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**Relationship of D-Dimers with the Duration of Cerebral Venous Sinus Thrombosis (CVST): A Descriptive Study in Tertiary Health Care Hospital of District Peshawar Pakistan**

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## Relationship of D-Dimers with the Duration of Cerebral Venous Sinus Thrombosis (CVST): A Descriptive Study in Tertiary Health Care Hospital of District Peshawar Pakistan

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### Abstract

**Purpose:** CVST is a serious condition with a recent incidence of 13 million persons per year. (1) It has a highly variable presentation and may manifest itself with no recognizable risk factor, Magnetic resonance venography (MRV) is the investigation of choice for its diagnosis. However, since MRV is not readily available and is costly, this study tried to find the relationship between the levels of D-dimers as marker and duration of CVST. D-dimers are degraded fibrin products which are found to be raised in pulmonary embolism and deep venous thrombosis.

**Materials and Methods:** Total 49 patients (male to female ratio 1:6) mean age  $36.37 \pm 13$  years) with MRV proven CVST were included in the study. This descriptive cross-sectional study was conducted from January 2015-April 2017, on 49 confirmed patients of CVST, in Lady Reading Hospital. In patients suspected of CVST, magnetic resonance imaging of the brain with MRV was performed without delay on a 1.5 tesla MR scanner using T1, T2, flair, and diffusion weighted imaging sequences with a two-dimensional time of flight MRV. D-dimers were estimated by a rapid latex agglutination slide test technique using monoclonal antibodies. Data was analyzed using SPSS version 19. Frequencies, mean were calculated for quantitative data while Chi-square test was used for qualitative data. Sensitivity and specificity were calculated.

**Findings:** The duration of symptoms was 3-60 days (mean  $22 \pm 0.97$  days). The mean value of D-dimers levels recorded in micrograms were recorded as  $1456 \pm 1742$ .

**Implications to Theory, Practice and Policy:** D-dimers levels were high in acute and subacute stage of CVST. However, there were cases in our study who despite having acute and subacute stage of CVST had normal D-dimers levels for unknown reasons.

**Keywords:** *Relationship, D-Dimers, Duration, Cerebral Venous Sinus Thrombosis (CVST)*

## 1.0 INTRODUCTION

It was first reported in 1825 by Ribs and carries the burden of 0.5-1 % of all the cerebrovascular events (2) Commonly affected age group is young to middle-aged adults (3) with a higher incidence in women (4) (5). It can be diagnosed via computerized tomography of brain but this radiographic test is not very reliable and is positive only in 70% of the cases of CVST (4, PG 18) (6). Definite diagnosis of CVST requires magnetic resonance venography (MRV), however it is not readily available and is also expensive. Other investigation found helpful in the diagnosis of CVST is estimation of D-dimers which are products of degraded fibrin. They are raised in a number of conditions including cerebral venous sinus thrombosis, pulmonary embolism, septicemia, cirrhosis liver, and deep vein thrombosis. According to American guidelines patients with a high clinical suspicion of CVST should receive neuro-imaging regardless of D-dimers results.

## 2.0 METHODOLOGY

In this Descriptive cross-sectional study total of 49 patients of MRV confirmed CVST patients were included in the study. Out of which 42 patients were female and 7 were male with. Age ranged from 12 years to 57 years. The study was conducted from January 2015 - April 2017 in Neurology unit of a tertiary care hospital called Lady Reading Hospital. The patients were subjected to a detailed history, clinical examination followed by investigations. In patients suspected of CVST, magnetic resonance imaging of brain with MRV was performed without delay on a 1.5 tesla MR scanner using T1, T2, flair and diffusion weighted imaging sequences with a two dimensional time of flight MRV. D-dimers were estimated by a rapid latex agglutination slide test technique using monoclonal antibodies. Frequency, ratio, percentage, standard deviation, positive and negative predictive values, sensitivity and specificity were calculated. Chi-square test and Pearson correlation tests were applied to evaluate the significance between quantitative data. P-values were calculated to find the significance of our study. Data was analyzed using SPSS version 19.

