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**ORIGINAL ARTICLE**

# C-reactive protein and D-dimer in cerebral vein thrombosis: Relation to clinical and imaging characteristics as well as outcomes in a French cohort study

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#### Abstract

**Introduction:** Cerebral venous sinus thrombosis (CVST) is a rare disease with highly variable clinical presentation and outcomes. Clinical studies suggest a role of inflammation and coagulation in CVST outcomes. The aim of this study was to investigate the association of inflammation and hypercoagulability biomarkers with CVST clinical manifestations and prognosis.

**Methods:** This prospective multicenter study was conducted from July 2011 to September 2016. Consecutive patients referred to 21 French stroke units and who had a diagnosis of symptomatic CVST were included. High-sensitivity C-reactive protein (hs-CRP), neutrophil-to-lymphocyte ratio (NLR), D-dimer, and thrombin generation using calibrated automated thrombogram system were measured at different time points until 1 month after anticoagulant therapy discontinuation.

**Results:** Two hundred thirty-one patients were included. Eight patients died, of whom 5 during hospitalization. The day 0 hs-CRP levels, NLR, and D-dimer were higher in patients with initial consciousness disturbance than in those without (hs-CRP: 10.2 mg/L [3.6-25.5] vs 23.7 mg/L [4.8-60.0], respectively; NLR: 3.51 [2.15-5.88] vs 4.78 [3.10-9.59], respectively; D-dimer: 950 µg/L [520-2075] vs 1220 µg/L [950-2445],

respectively). Patients with ischemic parenchymal lesions ( $n = 31$ ) had a higher endogenous thrombin potential<sub>5pM</sub> than those with hemorrhagic parenchymal lesions ( $n = 31$ ): 2025 nM min (1646-2441) vs 1629 nM min (1371-2090), respectively ( $P = .0082$ ). Using unadjusted logistic regression with values >75th percentile, day 0 hs-CRP levels of >29.7 mg/L (odds ratio, 10.76 [1.55-140.4];  $P = .037$ ) and day 5 D-dimer levels of >1060 mg/L (odds ratio, 14.63 [2.28-179.9];  $P = .010$ ) were associated with death occurrence.

**Conclusion:** Two widely available biomarkers measured upon admission, especially hs-CRP, could help predict bad prognosis in CVST in addition to patient characteristics. These results need to be validated in other cohorts.

#### KEYWORDS

cerebral venous sinus thrombosis, D-dimer, high-sensitivity C-reactive protein, thrombin generation assay

#### Essentials

- There are several clinical presentations of cerebral venous sinus thrombosis (CVST).
- Association between inflammation and CVST severity has been observed.
- D-dimer and C-reactive protein predicted bad prognosis in CVST.
- Elevated endogenous thrombin potential on admission was associated with ischemic parenchymal lesions.

## 1 | INTRODUCTION

Cerebral venous sinus thrombosis (CVST) is a rare thrombotic disorder with an estimated incidence of 1.3 to 1.57 per 100,000 person-years from studies of various European and Australian populations and 2.85 to 3.16 in the United States [1-4]. Several risk factors for CVST have been identified, including oral contraceptive use; pregnancy; thrombophilia; inflammatory diseases; infections; trauma; malignancy; medications, such as steroids; endocrine, and hematologic disorders [1,3-5]. Delays in diagnosis of CVST are common and substantial, with the first symptoms occurring from less than 48 hours until beyond 30 days [5]. Four main patterns have been identified as CVST clinical manifestations: isolated intracranial hypertension, focal syndrome, diffuse encephalopathy, and cavernous sinus syndrome [6]. Clinical presentation of CVST is affected by the patient's age, the time between the onset of symptoms and the admission to hospital, location of CVST, and the presence of cerebral parenchymal lesions.

