

D-Dimer Level Associated with Amount of Sinus involvement Using Digital Subtraction Angiography on Cerebral Venous Thrombosis Patients

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Background: Cerebral venous sinus thrombosis (CVST) is a form of the cerebrovascular disease characterized by varying degrees of obstruction of veins and cerebral sinuses caused by thrombus. Diagnosis is incredibly challenging due to the wide variety of symptoms and the distinct radiological aspects of affected vessels. In patients with venous thrombosis, the presence of D-Dimer is used as an indicator of the presence of endogenous fibrinolysis. D-Dimer is a by-product of fibrin polymer fragmentation.

Objective: To investigate the relationship between the level of D-Dimer and the number of sinuses in CVST by Digital Subtraction Angiography (DSA).

Methods: Retrospective data from September 2021 to September 2022 were used in this analytical observational with a cross-sectional study design. Chi-Square is used for data processing relationship analysis.

Results: Out of the 54 subjects with elevated levels of D-Dimer, 38 (70.4%) are females, whereas 16 (29.6%) are males. High levels of D-Dimer have been related to a greater risk of sinus thrombosis ($p < 0.001$). D-Dimer levels were similarly shown to rise in conjunction with the number of sinuses most severely damaged by thrombosis. The most common site for thrombosis to develop in this study were the left sigmoid and left transverse sinuses. Most risk factors were hormonal.

Conclusion: There is a statistically significant relationship between an increase in the D-Dimer level and the greater number of sinuses involved as determined by DSA in individuals diagnosed with CVST.

Keywords: cerebral venous sinus thrombosis, D-Dimer, sinus involvement

Introduction

Cerebral Venous Sinus Thrombosis, also known as CVST, is a form of cerebrovascular disease that manifests as a narrowing to occlusion in the vein channels and cerebral sinuses resulting from a thrombus. This condition, which may display a wide range of clinical symptoms and radiological findings, is very challenging to identify. Serious consequences, including infarction, hemorrhage, and death, may result from misdiagnosing this condition.¹⁻³ The yearly incidence rate was predicted to be 1.32 cases per 100.000 people in 2005, but it has since increased to 2.62 cases per 100.000 population.⁴⁻⁶ With 61% of females between the ages of 20 and 35 affected, the female's incidence rate is much greater than that of males. The female-to-male ratio is 3:1.^{4,5} This pertains to pregnancy or the usage of contraceptive pills. The research by Lisda Amalia at Hasan Sadikin General Hospital Bandung discovered that the largest incidence of CVST was in women (81%) with an average age of 37.68 years. This result was in accordance obtained with the findings of the study.⁷

In individuals with venous thrombosis, the presence of D-Dimer may be used as an indicator of endogenous fibrinolysis. Cross-linked fibrin fragments dissolved by plasmin, known as D-Dimers, have been demonstrated to aid in diagnosing venous thrombosis by measuring plasma levels. D-Dimer has a high sensitivity, but its specificity is poor. From the onset of symptoms until the subacute or chronic phase, D-Dimer levels might decline over time.^{3,4} The

structure of a thrombosed sinus has reported to play a role in the D-Dimer findings, and this might be another reason for a drop in D-Dimer levels.

Non-thrombotic pathological diseases, such as cancer, liver disease, renal disease, organ-graft healing, and thrombolysis therapy, may also produce significant levels of D-Dimer.^{8–10} The number of cerebral venous sinuses implicated was shown to have a substantial relationship with D-Dimer levels, with higher D-Dimer levels corresponding to a larger number of cerebral venous sinuses.^{11–14} The rise in D-Dimer levels has been linked to the development of thrombosis in numerous cerebral venous sinuses and to the hypothesis positing that such blockages account for the vast majority of cases with CVST.^{15,16} The greater the number and severity of blockages in CVST cases, the greater the formation of fibrin polymers, which are subsequently degraded into D-Dimer.^{11–13}

Digital Subtraction Angiography has a higher sensitivity (95%), and specificity (91%), respectively, than both Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) scans. DSA is thus preferable for evaluating normal anatomy and blockage (occlusion) in the veins.^{16,17} DSA is the gold standard test and should be performed on patients with clinical suspicion of CVST but normal results on CT Venography or Magnetic Resonance Venography (MRV).^{18–23} This research finding corresponds D-Dimer levels to DSA-measured sinuses in CVST patients.

