

# Clinical Significance of D-dimer Level and Numeric Rating Scale with Amount of Sinus Involvement in Cerebral Sinus Thrombosis Patients

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**Introduction:** Cerebral venous sinus thrombosis (CVST) is a cerebral vascular disorder that currently occurs quite often and has very varied clinical symptoms. Headache is the main symptom most commonly found in patients with CVST and multiple sinus involvement often have a more severe prognosis and poor clinical outcome. This study aimed to learn the relationship between D-dimer level, numeric rating scale (NRS), and amount of sinus involvement in CVST patients.

**Methods:** This study was a retrospective observational analytic study with a cross-sectional approach using medical records and supporting data (D-dimer level and imaging finding) on patients diagnosed with CVST at Dr Hasan Sadikin Hospital Bandung.

**Results:** Sixty-five CVST patients met the study criteria with mean age of 47 years and mostly female (76.9%). Patients with single sinus involvement had a median initial NRS of 4 (range 2–6) and multiple sinus involvement was higher at 8 (range 5–9). Statistical test results showed a significant difference between D-dimer level, NRS and amount of sinus involvement ( $P < 0.001$ ).

**Conclusion:** D-dimer level, NRS, and amount of sinus involvement are associated with amount of sinus involvement in CVST patients. Involvement of multiple sinus will cause higher NRS with higher D-dimer level.

**Keywords:** CVST, D-dimer, NRS, sinus involvement

## Introduction

Cerebral venous sinus thrombosis (CVST) is a brain blood vessel disorder that has very varied clinical symptoms refers to thrombosis in cerebral vein.<sup>1,2</sup> CVST is a neurological disorder that is currently common and has serious consequences, and can become irreversible if it is not diagnosed quickly and does not receive appropriate treatment.<sup>1,3</sup> Cerebral infarction, hemorrhage, and death are serious complications that could occur from misdiagnosing this condition.<sup>4</sup> CVST affects approximately two to seven cases per one million people each year, 61% of whom are women aged between 20 and 35 years.<sup>3,5</sup>

Headache (93.7%) is the most common symptom of CVST followed by decreased consciousness (90.6%), seizures (75%), and focal neurological deficits (46.8%).<sup>6–8</sup> Unilateral headaches ipsilateral to the involved sinus often occur in single sinus involvement caused by stretching of the dura innervated by branches of the trigeminal nerve. Multiple sinus involvement results in a predominance of increased intracranial pressure, causing widespread and extensive stretching of the dura.<sup>9</sup> The pain-sensitive structures involved may be cerebral sinuses or veins. With this mechanism, of course, the greater the number of pain-sensitive structures involved, the higher the degree of pain that appears. From previous study, it was said that if two sinuses were involved, the area of headache felt was wider than if one sinus was involved.<sup>9</sup>

The presence of D-dimer may be used as an indicator of endogenous fibrinolysis in CVST. D-dimers are cross-linked fibrin fragments that have a high sensitivity for investigating cerebral venous thrombosis, and elevation of D-dimer is

strongly associated with the number of sinus involvement because of the amount of thrombus formation circumstances that arise. High levels of D-dimer will cause presence of larger thrombi.<sup>4</sup>

The prognosis in CVST patients can be related to the number of sinuses involved, where multiple sinuses will have more severe clinical outcomes than single sinus involvement. Patil et al found that CVST patients with involvement of more than one sinus more often had sequelae and a more severe clinical outcome.<sup>10</sup> This study will investigate the relationship between D-dimer level, numeric rating scale (NRS), and amount of sinus involvement in CVST patients.

## Methods

### Study Design and Population

This research is a retrospective observational analytical study with a cross-sectional approach in CVST patients aged >18 years, confirmed by magnetic resonance venography or digital subtraction angiography examination, have D-dimer data, and do not meet the exclusion criteria such as of central nervous system infection, intracranial blood vessel inflammation, blood vessel rupture, nose infection, ear infection, deep vein thrombosis, pulmonary embolism, and also dental and mouth infections.

### Assessment of Pain Level

The level of pain is measured using the numeric rating scale and the level of pain is classified. The pain scale at 0 means no pain, 1–3 indicate mild pain, 4–6 are moderate pain, while 7–10 are in the severe pain category.

