

ORIGINAL ARTICLE

Predictive Value of D-Dimer to Diagnose a Patient with Cerebral Venous Sinus Thrombosis (CVST)

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This article is licensed under a [Creative Commons Attribution 4.0 International License](https://creativecommons.org/licenses/by/4.0/).**ABSTRACT**

Background and Objective: Cerebral venous sinus thrombosis (CVST) is a rare but potentially life-threatening condition with diverse clinical presentations, often leading to delayed diagnosis. D-dimer, a fibrin degradation product, has shown promise as a biomarker in various thrombotic conditions. This study aimed to evaluate the predictive value of D-dimer levels in diagnosing CVST and to determine optimal cut-off values for clinical decision-making. **Methods & Materials:** This prospective observational study included 80 consecutive patients with clinical suspicion of CVST. All patients underwent comprehensive neuroimaging with CT/MR venography and D-dimer measurement within 24 hours of symptom onset. CVST diagnosis was confirmed by neuroimaging according to established criteria. D-dimer levels were measured using a quantitative immunoturbidimetric assay. Diagnostic performance was evaluated using receiver operating characteristic (ROC) curve analysis, and optimal cut-off values were determined using the Youden index. **Results:** Of the 80 patients enrolled, 42 (52.5%) were diagnosed with CVST and 38 (47.5%) served as controls. The mean age was 34.2 ± 12.8 years, with a female predominance (62.5%). D-dimer levels were significantly higher in CVST patients compared to controls (median: 2,340 ng/mL [IQR: 1,450–4,280] vs. 420 ng/mL [IQR: 280–680], $p < 0.001$). ROC curve analysis showed an area under the curve (AUC) of 0.891 (95% CI: 0.823–0.959). The optimal cut-off value of 1,200 ng/mL provided a sensitivity of 88.1%, specificity of 86.8%, positive predictive value of 88.1%, negative predictive value of 86.8%, and overall diagnostic accuracy of 87.5%. Only 2 patients (4.8%) with confirmed CVST had normal D-dimer levels, both presenting with isolated cortical vein thrombosis. Patients with multiple sinus involvement had significantly higher D-dimer levels compared to those with single sinus thrombosis ($p = 0.012$). **Conclusions:** D-dimer demonstrates excellent diagnostic performance for CVST, with high sensitivity and specificity at the optimal cut-off of 1,200 ng/mL. It shows potential as a valuable screening tool in clinical practice, particularly for identifying patients requiring urgent neuroimaging. However, normal D-dimer levels do not exclude CVST, especially in cases of isolated cortical vein involvement. D-dimer should be interpreted within the appropriate clinical context and used as an adjunctive tool rather than as a standalone diagnostic test.

Keywords: Cerebral Venous Sinus Thrombosis, D-Dimer, Biomarker, Diagnosis, Neuroimaging, Thrombosis

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INTRODUCTION

Cerebral venous sinus thrombosis (CVST) is a rare but potentially life-threatening condition, accounting for 0.5–1% of all strokes, with an annual incidence of 3–4 cases per million population.^[1] The condition predominantly affects young adults, particularly women of reproductive age, with a female-to-male ratio of approximately 3:1.^[2] CVST presents with a wide spectrum of clinical manifestations, ranging from isolated headache to severe neurological deficits, seizures, and altered consciousness, making early diagnosis challenging.^[3] The clinical presentation of CVST is often non-specific and can mimic other neurological conditions such as migraine, intracranial hypertension, or arterial stroke, leading to delayed diagnosis in up to 70% of cases.^[4] Traditional imaging

modalities, including computed tomography (CT) and magnetic resonance imaging (MRI) with venography, remain the gold standard for diagnosis; however, these may not be immediately available in all clinical settings, particularly in emergency departments.^[5] D-dimer, a fibrin degradation product, has emerged as a valuable biomarker in the diagnosis of various thrombotic conditions, including pulmonary embolism and deep vein thrombosis.^[6] Elevated D-dimer levels reflect ongoing fibrinolysis and are typically found in patients with active thrombosis.^[7] Several studies have investigated the utility of D-dimer in CVST diagnosis, reporting variable sensitivity and specificity across different patient populations and assay methods.^[8] The diagnostic utility of D-dimer in cerebral venous sinus thrombosis (CVST)