Methods

This research is an analytical observational study using a retrospective cohort design, and it was conducted on 54 participants who were diagnosed with CVST between September 2021 and September 2022. The patient's medical records were retrieved in compliance with the hospital's ethical guidelines by maintaining confidentiality. Patients diagnosed with CVST had their demographic information, clinical features, risk factors, D-Dimer levels, and DSA (imaging) results defined. History of deep vein thrombosis and pulmonary embolism were excluded in this study. Chi-Square is used for data processing relationship analysis. 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 was followed. Ethical clearance for the study (LB.02.01/X.6.5/347/2022) was granted by the research ethics committee at Hasan Sadikin General Hospital in Bandung.

Results

Clinical Characteristics of Study Participants

The sample size of this research included 54 CVST patients ([Supplementary Material Table 1](#)), with a mean age of 44.31 (ranging from 29 to 70 years old) and a much higher proportion of female patients than male patients (70.4%). [Table 1](#) shows that Diabetes Mellitus (DM) and dyslipidemia are the most prevalent cause of sinus thrombosis, and the most common sites affected by thrombosis are the left transverse and sigmoid sinuses.

High D-Dimer Levels and Sinus Distribution

[Table 2](#) illustrates the relationship between elevated D-Dimer levels, the amount, and the location of sinuses subjects. D-Dimer levels rise in proportion to the number of sinuses. $P < 0.001$ ($p\text{-value} \leq 0.05$) indicates statistical significance.

Increased D-Dimer and Sinuses

[Table 3](#) displays the correlation between the location of the sinuses and elevated D-Dimer levels in individuals with CVST who underwent DSA. [Table 3](#) presents that the left transverse sinus and left sigmoid are the most common sites of sinus thrombosis. The relationship between sinus location and elevated D-Dimer levels is statistically significant ($p < 0.001$).

Factors Associated with Elevated D-Dimer Levels

[Table 4](#) depicts the relationship between risk factors and elevated D-Dimer levels in CVST patients who underwent DSA. The table indicates a significant relationship between elevated D-Dimer levels and risk factors at the $p\text{-value} 0.035$ ($p\text{-value} \leq 0.05$). Hormonal is the most prevalent risk factor identified in this study, affecting 14 subjects.

Table 1 Characteristic of Research Subjects

Variable	n	%	Mean(SD)
Age (year)			44.31 (12.347)
20–30 year	5	9.3	
31–40 year	18	33.3	
41–50 year	15	27.8	
51–60 year	8	16.7	
61–70 year	7	13.0	
Gender			
Male	16	29.6	
Female	38	70.4	
Amount of sinus involvement			
Single	34	63.0	
Multiple	20	37.0	
Sinus location			
Right Sinus Transversus	5	9.3	
Left Sinus Transversus	14	25.9	
Bilateral Transversus	1	1.9	
Sinus Sagitalis superior	1	1.9	
Left Sinus Transversus and sigmoid	26	48.1	
Bilateral Sinus Transversus and sigmoid	5	9.3	
Left Sinus Transversus and sagitalis superior	1	1.9	
Left Sinus Transversus and straight sinus	1	1.9	
Risk factors			
Autoimmune	1	1.9	
Hormonal	16	29.6	
Malignancy	2	3.7	
Hematological disorders	13	24.1	
Diabetes Mellitus/dyslipidemia	22	40.7	

Table 2 Relationship Between D-Dimer Level and Amount of Sinus Involvement

Variable	D-Dimer Level				Total		p value
	High Level		Normal		n	%	
	n	%	n	%			
Amount of sinus							<0.001*
Single	3	15	17	85	24	100.0	
Multiple	32	94.1	2	5.9	34	100.0	

Note: *Statistically significant.

