student t-test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters; SD: Standard deviation; **Strongly significant

Haemoglobin and Haematocrit (HCT): Haemoglobin levels ranged from 10.2 to 18.5 gm/dL in the control group with a mean of 14.3 (SD=1.9) and median of 14.5. Haemoglobin levels ranged from 6.7 to 20.3 gm/dL in the study group with a mean of 12.8 (SD=2.8) and median of 12.7 [Table/Fig-6].

HCT levels ranged from 29.2 to 51 in the control group with a mean of 40.4 (SD=5.3) and median 40.9. While, it ranged from 23.6 to 55.8 in the study group with a mean of 37.2 (SD=6.7) and median 37.7 [Table/Fig-7].

Age in years	Controls	Cases	Total
<20	0 (0%)	3 (10%)	3 (5%)
20-30	5 (16.7%)	10 (33.3%)	15 (25%)
31-40	8 (26.7%)	7 (23.3%)	15 (25%)
41-50	2 (6.7%)	3 (10%)	5 (8.3%)
51-60	5 (16.7%)	3 (10%)	8 (13.3%)
>60	10 (33.3%)	4 (13.3%)	14 (23.3%)
Total	30 (100%)	30 (100%)	60 (100%)
Mean±SD	50.80±18.96	38.33±17.06	44.57±18.96

[Table/Fig-5]: Table showing the age distribution between the groups studied.

Haemoglobin (g/dL)	Controls	Cases	Total
<12	4 (13.3%)	11 (36.7%)	15 (25%)
12-16	20 (66.7%)	16 (53.3%)	36 (60%)
>16	6 (20%)	3 (10%)	9 (15%)
Total	30 (100%)	30 (100%)	60 (100%)
Mean±SD	14.34±1.94	12.88±2.83	13.61±2.51

[Table/Fig-6]: Table showing haemoglobin (g/dL) distribution of patients studied.
SD: Standard deviation

Haematocrit	Controls	Cases	Total
<30	1 (3.3%)	4 (13.3%)	5 (8.3%)
30-40	11 (36.7%)	17 (56.7%)	28 (46.7%)
>40	18 (60%)	9 (30%)	27 (45%)
Total	30 (100%)	30 (100%)	60 (100%)
Mean±SD	40.4±5.3	37.2±6.7	38.8±6.2

[Table/Fig-7]: Table showing Haematocrit (HCT) distribution of patients studied.
SD: Standard deviation

Attenuation of nonthrombosed sinus and thrombosed sinus vs Haematocrit (HCT)

The attenuation of the normal sinuses was measured using a cursor and an average value was noted in the control group. After confirmation of the CVST on CTV, the attenuation value of the thrombus was measured and documented [Table/Fig-8].

HU: Haematocrit ratio was calculated in both the control and study groups [Table/Fig-9].

HU attenuation	Controls	Cases	Total
<60	5 (16.7%)	0 (0%)	5 (8.3%)
60-80	25 (83.3%)	3 (10%)	28 (46.7%)
>80	0 (0%)	27 (90%)	27 (45%)
Total	30 (100%)	30 (100%)	60 (100%)

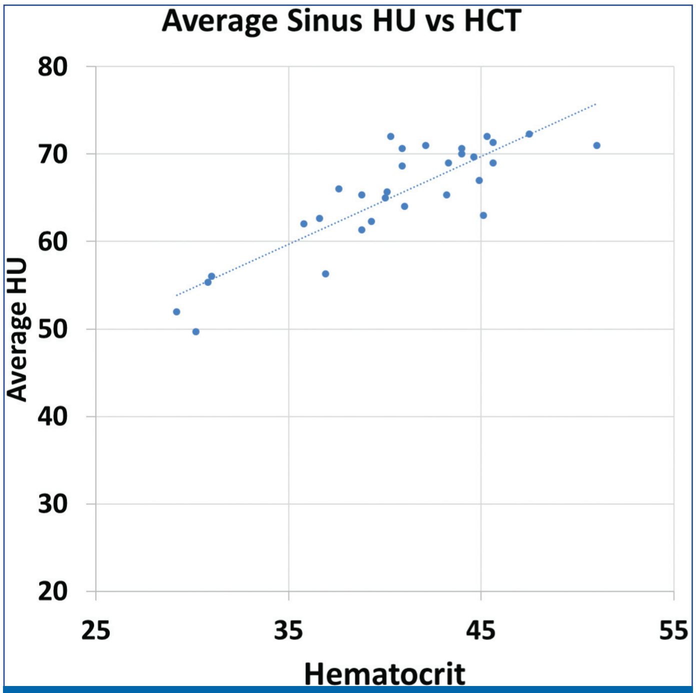
[Table/Fig-8]: Table showing HU Attenuation distribution of patients studied.
HU: Hounsfield unit