### Statistical Analysis

Mann–Whitney and chi-squared tests were used for data processing relationship analysis. A *P*-value of less than 0.05 was considered statistically significant.

### Ethical Clearance

All patients gave their informed permission in writing. This study complied with all relevant ethical regulations (including The Declaration of Helsinki) and covering patient data confidentiality. The correct ethics procedure were followed. Ethical clearance for the study (LB.02.01/X.6.5/461/2023) was granted by the research ethics committee at Hasan Sadikin General Hospital in Bandung, Indonesia.

## Results

Sixty-five patients met the inclusion criteria in this study. In general, the CVST patient population in this study was dominated by women, (76.9%), indicating that women have a higher risk of developing CVST.

In Table 1, the mean age of CVST patients was 47 years, and transversus sinus was the most sinus involvement. It was found that a number of patients had a history of previous disease, with dyslipidemia being the most common.

Patients with multiple sinus involvement had initial, after treatment, and delta NRS higher than single sinus involvement (Table 2). Most of patient with multiple sinus had moderate level using NRS, which higher NRS compared with single sinus involvement (Table 3).

**Table 1** Clinical Characteristic of Research Subjects

Variable	N=65
Gender, N (%)	
Male	15 (23.1)
Female	50 (76.9)
Age (year)	
Mean ±SD	47±12

(Continued)

**Table 1** (Continued).

Variable	N=65
History of disease, N (%)	
Autoimmune	7 (10.8)
Cancer	4 (6.2)
Dyslipidemia	15 (23.1)
Diabetes mellitus	3 (4.6)
Hormonal contraception	5 (7.7)
Brain injury	5 (7.7)
None	26 (40.0)
Amount of sinus involvement, N (%)	
Single	34 (52.3)
Multiple	31 (47.7)
Location of sinus involvement	
Transversus sinus	36
Sigmoid sinus	21
Sagitalis superior sinus	18
Sagitalis inferior sinus	6
Cavernous sinus	3
Initial NRS	
Median (IQR)	6 (4–8)
Min – max	2–9
Level of initial NRS, N (%)	
Mild	8 (12.3)
Moderate	30 (46.2)
Severe	27 (41.5)

**Table 2** Relationship Between NRS and Amount of Sinus Involvement

Variable	Amount of Sinus Involvement		P-value
	Single N=34	Multiple N=31	
	Median (Min – Max)	Median (Min – Max)	
Initial NRS	4 (2–6)	8 (5–9)	<0.001*
After NRS treatment	2 (0–5)	5 (2–8)	<0.001*
Delta NRS	2 (0–5)	3 (0–6)	0.019*

**Note:** \*statistically significant.

**Table 3** Relationship Between Level of NRS and Amount of Sinus Involvement

Variable	Amount of Sinus Involvement		P-value
	Single N=34	Multiple N=31	
	N (%)	N (%)	
Level of initial NRS			<0.001*
Mild	8 (23.5)	0 (0.0)	
Moderate	26 (76.5)	4 (12.9)	
Severe	0 (0.0)	27 (87.1)	
Level after NRS treatment			<0.001*
No pain	7 (20.6)	0 (0.0)	
Mild	22 (64.7)	11 (35.5)	
Moderate	5 (14.7)	16 (51.6)	
Severe	0 (0.0)	4 (12.9)	
Improvement of NRS after treatment			0.456
Improved	26 (76.5)	26 (83.9)	
Not improved	8 (23.5)	5 (16.1)	

Note: \*statistically significant.

Table 4 shows the relationship between elevated D-dimer levels, NRS level, and amount of sinus involvement. There was a clinical significant relationship between D-dimer level, NRS values, and amount of sinus involvement in CVST patients.

Figure 1 shows area under curve of D-dimer level and amount of sinus involvement. Cutoff D-dimer level is 0.0342 that has higher risk for multiple sinus involvement in CVST patients.