Only a few studies have focused on the potential interest of biomarkers in CVST diagnosis and prognosis. Although plasma D-dimer has been widely validated as an effective tool for excluding the diagnosis of deep venous thrombosis or pulmonary embolism, its potential usefulness in the management of patients with suspected CVST is debated [7,8]. Indeed, D-dimer testing is of little use for CVST diagnosis [9]. No study has yet evaluated the association of D-dimer with CVST clinical manifestations. Besides, thrombin generation (TG) has been proposed as a global assay to evidence hypocoagulable

[10,11] and hypercoagulable states [12-14]: increased TG is an independent predictor of recurrent venous thrombosis [15]. Inflammation biomarkers, such as fibrinogen and high-sensitivity C-reactive protein (hs-CRP), have been recently described as possible predictors of poor prognosis in CVST [16]. The neutrophil-to-lymphocyte ratio (NLR) reflects subclinical inflammation, predicting mortality in myocardial infarction and cardiovascular risk [17].

We recently described the clinical and imaging features of patients presenting with CVST enrolled in a French prospective cohort [18]. The aim of the present study was to investigate, in the French prospective cohort, the association of inflammation biomarkers, D-dimer, and TG parameters with clinical or imaging characteristics in the patients with CVST in this cohort at diagnosis and during the follow-up months.

## 2 | METHODS

### 2.1 | Population study

The "French prospective cohort-cerebral vein thrombosis" (FPCCVT) multicenter study was prospectively conducted from July 2011 to September 2016 [18]. Briefly, symptomatic patients with CVST from 21 French stroke unit centers were included. This study was funded through a clinical research program (N° 2010/087/HP) of the French Ministry of Health and registered on [clinicaltrials.gov](https://clinicaltrials.gov)

(NCT02013635). Patients were included regardless of race/ethnicity, and fully covered by the French health system.

## 2.2 | Clinical and imaging characteristics

The diagnosis of CVST had to be confirmed by cerebral tomodesintometry venography and/or magnetic resonance imaging (MRI) combined with magnetic resonance venography and/or digital subtraction angiography following established diagnostic criteria [19]. Patients' data were recorded. Clinical status was evaluated at admission using the Glasgow Coma Scale and the National Institutes of Health Stroke Scale (NIHSS). Presenting syndromes were categorized as isolated intracranial hypertension and/or isolated headache, focal syndrome, cavernous sinus syndrome, and diffuse encephalopathy. Radiological evolution was evaluated at 3 months using preferably MRI with magnetic resonance venography. "Partial recanalization" was defined as recanalization of at least one previously thrombosed sinus or vein in an individual patient with CVST. "No recanalization" was defined as total absence of any type of recanalization in any previously thrombosed sinus or vein. "Complete recanalization" was considered when all previously thrombosed structures met the criteria of complete recanalization. Three categories were predefined according to the time from the onset of symptoms to diagnosis: within 2 days (acute), between 2 and 30 days (subacute), and beyond 30 days (chronic).

The extent of the parenchymal lesions was classified as minor ( $\leq 1/3$  of lobe lesions), moderate (between  $1/3$  and  $2/3$  of lobe lesions), and severe ( $> 2/3$  of lobe lesions). The type of parenchymal lesion was described as ischemic, hemorrhagic, or both. Follow-up visits were planned at 3 months, and one month after stopping an antithrombotic treatment or after a maximum of 13 months if antithrombotic treatment was continued [18].

## 2.3 | Laboratory parameters and assays

Laboratory tests, including whole blood count and plasma fibrinogen, were locally performed for each patient upon admission before any initiation of anticoagulant therapy ( $D_0$ ). Additional blood was collected on EDTA, 0.109M citrate, and dry tubes to build a plasma and serum bank. In addition to  $D_0$  sampling, blood samples were taken at different times, especially at day 5 ( $D_5$ ) after the diagnosis.

Anemia was defined by decreased hemoglobin  $< 12.0$  g/dL in females and  $13.0$  g/dL in males.

Platelet-poor plasma (PPP) was prepared as recommended by the "Groupe Français d'études sur l'Hémostase et la Thrombose," ie, double-centrifuged at  $2000$  g for 10 minutes, and aliquots were kept frozen at  $-80$  °C ([www.geht.org](http://www.geht.org)). Samples were transported on dry ice for central analysis. Plasma D-dimer was assessed using Liatest DDI+ (Diagnostica Stago) on a STAR analyzer and serum hs-CRP using C-reactive protein (CRP)-Vario on a C8000 analyzer (Abbott) at Lariboisière Hospital (Paris). TG was performed on a calibrated automated thrombogram system using a microplate fluorometer (Fluorocan

Ascent, ThermoScientific Labsystems) at Rouen University Hospital. PPP samples were run using either PPP reagent (5pM tissue factor and  $4\mu\text{M}$  phospholipid vesicles) or low PPP reagent (1pM tissue factor and  $4\mu\text{M}$  phospholipid vesicles) (Diagnostica Stago). We recorded and analyzed the following parameters: lag time, time to peak, endogenous thrombin potential (ETP) (area under the thrombin time-concentration curve), maximal thrombin peak, and velocity. TG assay was not performed if patients were on anticoagulant therapy before  $D_0$  sampling; activity was systematically measured to detect anti-Xa inhibitors.