HU: Haematocrit ratio	Controls	Cases	Total
<1.5	3 (10%)	0 (0%)	3 (5%)
1.5-3	27 (90%)	28 (93.3%)	55 (91.7%)
>3	0 (0%)	2 (6.7%)	2 (3.3%)
Total	30 (100%)	30 (100%)	60 (100%)

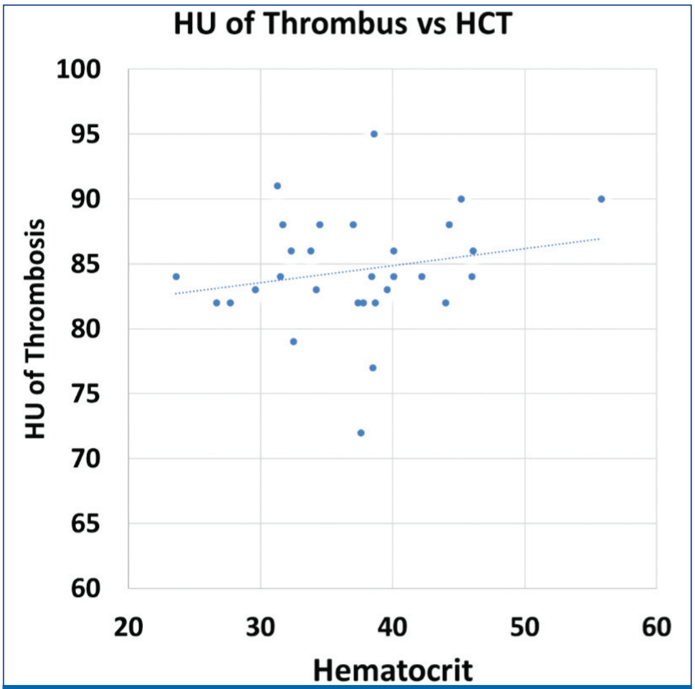
[Table/Fig-9]: Table showing HU: Haematocrit (HCT) ratio- distribution of patients studied.
HU: Hounsfield unit

Haemorrhagic venous infarct was seen in 6 of 30 patients with acute CVST. There was a positive correlation between the sinus HU and the HCT as well as between the thrombus HU and the HCT [Table/Fig-10,11].

A bar and whisker plot was plotted for HU which revealed values of 65.2 HU (M=65.2, SD=4.3) for the control group and 84.5 HU (M=84.5, SD=6.1) for the study group which demonstrated significant difference of p<0.0001. The bar and whisker plot was

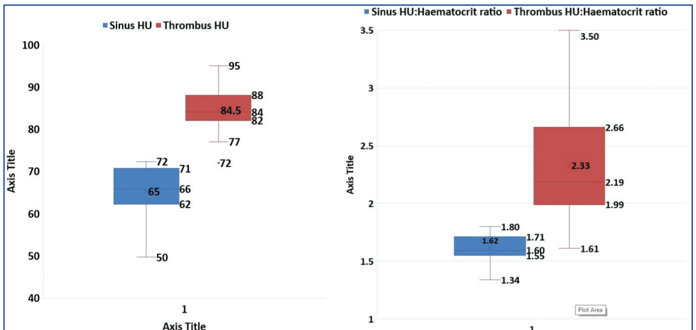


[Table/Fig-10]: Figure showing the scatter plot for the attenuation of dural sinus vs Haematocrit (HCT).



[Table/Fig-11]: Figure showing the scatter plot for the attenuation of thrombus vs Haematocrit (HCT).

also plotted for H:H ratio, which led to the H:H ratio values of 1.6 (SD=0.1) in the control group and H:H ratio of 2.3 (SD=0.4) in the study group which demonstrated significant difference of p<0.0001 [Table/Fig-12].



[Table/Fig-12]: Figure showing the Bar and whisker plot for the attenuation of the sinus vs thrombus and H:H ratio of sinus vs thrombus.