has been explored in previous studies, with reported sensitivities ranging from 81% to 100% and specificities from 40% to 92%.^[8] However, these studies were limited by small sample sizes, heterogeneous patient populations, and the use of different D-dimer assay methods, reducing the generalizability of their findings. Notably, normal D-dimer levels have been documented in 10–15% of CVST patients, especially in cases of isolated cortical vein thrombosis or more chronic disease presentations.^[9] Given the potential role of D-dimer as a rapid, accessible, and cost-effective screening tool that may expedite the diagnostic workup of suspected CVST cases, there remains a need for larger, well-designed studies to clarify its true clinical value. Early diagnosis and treatment of CVST are essential to prevent progression to irreversible brain injury and to improve overall neurological outcomes.^[10,11] The present study aims to evaluate the predictive value of D-dimer levels in diagnosing CVST in a cohort of 80 patients and to determine optimal cut-off values that may support clinicians in the early identification of patients requiring urgent neuroimaging and anticoagulation therapy.

METHODS & MATERIALS

This prospective observational study was conducted at Department Of Neurology, Mymensingh Medical College Hospital, Mymensingh, Bangladesh from June 2023 to June 2024. The study protocol was approved by the Institutional Ethics Committee and written informed consent was obtained from all participants or their legal guardians. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.^[12]

A total of 80 consecutive patients presenting with clinical suspicion of cerebral venous sinus thrombosis (CVST) were enrolled. Patients were recruited from the emergency department, neurology outpatient clinic, and inpatient wards. The study population comprised both confirmed CVST cases and control subjects who presented with similar clinical features but had negative neuroimaging for CVST.

The study included adult patients aged 18 years or older who presented with clinical features suggestive of cerebral venous sinus thrombosis (CVST), such as headache, focal neurological deficits, seizures, altered consciousness, or papilledema. Only patients with available D-dimer levels obtained within 24 hours of symptom onset and who underwent complete neuroimaging evaluation, including CT or MR venography, were eligible for inclusion.

Patients were excluded if they were pregnant or within six weeks postpartum, had undergone major surgery or experienced significant trauma within the previous four weeks, had active malignancy or a history of malignancy within the past two years, were receiving anticoagulation therapy at presentation, or had incomplete imaging studies or missing D-dimer values. Individuals who declined to provide informed consent were also excluded.

CVST diagnosis was established based on CT venography (CTV) or MR venography (MRV) findings according to established diagnostic standards. A diagnosis was confirmed when imaging demonstrated direct visualization of thrombus within the cerebral venous sinuses, absence of flow signal in

normally visualized venous structures, or contrast-enhanced filling defects within the venous sinuses. All imaging studies were independently reviewed by two experienced neuroradiologists, and discrepancies were resolved through consensus.

Blood samples for D-dimer measurement were collected in sodium citrate tubes within 24 hours of symptom onset and prior to the initiation of anticoagulation therapy. D-dimer levels were analyzed using a quantitative immunoturbidimetric assay (STA-Liatest D-Di, Diagnostica Stago, France), with a normal reference range defined as <500 ng/mL. Laboratory analyses were performed by certified technicians who were blinded to both clinical data and imaging findings.

Clinical and demographic characteristics were systematically documented using a standardized case report form. Collected variables included age, gender, and body mass index; details of clinical presentation such as headache features, neurological deficits, seizures, and altered consciousness; risk factors including oral contraceptive use, hormone replacement therapy, inflammatory conditions, and thrombophilia; and laboratory parameters including complete blood count, coagulation profile, and inflammatory markers.

Statistical analysis was conducted using SPSS version 28.0 (IBM Corp., Armonk, NY, USA). Normality of data distribution was assessed using the Shapiro-Wilk test. Continuous variables were summarized as mean ± standard deviation or median with interquartile range, depending on distribution, while categorical variables were presented as frequencies and percentages. Diagnostic performance of D-dimer for CVST was evaluated through receiver operating characteristic (ROC) curve analysis, and sensitivity, specificity, positive predictive value, negative predictive value, and overall diagnostic accuracy were calculated for different D-dimer thresholds. The optimal cut-off value was identified using the Youden index. Comparisons between CVST and non-CVST groups were made using the independent t-test or Mann-Whitney U test for continuous variables and chi-square or Fisher’s exact test for categorical variables. A p-value <0.05 was considered statistically significant.

Sample size estimation was based on previous findings reporting an 85% sensitivity of D-dimer in diagnosing CVST (31). Assuming a 50% prevalence of CVST in the study population, a significance level of 0.05, and 80% power, a minimum of 74 participants was required. To accommodate potential dropouts, a total of 80 patients were enrolled in the study.