## Discussion

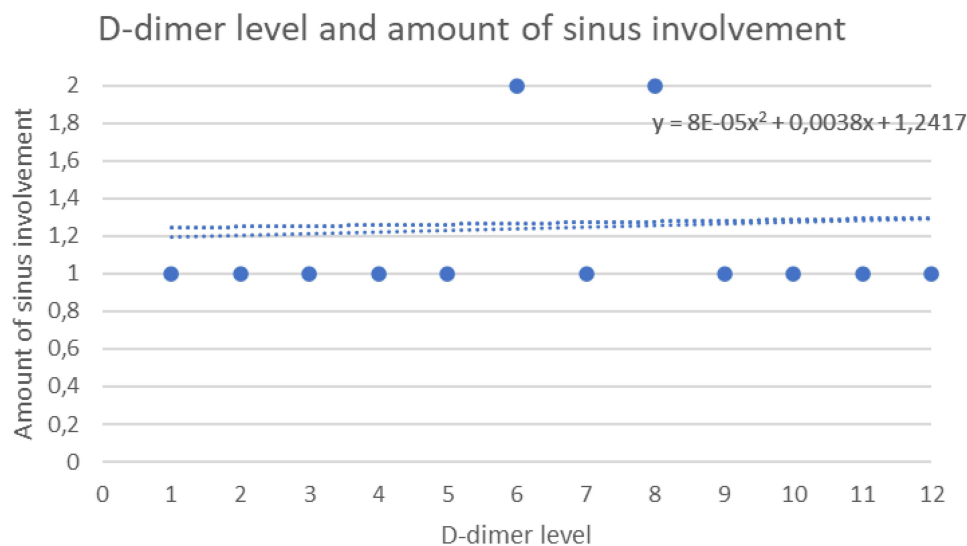
### Characteristics of Research Subjects

This study involved 65 CVST patients, mostly women (76.9%), indicating that women have a higher risk of developing CVST. Hormonal factors, hypercoagulation condition such as antiphospholipid syndrome, genetic susceptibility, and

**Table 4** Relationship Between D-Dimer Level, NRS, and Amount of Sinus Involvement

Variable	D-dimer Level				P-value
	High level		Normal		
	N	%	N	%	
Amount of sinus					<0.001*
Single	3	15	20	85	
Multiple	38	94.1	4	5.9	
Level of NRS					<0.001*
Mild	0	0.0	8	23.5	
Moderate	4	12.9	26	76.5	
Severe	27	87.1	0	0.0	

Note: \*statistically significant.



**Figure 1** Area under the curve of D-dimer level and amount of sinus involvement.

acquired prothrombotic disorders such as pregnancy, puerperium, contraceptive pills, malignancy, infection, and trauma are the main risk factors for developing CVST.<sup>5</sup> The mean age of the patients in this study was  $47 \pm 12$  years. Uluduz et al reported that CVST is more common in women than men (3:1) compared to men with a mean age of  $43.2 \pm 13$  years.<sup>11</sup>

A number of CVST patients involved in this study had a history of previous diseases such as autoimmune disease, carcinoma, dyslipidemia, diabetes mellitus, head injury, and a medical history of injectable birth control. The most common in this study was dyslipidemia. This is different from several studies that the characteristics of the disease history in CVST patients are not dominated by dyslipidemia. This shows that there is a correlation in several medical histories that have the potential to be risk factors for CVST.<sup>12,13</sup>

In this study it was found that CVST patients had the possibility of sinus involvement ranging from single to multiple, several sinuses may be involved, namely the transverse sinus, sigmoid sinus, sagittal sinus, and cavernous sinus. The sinus most frequently involved in the patients in this study was the left transverse sinus with some patients involving more than one sinus. In accordance with previous research, the sinuses most often affected are the transverse and sagittal sinuses, which can be involved singly or involve several sinuses simultaneously in one patient.<sup>14</sup>

## Differences in NRS Values with the Number of Sinuses Involvement

Headache is the mostly common symptom of CVST suffered followed by decreased consciousness, seizures, and focal neurological deficits. Headache complaints themselves can be measured in intensity using the numeric rating scale (NRS) on a pain scale from 0 to 10 with the criteria of no pain, mild to severe.<sup>10</sup>