## 2.4 | Statistical analysis

The Shapiro-Wilk test was used to test normality of continuous variables. Normally, distributed data were presented as mean  $\pm$  standard deviations and non-Gaussian variables as median  $\pm$  IQR. We performed analyses to test relationships between biomarkers, namely inflammation biomarkers, D-dimer, and TG parameters measured at different times and i/clinical presentation or imaging data upon admission; ii// clinical evolution evaluated by modified Rankin Score, NIHSS, and death occurrence; iii/clinical/imaging evolution on 3 months. Univariate subgroup comparisons were analyzed using the Mann-Whitney U-test. Multiple group comparisons were performed using the Kruskal-Wallis test completed with the two-stage step-up method of Benjamini, Krieger, and Yekutieli. The correlation between clinical and biological parameters was evaluated with Spearman and Pearson correlation. Univariate logistic regression analysis of clinical outcome (death, presence of a parenchymal lesion) was performed using the following variables as predictors: age  $> 75$ th percentile, sex, body mass index, dyslipidemia, tobacco, diabetes, initial consciousness disturbances, D-dimer  $> 75$ th percentile, hs-CRP  $> 75$ th percentile, and maximal thrombin peak. *P* values of  $< .05$  were considered significant. Data were analyzed using GraphPad Prism 9.4 and the R software, version 4.0.0.

# 3 | RESULTS

## 3.1 | Clinical characteristics

Two hundred thirty-one patients with a diagnosis of CVST were included. The main demographic and clinical characteristics at baseline are shown in Table 1. Briefly, the median age was 41.2 years (IQR, 28-51). The cohort comprised a majority of women (68.4%), 67.1% of whom took oral contraceptives. The median time from the onset of symptoms to diagnosis was 5 days (range, 0-205). The mode of onset was acute in 82 patients, subacute in 131, and chronic in 18. The median number of vein sinuses with thrombosis was 3 (IQR, 1-15). Twenty-nine (12.5%) had only 1 vein with thrombosis. Thirty-one (13.4%) had isolated thrombotic parenchymal lesions, 31 (13.4%) had isolated hemorrhagic parenchymal lesions, and 27 (11.7%) had both. The median duration of follow-up was 11.9 months (range, 76-543 months) for 197 (88.3%) of 223 surviving patients. Five patients died during hospitalization, 4 of brain herniation (despite

**TABLE 1** Epidemiologic, demographic, and clinical characteristics of patients with cerebral venous sinus thrombosis.

| Parameters                                       | All (n = 231)      |
|--|--------------------|
| Demographic characteristics                      |                    |
| Age (y)  | 41.2 (28-51)       |
| Female   | 158 (68.4%)        |
| Body mass index (kg/m <sup>2</sup> )             | 25.4 (22.6-28.5)   |
| Underlying comorbidity                           |                    |
| Dyslipidemia                                     | 27 (11.7%)         |
| Hypothyroidism                                   | 12 (5.2%)          |
| Diabetes   | 11 (4.8%)          |
| Smoking history                                  | 32 (13.9%)         |
| History of thrombosis                            | 36 (15.6%)         |
| Contraceptive                                    | 106 (67.1%)        |
| Initial clinical presentation                    |                    |
| Time between onset of symptoms and diagnosis (d) | 5 (range, 0-205)   |
| ≤2   | 82                 |
| 2-30   | 131                |
| >30  | 18                 |
| Clinical presentation                            |                    |
| Isolated intracranial hypertension               | 117 (50.6%)        |
| Focal syndrome                                   | 96 (41.5%)         |
| Diffuse encephalopathy                           | 16 (6.9%)          |
| Initial consciousness disturbances               | 35 (15.2%)         |
| Median GCS score                                 | 15 (8-15)          |
| Mean NIHSS score                                 | 1.59 (range, 0-26) |
| 0  | 149 (64.5%)        |
| ≤5   | 208 (90%)          |
| >5   | 23 (10%)           |
| Initial imaging                                  |                    |
| Number of sinus thrombosis                       |                    |
| 1  | 29 (12.6%)         |
| 2  | 33 (14.3)          |
| 3  | 58 (25.1)          |
| 4  | 29 (12.6%)         |
| 5  | 26 (11.3)          |
| 6  | 14 (6%)            |
| 7  | 9 (3.9%)           |
| 8  | 8 (3.5%)           |
| ≥9   | 6 (2.6%)           |