Discussion

Patients with CVST diagnosed between September 2021 and September 2022 at Hasan Sadikin Bandung General Hospital are profiled in this study, including their ages, sexes, D-Dimer levels, and the number of affected sinuses. The proportion of the research participants in this study was more females than males, with an average age distribution of 44.31 years (Table 1). This feature is consistent with the finding that CVST is more common in females, as reported in prior research.^{7,16}

Antiphospholipid syndrome, genetic susceptibility, and other acquired prothrombotic disorders such as pregnancy, postpartum period, contraceptive pills, malignancy, infection, and trauma are major risk factors for developing CVST.^{24–28} The pathogenesis of cerebral venous sinus thrombosis may be inferred to include two distinct processes. Intracranial

Table 3 Relationship Between D-Dimer Level and Sinus Location Involvement

Variable	D-Dimer Level				Total		p-value
	High		Normal		n	%	
	n	%	n	%			
Sinus location							<0.001*
Right Sinus Transversus	0	0.0	5	100.0	5	100.0	
Left Sinus Transversus	3	21.4	11	78.6	14	100.0	
Bilateral Sinus Transversus	1	100.0	0	0.0	1	100.0	
Sinus Sagitalis superior	0	0.0	1	100.0	1	100.0	
Left Sinus Transversus and sigmoid	25	96.2	1	3.8	26	100.0	
Right Sinus Transversus and sigmoid	5	100.0	0	0.0	5	100.0	
Left Sinus Transversus and sagitalis superior	1	100.0	0	0.0	1	100.0	
Left Sinus transversus and straight sinus	0	0.0	1	100.0	1	100.0	

Note: *Statistically significant.

Table 4 Relationship Between D-Dimer Level and Risk Factors

Variable	D-Dimer Level				Total	p-value
	High		Normal/Low			
	n	%	n	%		
Risk factors						0.044*
Autoimmune	1	100	0	0	1	
Hormonal	14	87.5	2	12.5	16	
Malignancy	2	66.7	1	33.3	3	
Hematology disorders	8	53.3	7	46.7	15	
Diabetes Mellitus/ Dyslipidemia	10	43.5	13	56.5	23	

Note: *Statistically significant.

pressure increases in the case of cerebral sinus thrombosis, while localized effects in the case of cerebral venous thrombosis owing to venous blockage. The vast majority of patients can go through both of these mechanisms simultaneously.^{23–34} Elevated D-Dimer levels are often used as a standard for measuring the coagulation process. However, medical and physical conditions may affect plasma D-Dimer levels. D-Dimer levels were elevated in individuals suffering from pulmonary embolism, deep vein thrombosis (DVT), and disseminated intravascular coagulation (DIC).³⁴

Additionally, patients with infections and after major surgery often experienced elevated D-Dimer levels because of the accelerated breakdown of extravascular fibrin.^{28–33} In this study, hormonal usage in women between the ages of 20 and 35 was the risk factor related to elevated D-Dimer levels (Table 4).^{7,35} This confirms the findings of the previous research, which found that hormonal imbalance is a significant risk factor in CVST patients.^{6,7,36}

Diagnosing CVST is complicated by patients' often-atypical symptoms, a wide range of risk factors, and thrombus often develops in the brain's veins and sinuses.^{4,5,23–32} DSA is a gold standard for identifying vascular diseases like thrombosis, aneurysms, and ulcerative plaques. DSA is essential to determine the diagnosis of CVST.^{7,34,35,37–43} CVST causes 1–2% of adult strokes and affects all ages. CVST is more frequently observed in the transverse sinuses (62%).¹⁰ In this study, the most prevalent sites for thrombosis were the left transverse sinus and left sigmoid sinus (Table 3).

D-Dimer elevations in CVST patients were observed to be strongly associated with the number of sinus involvement (Table 2).^{17,44–48} Multiple sinuses are impacted when the D-Dimer level is higher because additional thrombus formation circumstances arise.^{6,47,49–54} D-Dimer levels were positively correlated with thrombus extension, with high levels in the presence of larger thrombi. D-Dimer levels had an inverse relation with a duration between the onset of symptoms and testing, typically reaching 25% of the initial value after 1–2 weeks.⁵⁵

Limitation of Study

1. Since the data is retrospective, patients could not be followed up after DSA.
2. Without a comparison group, it is impossible to determine if asymptomatic individuals exhibit any structural abnormalities in their blood vessels when exposed to CVST.
3. Neither DSA nor any similar follow-ups were attempted.

Conclusion

There is a significant relationship between the D-Dimer level and the number of sinus involvement in CVST patients utilizing DSA, which often affects the left transverse sinus and left sigmoid.

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Disclosure

The author reports no conflicts of interest in this work.

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