In this study, the mean H:H value in the patients with acute CVST was 2.3 (SD=0.4) vs 1.6 (SD=0.1) in patients without CVST [Table/Fig-13]. As evidenced in the bar and whisker plot [Table/Fig-12], there is certainly no overlap in the distribution of H:H ratio between the two groups of having CVST and those without CVST.

Variables	Controls	Cases	Total	p-value#
Haemoglobin (g/dL)	14.34±1.94	12.88±2.83	13.61±2.51	0.023*
Haematocrit	40.48±5.31	37.23±6.78	38.85±6.26	0.043*
HU Attenuation	65.21±6.21	84.50±4.39	74.86±11.09	<0.001**
HU: Haematocrit ratio	1.62±0.11	2.33±0.43	1.97±0.48	<0.001**

[Table/Fig-13]: Table showing comparative analysis of the variables in the two groups studied.
#Student t-test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters; HU: Hounsfield unit; *Moderately significant; **Strongly significant

On the basis of ROC curves, with 72 HU as cut-off value, the study determined a sensitivity of 100% and a specificity of 96.6% [Table/Fig-14-16]. The study determined a cut-off H:H ratio of 1.8 for a 100% sensitivity and a specificity of 96.6% [Table/Fig-14-16].

DISCUSSION

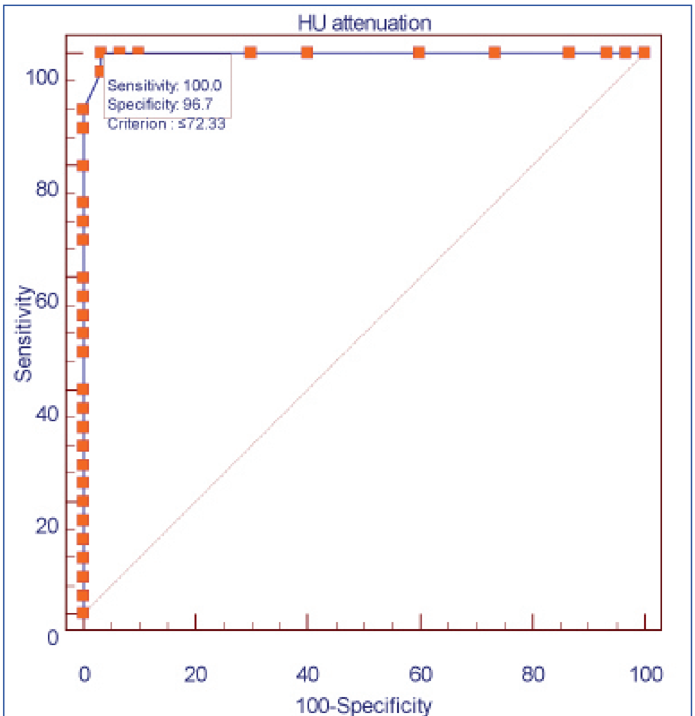
As clot retracts, there is elimination of water with resultant increase in clot attenuation and further raising the per volume concentration of red blood corpuscles and the haemoglobin contents [9-11]. This extent of increase in attenuation in clot is found elsewhere in the body too as found by Cobelli R et al., in their study of pulmonary embolism [12]. The attenuation of the clot doesn't remain constant, it decreases over time approximately in 1-2 weeks due to fibrinolysis, after which the clot may not be differentiated from unclotted blood [13]. There is a positive correlation between haemoglobin, HCT and attenuation of blood on unenhanced CT scans as demonstrated by Stein J and Huerta K, Provenzale JM and Kranz PG [14,15]. Mean age was 50.8 years (SD=18.9) in the control group and 38.3 (SD=17) years in the study group. In this study, about 50% of the patients belonged to the age group of 20-40 years, which was in close accordance with the findings from studies of Coutinho JM et al., [4].

There was a positive correlation between the HU attenuation of the non-thrombosed sinus and thrombosed sinus (p<0.001). This was similar to the results obtained from the studies of Black DF et al., and Buyck PJ et al., [1,2].