Patients with multiple sinus involvement in this study had a higher average initial NRS, namely 8 (severe pain) compared to those with single sinus involvement, which averaged 4 (moderate pain). This supports that patients with more than one of sinus involvement tend to have higher levels of initial headache intensity compared with patients with one of sinus involvement. In accordance with research conducted by Patil et al and Fan Y et al, headache symptoms and remaining neurological deficits were more severe in CVST patients involving multiple sinuses.<sup>10,15</sup> The types of headaches that appear are said to be different, some are said they were similar to migraines, cluster headaches, tension type headaches, and thunderclap headaches. The location of the pain is also mentioned differently, such as the sinuses most often involved, namely the transverse sinus and superior sagittal sinus, severe headaches that are felt are often called holocranial or bifrontal.<sup>9</sup> From previous research in France, approximately 123 CVST patients were found to have sinus headaches and most frequently involved is the transverse sinus, the headache that appears is often ipsilateral to the sinus involved. Involvement of sigmoid sinus only or with the transverse sinus, headaches often occur in the occipital area.<sup>9</sup>

Single sinus involvement in patients had a difference between initial NRS and NRS after therapy of 2 with a range of 0–5, while patients with multiple sinus involvement had a higher difference, namely 3 with a range of 0–6. So, single sinus involvement patients have significant improvement in pain compared to multiple sinus involvement using NRS after initial therapy. According to Botta et al, headache with multiple sinus involvement has a wider headache area and higher intensity because it involves a mechanism of increasing intracranial pressure, causing widespread stretching of the dura, but headache in single sinus involvement because of stretching of the dura which is innervated by branches of the trigeminal nerve area.<sup>9</sup>

Patients with multiple sinus involvement have an average NRS is higher than patients with single sinus involvement. So, it can be concluded that despite therapy, patients with multiple sinus involvement still tend to experience higher levels of pain, it means more severe than in patients with single sinus involvement. There is no any difference definitive treatment between single and multiple sinus involvement, but in multiple sinus involvement have longer duration of treatment and experience symptoms compared with single sinus. These significant results are supported by research conducted by Patil et al and Shakibajahromi et al, namely that if a patient's CVST involves more than one sinus, the headache felt will be more extensive and severe, and the sequelae and clinical outcomes will be more severe than single sinus involvement.<sup>10,16</sup>

Thus, in the analysis of this study it was found that multiple sinus involvement was more likely to cause a more severe level of pain, both before and after therapy, but the results of changes in the NRS criteria loss a significant difference between these two groups of patients after analysis. This study result provides important insights for further understanding the influence of the number of sinuses involved on pain levels and response to therapy in CVST patients.

## D-dimer Level, NRS, and Amount of Sinus Involvement

The presence of D-Dimer may be used as an indicator of endogenous fibrinolysis in CVST. D-dimers are cross-linked fibrin fragments that have a high sensitivity for investigating cerebral venous thrombosis, and elevation of D-dimer is strongly associated with the number of sinuses involved because of the amount of thrombus formation circumstances that arise. High levels of D-dimer will cause presence of larger thrombi.<sup>4</sup>

Increasing of D-dimer level in CVST patients were observed to be strongly associated with the number of sinus involvement and also with NRS. Multiple sinus involvement has a wider headache area and higher intensity because it involves a mechanism of increasing intracranial pressure, causing widespread stretching of the dura due to wider thrombus formation and extension in cerebral sinus, and it will influence NRS level.<sup>4</sup>

Based on this research, the initial headache intensity in CVST patients assessed using NRS as well as the number of sinus involvement and level of D-dimer, can be used as objective indicators by clinicians in the future to assess the prognosis of CVST patients.

## Limitation of Study

This research is retrospective in nature so the data taken may be limited to the notes listed in the medical record, which may not always be complete and accurate and does not take into account the treatment of the patient, so it is possible that the research patients are not homogeneous. The pain scale assessment in this study was still high in subjectivity so it was considered to influence the assessment results.

## Conclusion

Based on the results of the research above, it was concluded that D-dimer level, NRS, and amount of sinus involvement are associated with amount of sinus involvement in CVST patients. Involvement of multiple sinus will cause higher NRS with higher D-dimer level. Further research needs to be carried out prospectively with a more homogeneous sample size by carrying out subjective assessments of pain.

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## Disclosure

The authors report no conflicts of interest in this work.

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