(Continues)

**TABLE 1** (Continued)

| Parameters  | All (n = 231) |
|---|---------------|
| Parenchymal lesion severity                               |               |
| Minor   | 57 (24.7%)    |
| Moderate  | 25 (10.8%)    |
| Severe  | 4 (1.7%)      |
| Type of lesion  |               |
| Ischemic  | 31 (13.4%)    |
| Hemorrhagic   | 31 (13.4%)    |
| both  | 27 (11.7%)    |
| Evolution   |               |
| NIHSS score variation between day 0 and 5                 |               |
| Stable  | 159 (68.8%)   |
| Improvement   | 59 (25.5%)    |
| Worsening   | 11 (4.8%)     |
| Modified Rankin Score variation between day 5 and month 3 |               |
| Stable  | 95 (41.1%)    |
| Improvement   | 70 (30.3%)    |
| Worsening   | 47 (20.3%)    |

GCS, Glasgow Coma Scale; NIHSS, National Institutes of Health Stroke Scale.

decompressive craniectomy in 1 patient), and 1 of uncontrolled cancer. Three more patients died because of underlying conditions such as cancer at 3 (n = 2) and 12 months. Twenty-six were lost to follow-up (they did not come to the control visit at 3 and 12 months). Among the 205 survivor patients who had a complete follow-up, 97 (47.3%) were no longer treated with anticoagulants, 85 patients (41.5%) were still on anticoagulants, and 20 (9.8%) were on aspirin. The median duration of antithrombotic treatments was 356 days (IQR, 228-387).

### 3.2 | Laboratory parameters and clinical presentation characteristics

Laboratory results obtained at D<sub>0</sub> are shown in [Supplementary Table 1](#). They are displayed according to the time between the onset of symptoms and diagnosis and the different clinical presentations ([Table 2](#)).

#### 3.2.1 | Association with the initial clinical presentation

We analyzed the association of biomarkers with symptoms at presentation categorized as isolated intracranial hypertension and/or

isolated headache, focal syndrome, cavernous sinus syndrome, and diffuse encephalopathy. A lower D<sub>0</sub> hs-CRP was observed in patients with isolated intracranial hypertension (8.7 mg/L [IQR, 2.2-23.3]) and diffuse encephalopathy (31.0 mg/L [13.0-66.5];  $P = .0045$ ). The presence of initial consciousness disturbance was considered a factor of severity. D<sub>0</sub> hs-CRP levels were significantly higher in patients with initial consciousness disturbance than in those without (hs-CRP: 10.2 mg/L [3.6-25.5] vs 23.7 mg/L [4.8-60.0], respectively;  $P = .0086$ ).

Concerning the NIHSS score, higher D<sub>0</sub> hs-CRP was associated with worse initial NIHSS score (>5) compared with NIHSS score of ≤5 ( $P = .0009$ ). No significant differences were observed for NLR, fibrinogen, or TG parameters.

Finally, D<sub>0</sub> NLR (odds ratio [OR], 1.088 [1.011-1.178];  $P = .0246$ ) and hs-CRP (OR, 1.013 [1.03-1.025];  $P = .01$ ) were associated with parenchymal lesions.

### 3.3 | Laboratory parameters and imaging at presentation

Laboratory parameters on D<sub>0</sub> according to imaging data are displayed in [Table 3](#).