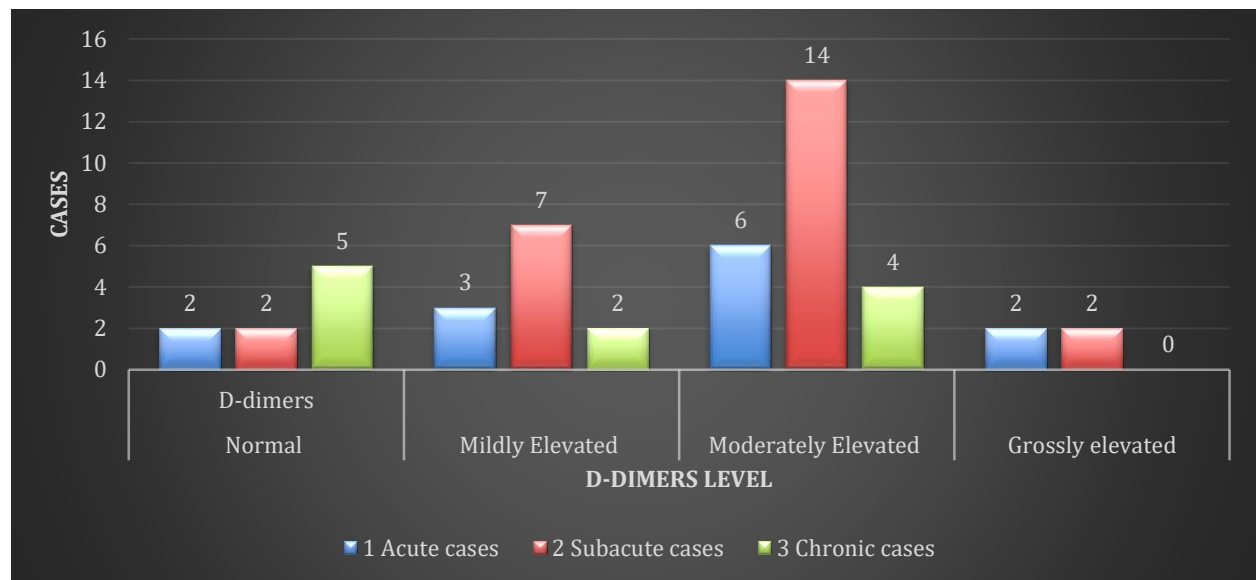
## 3.0 FINDINGS

Total n=49 patients with MRV proven CVST were included in this study. Out of which 42 were female and 7 were male. The whole sample of 49 patients was divided in three groups on the basis of duration of illness. Group-1 included patients with acute duration of illness (1-7 days). Group-2 comprised of 22 patients presenting in subacute stage (7-21 days) of illness. Group-3 of 14 patients presenting beyond 21 days (chronic illness). Descriptive statistics of the three group is given in Table 1.

**Table 1: Descriptive Statistics of the Three Groups**

Group No	Groups	N	Age in Years Mean (SD)	Duration in Days Mean (SD)	D-dimers Level Mean (SD)
1	Acute	13	37(10)	4(1)	944 (575)
2	Sub-Acute	22		12(4)	1897(2499)
3	Chronic	14		57(30)	1254(561)
	Total	49		22(27)	1456(1752)

The correlation measures for linear relationship between duration of illness and D-dimers levels was -0.04 but was  $P > 0.05$  (0.981). The correlation measures for the Acute, Sb Acute and Chronic Group for relationship between duration of illness and D-dimers levels was 0.018 with  $P > 0.05$  (.953), 0.312 with  $P > 0.05$  (0.158), 0.017 with  $P > 0.05$  (0.955). Patients with D-dimers level were recorded, as given in Fig 1.



*Figure 1: Patients with D-Dimers Levels at Various Stages of CVST*

Data of the patients with various risk factors identified among the patients was recorded as Table 2:

**Table 2: Patients with Various Risk Factors**

Risk factors	No. of patients	Percentage (%)
Pregnancy/puerperium	29	59.1
Bad obstetrical history/oral contraceptives	6	12.2
Paranasal/mastoid infection	5	10.2
Meningitis/encephalitis	6	12.2
No risk factor	3	6.1
Other co-morbid conditions ( diabetes Mellitis, hypertension, cardiac problems)	11	22.4



## Discussion

Total (49) patients with MRV proven CVST were included in this study out of which 42 were female and 7 were male (male to female ratio 6:1). Age ranged from 12-57 (mean  $36 \pm 0.67$ ) years. The duration of symptoms was from 3- 60 (mean 22) days, with acute duration of illness (1-7 days) in 13 patients, subacute (7-21 days) in 25 patients and chronic illness (more than 21 days) in 11 patients. Most common risk factor was pregnancy/puerperium in 29 patients, bad obstetrical history or use of oral contraceptives in 6 patients, paranasal/mastoid infection in 5 patients, cerebral infections (meningitis/encephalitis) in 6 patients, while no risk factor was found in 3 patients. Eleven patients had other co-morbid conditions like diabetes mellitus, hypertension, and cardiac problems.

D-dimers were normal ( $<250\mu\text{g/ml}$ ) in 9 patients, mildly increased ( $250\mu\text{g/ml}$ -  $700\mu\text{g/ml}$ ) in 12 patients, moderately increased ( $700\mu\text{g/ml}$ -  $1800\mu\text{g/ml}$ ) in 24 patients while 4 patients had grossly elevated ( $>1800\mu\text{g/ml}$ ) D-dimers levels. The distribution of these levels varied with the duration of illness. However, one noticeable finding was that two of our acute and two subacute cases had normal D-dimers levels. While five of chronic cases had normal D-dimers levels. Another finding worth mentioning is the moderately elevated D- dimers found in four of the chronic cases of CVST. Current study did not find any relationship between levels of D-dimers with the number of sinuses involved and /or hemorrhagic transformation of venous infarct. However there was a definite rise in D-dimers with the rise in total leucocyte count (TLC) indicative of infection somewhere in the body. Which measured D-dimers levels in 49 cases of MRV proven CVST with variable presentations and duration of illness ranging from 3 days to 90 days. Forty out of these forty nine patients had raised D-dimers levels, with mildly raised levels in 12 patients (3 patients in acute stage, 7 patients in subacute stage and 2 patients in chronic stage), moderately raised D-dimers levels in 24 patients (6 in acute stage, 14 in subacute stage and 4 in chronic stage) and grossly raised levels in 4 patients (2 in acute and 2 in subacute stage).