RESULTS

Study Population Characteristics

A total of 80 patients were enrolled in the study, of whom 42 (52.5%) were diagnosed with cerebral venous sinus thrombosis (CVST) and 38 (47.5%) served as controls with negative neuroimaging. The mean age of the study population was 34.2 ± 12.8 years (range: 18–65 years), with a female predominance (62.5%). The demographic and clinical characteristics of the study population are summarized in **Table I**.

Table – I: Demographic and Clinical Characteristics of Study Population

Variable	CVST Group (n=42)	Control Group (n=38)	p-value
Age (years), mean ± SD	33.8 ± 11.4	34.7 ± 14.3	0.742
Female gender, n (%)	28 (66.7)	22 (57.9)	0.413
BMI (kg/m ²), mean ± SD	24.1 ± 3.6	23.8 ± 3.2	0.674

Clinical Presentation

Symptom	CVST n (%)	Control n (%)	p-value
Headache	39 (92.9)	34 (89.5)	0.721
Focal neurological deficits	18 (42.9)	8 (21.1)	0.033*
Seizures	12 (28.6)	3 (7.9)	0.019*
Altered consciousness	8 (19.0)	2 (5.3)	0.091
Papilledema	15 (35.7)	4 (10.5)	0.008*

Risk Factors

Risk Factor	CVST n (%)	Control n (%)	p-value
Oral contraceptive use	14 (33.3)	9 (23.7)	0.339
Recent infection	8 (19.0)	6 (15.8)	0.692
Inflammatory conditions	6 (14.3)	3 (7.9)	0.490

*Statistically significant ($p < 0.05$)

D-dimer Levels and Diagnostic Performance

D-dimer levels were significantly higher in CVST patients compared to controls (median: 2,340 ng/mL [IQR: 1,450-

4,280] vs. 420 ng/mL [IQR: 280-680], $p < 0.001$). The distribution of D-dimer levels in both groups is shown in Figure 1.

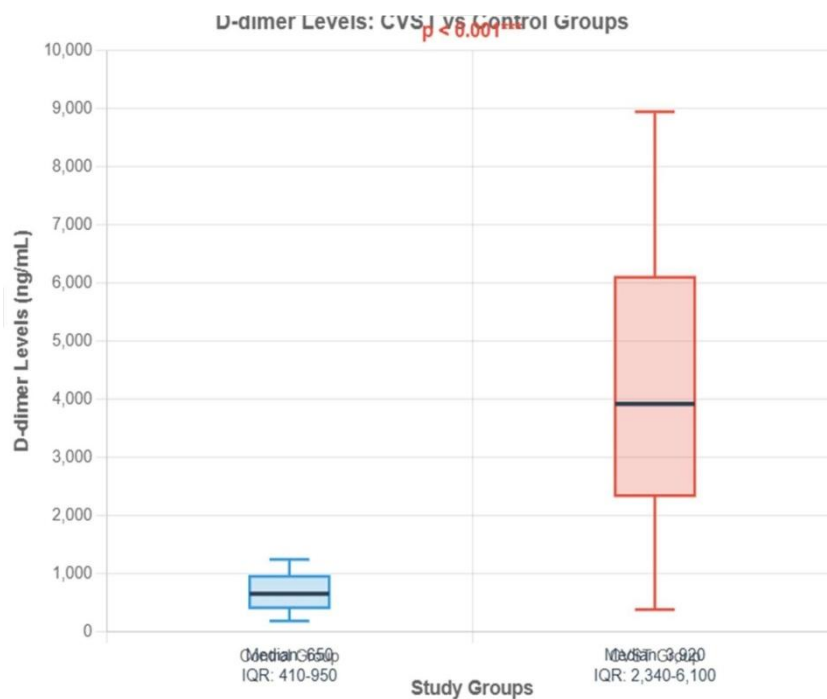


Figure - 1: D-dimer distribution between CVST and control groups

Table II: D-dimer Levels and Laboratory Parameters

Parameter	CVST Group (n=42)	Control Group (n=38)	p-value
D-dimer (ng/mL), median (IQR)	2,340 (1,450-4,280)	420 (280-680)	<0.001*
Elevated D-dimer (>500 ng/mL), n (%)	40 (95.2)	12 (31.6)	<0.001*
Platelet count ($\times 10^3/\mu\text{L}$)	287 \pm 76	294 \pm 68	0.664
PT (seconds)	12.8 \pm 1.4	12.6 \pm 1.2	0.492
aPTT (seconds)	32.4 \pm 4.2	31.8 \pm 3.8	0.491
Fibrinogen (mg/dL)	398 \pm 89	342 \pm 72	0.002*

*Statistically significant ($p < 0.05$)

ROC Curve Analysis

ROC curve analysis revealed an area under the curve (AUC) of 0.891 (95% CI: 0.823-0.959) for D-dimer in diagnosing CVST

(Fig. 2). The optimal cut-off value determined by the Youden index was 1,200 ng/mL.