#### 3.3.1 | Association with cerebral parenchymal lesions

A significant difference in D-dimer levels was also observed in patients with minor vs moderate-to-severe parenchymal lesions (1070 μg/L [543-2175] vs 2220 [1108-3885], respectively;  $P = .0058$ ). Patients with parenchymal ischemic parenchymal lesions ( $n = 31$ ) had higher ETP<sub>5pM</sub> than those with hemorrhagic parenchymal lesions ( $n = 31$ ): 2025 nM min [1646-2441] vs 1629 nM min [1371-2090], respectively;  $P = .0082$ ).

#### 3.3.2 | Association with etiological characteristics

D<sub>0</sub> TG was increased in women under contraceptives: higher ETP<sub>5pM</sub>, maximal thrombin peak<sub>5pM</sub>, and velocity<sub>5pM</sub> (1892 nM min [IQR, 1573-2407] vs 1489 nM min [IQR, 1489-1840],  $P = .0042$ ; 354 nM [IQR, 255-419] vs 253 [IQR, 189-345],  $P = .0029$ ; and 127.6 nM/min [IQR, 66.0-160.1] vs 51.2 [IQR, 21.2-82.9],  $P < .001$ ; respectively).

### 3.4 | Laboratory parameters and evolution

#### 3.4.1 | NIHSS evolution from D<sub>0</sub> to D<sub>5</sub> and biomarkers

We calculated the NIHSS variation from D<sub>0</sub> to D<sub>5</sub> ([Supplementary Table 2](#)): 11 patients had a worsening score, 159 patients had a stable score, and 59 patients had an improving score. In patients with

worsening scores, the D<sub>0</sub> hs-CRP and NLR were significantly higher than those with stable or improving scores (32.7 mg/L [18.6-105.1] vs 9.6 mg/L [2.8-23.4] vs 13.4 mg/L [5.7-31.4]; 6.9 [4.7-12.7] vs 3.5 [2.1-5.9] vs 3.9 [2.1-6.5];  $P = .003$  and  $P = .0041$ , respectively).

#### 3.4.2 | Death occurrences during hospitalization and biomarkers

Five patients died during hospitalization. No significant correlations were observed between D<sub>0</sub> hs-CRP and D-dimer ([Supplementary Table 3](#)). The D<sub>0</sub> hs-CRP and D-dimer were significantly higher in patients who died during hospitalization (hs-CRP: 71.2 mg/L [IQR, 9.1-110.8] vs 10.6 mg/L [IQR, 3.6-29.1],  $P = .017$ ; D-dimer: 2405 μg/L [IQR, 2085-10250] vs 965 μg/L [IQR, 550-2123],  $P = .020$ ; respectively). On D<sub>5</sub>, hs-CRP and D-dimer were also higher (hs-CRP: 223.5 mg/L [IQR, 31.3-393.1] vs 4.3 mg/L [IQR, 1.9-12.7],  $P < .0001$ ; D-dimer: 1160 μg/L [IQR, 1140-10,450] vs 650 μg/L [IQR, 380-1030],  $P = .016$ ; respectively). No significant differences were observed for NLR or TG parameters.

### 3.5 | Clinical characteristics and biomarkers as predictors of death occurrence

We evaluated clinical characteristics and biomarkers to predict death occurrence during hospitalization. Age >75th percentile (>51.5 years) was associated with death occurrence (OR, 12.51 [1.98-153.7];  $P = .016$ ) ([Supplementary Table 4](#)). Dyslipidemia and initial hemorrhagic parenchymal lesion were associated with death occurrence (OR, 25.38 [3.11-524.2],  $P = .028$ ; OR, 21.32 [2.63-439.2],  $P = .0045$ ; respectively). No other clinical characteristics were associated with death occurrence. In unadjusted logistic regression, D<sub>0</sub> hs-CRP level >75th percentile (>29.7 mg/L) was associated with odds of death (OR, 10.76 [1.55-140.4],  $P = .04$ ). D<sub>0</sub> D-dimer level >75th percentile (>2198 mg/L) was not associated with death occurrence (OR, 1.272 [0.20-15.95];  $P = .99$ ). The OR of death for D<sub>5</sub> hs-CRP >75th percentile (>13.7 mg/L) was 13.08 (2.06-160.8) ( $P = .01$ ), and for D<sub>5</sub> D-dimer >75th percentile (>1060 mg/L), it was 14.63 (2.28-179.9) ( $P = .01$ ).