Nine of our patients had normal D-dimers levels three of these patients had duration of illness of 4,6 and 15 days i.e. acute/subacute illness, and thus normal D-dimers levels in these patients was contrary to the expectation. If take number of sinuses involved into consideration one of these patient with duration of illness of 4 days with no known risk factor had left transverse sinus thrombosis and left fronto-parietal and occipital infarcts. Another patient with 6 days duration of illness had left frontal, right fronto-parietal, right temporal and thalamic infarcts with superior sagittal sinus thrombosis while another 15 days postnatal patient with history of headache, vomiting and fits had right transverse sinus and right sigmoid sinus thrombosis. Thus lack of relationship between level of D-dimers and number of venous sinus thrombosis was observed in the current study. Misra UK found normal D-dimers levels in 2 out of 6 patients with extensive CVST involving all the sinuses. (7) Similar observation has been reported by others. (8)

In a study all the patients of CVST of less than a month had abnormal D-dimers levels. (11) (9) Talbot reported normal D-dimers in 2 out of 5 patients with recent CVST. (10) In acute DVT of legs, initially high D-dimers levels may fall to normal value within the first week. So if consider such a situation in CVST two of our three cases of acute/subacute CVST at least should have high D-dimers levels. found the sensitivity 81% and specificity 18.5% while positive predictive value was 45% and negative predictive value was 55%. Meng (12) found the sensitivity and specificity

of 94.1% and 97.5% respectively with a positive predictive value of 96.5% and negative predictive value of 98.9% respectively. His study was also prospective study however it involved patients younger than 45 years with onset of symptoms within 7 days. Jashem Y Al Hashel found the sensitivity and specificity of predicting CVST using D-dimers level as 64.6% and 71.5% respectively. Misra UK et al reported 6 cases of MRV confirmed CVST and all of them had raised d-dimers levels (7) however the duration of illness was not mentioned in their case series. Smith E in 2017 does a normal D-dimers to rule out cerebral venous sinus thrombosis (CVST) Smith found lower D-dimers levels in patients with symptoms of more than 30 days duration .He also reported lower D-dimers levels in patients presenting with isolated headache and only a single sinus involvement. Lack of relationship between level of D-dimers and extent of venous sinus thrombosis was observed in my study. Misra UK founded normal D-dimers levels in 2 out of 6 patients with extensive CVST involving all the sinuses. Similar were the results reported by some other researchers (13).

If Extent of sinuses into consideration, one of these with duration of illness of 4 days and no known risk factor had left transverse sinus thrombosis and left fronto-parietal and occipital infarcts while another patient with 6 days duration of illness had left frontal, right fronto-parietal, temporal and thalamic infarcts with superior sagittal sinus thrombosis while another 15 days postnatal lady with history of headache, vomiting and fits had right transverse sinus and right sigmoid sinus thrombosis. High D-dimers in chronic stage of the disease could most likely be attributable to concomitant infection, pregnancy, post-partum state etc. since there is a definite relationship between these conditions and levels of D-dimers. The correlation measures for linear relationship between duration of illness and D-dimers levels was -0.04 but P value was not significant  $P > 0.05$  (0.981). This exhibits that the longer the duration of illness the lower the D-dimers levels i.e. duration of illness is negatively related to D-dimers level, which is quiet normal. The correlation measures for the Group-1 was significant 0.018 and shows a positive relationship between duration of illness and D-dimers levels but with insignificant  $P > 0.05$  (.953). The correlation measure for Group-2 is thus showing a strong 0.312 linear relationship between duration of illness and D-dimers levels but  $P > 0.05$  (0.158). In chronic group the linear relationship between duration of illness and D-Dimers levels showed a positive trend 0.017 but P value was  $> 0.05$  (0.955).

### **Limitations of the Study**

There were some patients who were missed because of early discharges, referral to other units, death or financial restraints in doing MRV. D-dimers levels were done from different laboratories which may have reduced reliability of the study. Also some of the patients selected for this study had concomitant infection which would have attributed to raised D-dimers levels.

### **4.0 CONCLUSION AND RECOMMENDATIONS**

D-dimers levels were found high in acute and subacute duration of illness of CVST. However, there were cases in our study who had normal D-dimers level despite having acute and subacute stage of CVST.

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