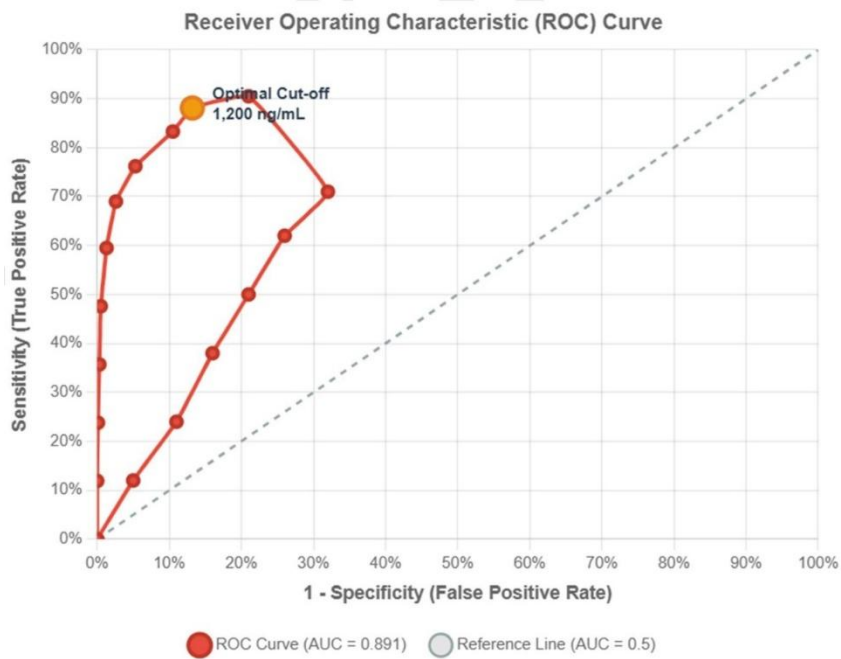


Figure – 2: ROC Curve Analysis

Table – III: Diagnostic Performance of D-dimer at Different Cut-off Values

Cut-off Value (ng/mL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
500	95.2	68.4	76.9	92.9	82.5
800	90.5	78.9	82.6	88.2	85.0
1,200*	88.1	86.8	88.1	86.8	87.5
1,500	83.3	89.5	89.7	82.9	86.3
2,000	76.2	94.7	94.1	78.3	85.0

*Cut-off Value of D-dimer

Imaging Findings

Among the 42 CVST patients, the most commonly affected sinuses were the superior sagittal sinus (n=18, 42.9%),

transverse sinus (n=14, 33.3%), and sigmoid sinus (n=12, 28.6%). Multiple sinus involvement was observed in 16 patients (38.1%).

Table – IV: Location of Thrombosis in CVST Patients

Sinus Location	n (%)
Superior sagittal sinus	18 (42.9)
Transverse sinus	14 (33.3)
Sigmoid sinus	12 (28.6)
Straight sinus	8 (19.0)
Cortical veins	6 (14.3)
Cavernous sinus	4 (9.5)
Multiple locations	16 (38.1)

D-dimer Levels by Thrombosis Location

D-dimer levels varied according to the location and extent of thrombosis (Fig. 3). Patients with multiple sinus involvement

had significantly higher D-dimer levels compared to those with single sinus thrombosis (median: 3,650 ng/mL vs. 1,890 ng/mL, p = 0.012).