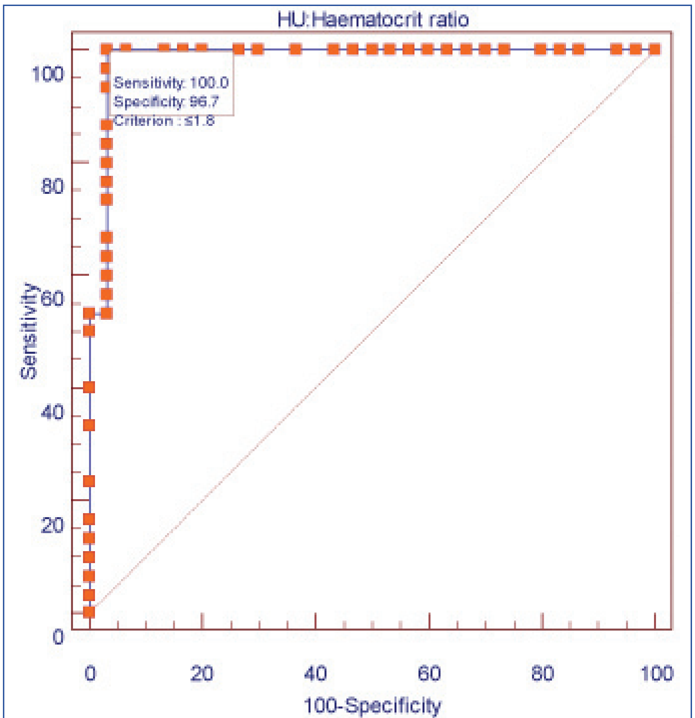
Black DF et al., were the first to use the H:H ratio to demonstrate the correlation between the hyperattenuation of dural sinus, noted on CT scans and their respective blood HCT level and they even successfully applied their new found observations in 8 patients having CVST. They found mean H:H values of 2.20 in patients with CVST and 1.44 in patients CVST and suggested a H:H cutoff value of 1.8 as threshold to suspect the presence of thrombosis [1]. Similar study conducted by Buyck PJ et al., [2] showed a mean HU of 73.9 in the test group and 52.8 HU in the control group. They determined a H:H ratio of 1.91 in test group with CVST vs 1.33 in patients. Optimal thresholds of 62 HU for average sinus attenuation lead to accuracies of 95% and H:H ratio of 1.52 lead to accuracy of 97.5% for the H:H ratio [Table/Fig-17] [1,2]. In the present study, On the

Variables	ROC results to predict cases				Cut-off	Area under ROC	SE	p-value#
	Sensitivity	Specificity	LR+	LR-				
HU attenuation	100.00	96.67	30.00	0.0	>72.33	0.9667	0.0026	<0.001**
HU: haematocrit ratio	100.00	96.67	30.00	0.0	>1.80	0.9667	0.0159	<0.001**

[Table/Fig-14]: Table showing the outcome of the ROC analysis.
#Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters; HU: Hounsfield unit; SE: Standard error; ROC: Receiver operating characteristic curve; LR: Likelihood ratio; *Moderately significant; **Strongly significant



[Table/Fig-15]: ROC curve of the HU attenuation.



[Table/Fig-16]: ROC curve of the HU: Haematocrit (HCT) ratio.

Study	Mean non-thrombosed HU	Mean Thrombosed HU	Mean control H: H ratio	Mean test H:H ratio	Cut-off HU	Cut-off H: H ratio
Black DF et al., [1]	-	77	1.4	2.2	70	1.8
Buyck PJ et al., [2]	52.8	73.9	1.33	1.91	62	1.52
Present study	65.2	84.5	1.6	2.3	72	1.8

[Table/Fig-17]: Table comparing the present study with previous similar studies [1,2].

basis of ROC curves, with 72 HU as cut-off value, we determined a sensitivity of 96.6% and a specificity of 100% [Table/Fig-14]. The study determined a cut-off H: H ratio of 1.8 for 100% sensitivity and a specificity of 96.6% [Table/Fig-14], which is consistent with the results obtained by Black DF et al., [1].

Limitation(s)

As mentioned before, the condition of CVST is rare in the general population which accounted for the low incidence. Retrospectively, analysing the number of patients with acute CVST in enrolled in this current study.

CONCLUSION(S)

Brain CT scan is the initial technique of choice in patients with acute neurologic symptoms Both density measurement in the venous sinus and calculation of the H:H ratio will increase the confidence of the radiologist in a primary centre where only CT is available. Calculating the density measurement in the venous sinus and H:H ratio will increase the confidence of the radiologist in a setting with only CT being available, and it may help decide on the need for confirmatory CT or MR imaging studies.

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