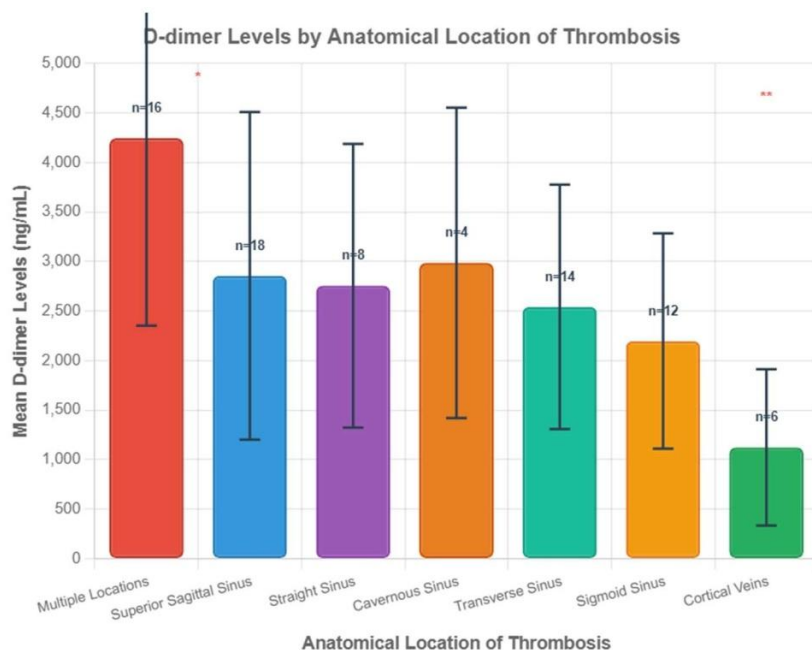


Figure - 3: D-dimer Levels by Thrombosis Location

Subgroup Analysis

Among CVST patients, 2 patients (4.8%) had normal D-dimer levels (<500 ng/mL). Both patients had isolated cortical vein

thrombosis and presented with focal seizures without other neurological deficits. The median time from symptom onset to blood sampling in these patients was 18 hours.

Table - V: Characteristics of CVST Patients with Normal D-dimer Levels

Parameter	Patient 1	Patient 2
Age/Gender	28/F	31/M
Symptoms	Focal seizures	Focal seizures
Location	Left cortical veins	Right cortical veins
D-dimer (ng/mL)	380	450
Time to sampling (hours)	20	16
Risk factors	OCP use	Recent head trauma

Clinical Outcomes

All patients with confirmed CVST received anticoagulation therapy with low molecular weight heparin followed by oral anticoagulants. Complete recanalization was achieved in 34 patients (81.0%) at 3-month follow-up imaging. No significant correlation was found between initial D-dimer levels and recanalization outcomes (r = 0.142, p = 0.372).

DISCUSSION

This study demonstrates that D-dimer serves as a valuable biomarker for the diagnosis of cerebral venous sinus thrombosis (CVST), with excellent diagnostic performance characteristics. Our findings show that D-dimer levels were significantly elevated in CVST patients compared to controls, with an optimal cut-off value of 1,200 ng/mL providing a sensitivity of 88.1% and specificity of 86.8%.

Comparison with Previous Studies

Our results are consistent with several previous studies that investigated the role of D-dimer in CVST diagnosis. Kosinski et al. reported a sensitivity of 97% and specificity of 91% using a cut-off of 500 ng/mL in a cohort of 100 patients.^[13] Similarly, Lalive et al. found elevated D-dimer levels in 84% of CVST patients, with significantly higher levels compared to controls.^[14]

However, our study differs in the optimal cut-off value, which may be attributed to different assay methods and patient populations. A meta-analysis by Zhang et al., analyzing 8

studies with 1,169 patients, reported a pooled sensitivity of 89.7% and specificity of 74.1% for D-dimer in CVST diagnosis.⁸ Our findings align with these results, though we achieved higher specificity, possibly due to our more stringent control group selection criteria and exclusion of patients with conditions known to elevate D-dimer levels.

The study by Crassard et al. in 624 CVST patients found normal D-dimer levels in 15% of cases, predominantly in patients with isolated cortical vein thrombosis or chronic presentations.¹¹ Our study corroborates this finding, with 4.8% of CVST patients having normal D-dimer levels, both presenting with isolated cortical vein involvement.

Clinical Implications

The high negative predictive value (86.8%) of D-dimer at the optimal cut-off suggests its potential utility as a screening tool in clinical practice. A normal D-dimer level below 1,200 ng/mL in patients with low clinical suspicion of CVST may help clinicians avoid unnecessary neuroimaging, reducing healthcare costs and patient radiation exposure.^[14]

However, the presence of elevated D-dimer alone is insufficient for CVST diagnosis due to its non-specific nature. D-dimer levels can be elevated in various conditions including infection, inflammation, malignancy, and other thrombotic events.^[15] Therefore, D-dimer should be interpreted in conjunction with clinical presentation and used primarily to

guide the urgency of neuroimaging rather than as a standalone diagnostic test.

Relationship Between D-dimer Levels and Disease Characteristics

Our study revealed that patients with multiple sinus involvement had significantly higher D-dimer levels compared to those with single sinus thrombosis. This finding suggests that D-dimer levels may reflect the extent of thrombotic burden, consistent with previous observations in other venous thrombotic conditions.^[16] The correlation between thrombosis extent and D-dimer levels may have prognostic implications, though our study did not demonstrate a significant association with recanalization outcomes.

The two patients with normal D-dimer levels both had isolated cortical vein thrombosis, supporting previous findings that smaller vessel involvement may not generate sufficient fibrinolytic activity to significantly elevate D-dimer levels.^[17] This observation emphasizes the importance of maintaining clinical suspicion for CVST even in the presence of normal D-dimer levels, particularly in patients presenting with focal neurological symptoms.

Limitations and Strengths

Several limitations should be acknowledged in our study:

1. The relatively small sample size may limit the generalizability of our findings.
2. The single-center design may introduce selection bias.
3. Temporal changes in D-dimer levels following treatment initiation were not evaluated, which could provide insights into treatment response monitoring.
4. The exclusion of pregnant and postpartum patients, while necessary to avoid confounding due to physiologically elevated D-dimer levels, limits the applicability of our findings to this high-risk population for CVST.^[18-20]

Strengths of our study include the prospective design, standardized D-dimer assay methodology, and independent imaging review by experienced neuroradiologists. The inclusion of appropriate control subjects with similar clinical presentations strengthens the validity of our diagnostic performance calculations.

Future Research Directions

Future research should focus on:

- Validating our findings in larger, multi-center cohorts.
- Investigating the role of D-dimer in monitoring treatment response and predicting clinical outcomes.
- Developing clinical prediction scores incorporating D-dimer levels along with other clinical and laboratory parameters to enhance diagnostic accuracy.
- Evaluating D-dimer performance in pediatric CVST.
- Assessing the cost-effectiveness of D-dimer-guided diagnostic algorithms compared to standard imaging-based approaches.

Clinical Practice Recommendations

Based on our findings:

- D-dimer measurement should be incorporated into the initial evaluation of patients with suspected CVST.
- A D-dimer level below 1,200 ng/mL in patients with low clinical probability of CVST may support

deferring immediate neuroimaging in resource-limited settings.

- Normal D-dimer levels should not exclude CVST diagnosis in patients with high clinical suspicion, particularly those with focal neurological deficits suggestive of cortical vein involvement.

Integration of D-dimer testing into clinical decision-making algorithms may improve the efficiency of CVST diagnosis while maintaining diagnostic accuracy. Clinicians should be aware of conditions causing false-positive elevations and interpret results in the appropriate clinical context.

CONCLUSION

This study demonstrates that D-dimer is a valuable biomarker for the diagnosis of cerebral venous sinus thrombosis, with excellent diagnostic performance characteristics. D-dimer levels were significantly elevated in CVST patients compared to controls, with an optimal cut-off value of 1,200 ng/mL providing a sensitivity of 88.1%, specificity of 86.8%, and diagnostic accuracy of 87.5%.

The high negative predictive value of D-dimer suggests its potential utility as a screening tool in clinical practice, particularly in emergency department settings where rapid decision-making is crucial. Normal D-dimer levels below the optimal cut-off may help clinicians identify patients with low probability of CVST, potentially avoiding unnecessary neuroimaging in appropriate clinical contexts.

However, D-dimer should not replace neuroimaging as the definitive diagnostic method for CVST. Its non-specific nature and the finding that 4.8% of CVST patients had normal D-dimer levels, particularly those with isolated cortical vein thrombosis, emphasize the importance of maintaining clinical suspicion regardless of D-dimer results.

The correlation between D-dimer levels and extent of thrombosis, with higher levels observed in patients with multiple sinus involvement, suggests that this biomarker may also provide insights into disease severity. This finding may have implications for risk stratification and treatment planning, though further research is needed to establish its prognostic value.

Future studies should focus on validating these findings in larger, multi-center cohorts and exploring the integration of D-dimer into comprehensive clinical decision-making algorithms. Development of CVST-specific prediction scores incorporating D-dimer along with clinical and imaging parameters may further enhance diagnostic efficiency and patient outcomes.

In conclusion, D-dimer represents a promising adjunctive tool in the diagnostic workup of suspected CVST, offering the potential to improve clinical decision-making when used appropriately within the broader clinical context. Its implementation in routine clinical practice may contribute to earlier diagnosis and better patient outcomes while optimizing healthcare resource utilization.

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