#### 3.5.1 | Evolution at 3 months

Imaging was evaluated at 3 months ([Supplementary Table 3](#)): 4 patients had worse imaging findings, 15 patients had no change, and 193 patients had improved imaging findings with partial ( $n = 112$ ) or complete ( $n = 81$ ) recanalization. The improvement was associated with a lower D<sub>0</sub> NLR than that with no change (4.10 [2.54-5.76] vs 6.37 [5.02-9.57], respectively;  $P = .0246$ ). No significant differences were observed for hs-CRP, D-dimer, or TG parameters. No laboratory marker predicted improvement, worsening, or stable modified Rankin Score.

**TABLE 2** Laboratory markers on D<sub>0</sub> were associated with the initial clinical presentation.

| Biomarkers                       | Time to diagnosis |                   |                   | Clinical presentation             |                          |                          | Initial consciousness                |                                   |
|----------------------------------|-------------------|-------------------|-------------------|-----------------------------------|--------------------------|--------------------------|--------------------------------------|-----------------------------------|
|                                  | <2 d              | 2-30 d            | >30 d             | ICHT                              | Focal syndrome           | Diffuse encephalopathy   | No initial consciousness disturbance | Initial consciousness disturbance |
| hs-CRP (mg/L)                    | 10.8 (5.0-29.6)   | 10.6 (3.2-28.5)   | 5.3 (2.2-33.4)    | 8.7 (2.2-23.3) $\alpha$ , $\beta$ | 13.4 (5.6-30.2) $\alpha$ | 31.0 (13.0-66.5) $\beta$ | 10.17 (3.6-25.5) $\gamma$            | 23.71 (4.80-60.0) $\gamma$        |
| NLR                              | 3.40 (2.06-5.42)  | 3.40 (2.06-5.42)  | 3.46 (2.29-5.83)  | 3.32 (2.13-5.87)                  | 4.13 (2.15-6.46)         | 4.00 (2.15-7.19)         | 3.51 (2.12-5.88) $\delta$            | 4.78 (3.10-9.59) $\delta$         |
| D-dimer ( $\mu$ g/L)             | 830 (475-2365)    | 1160 (680-2220)   | 655 (413-1535)    | 925 (500-1680)                    | 1170 (670-2425)          | 1220 (625-2370)          | 950 (520-2075) $\alpha$              | 1220 (950-2445) $\alpha$          |
| Fibrinogen (g/L)                 | 4.1 (3.6-4.7)     | 3.8 (3.3-4.6)     | 4.7 (3.5-5.5)     | 3.9 (3.4-4.8)                     | 4.3 (3.6-4.7)            | 3.9 (3.4-4.8)            | 4.0 (3.4-4.7)                        | 4.3 (3.4-4.8)                     |
| Thrombin generation assay 1 pM   |                   |                   |                   |                                   |                          |                          |                                      |                                   |
| N                                | 82                | 131               | 18                | 106                               | 75                       | 10                       | 148                                  | 25                                |
| Lagtime <sub>1pM</sub> (min)     | 7.9 (5.6-9.2)     | 7.7 (6.1-8.8)     | 8.33 (6.9-9.5)    | 7.5 (5.8-9.0)                     | 7.9 (6.6-8.9)            | 9.4 (5.9-10.3)           | 7.8 (6.0-8.9)                        | 8.0 (5.8-10.3)                    |
| TTP <sub>1pM</sub> (min)         | 11.9 (9.0-13.8)   | 11.7 (10.1-13.3)  | 12.3 (9.8-13.2)   | 11.5 (9.8-13.3)                   | 11.9 (10.2-13.4)         | 12.9 (8.5-14.8)          | 11.7 (10.0-13.3)                     | 12.3 (9.1-15.1)                   |
| ETP <sub>1pM</sub> (nM min)      | 1370 (922-1793)   | 1314 (1068-1726)  | 1370 (970-1559)   | 1333 (929-1699)                   | 1440 (1095-1827)         | 1141 (998-1463)          | 1374 (1023-1753)                     | 1121 (954-1505)                   |
| Peak <sub>1pM</sub> (nM)         | 207 (117-303)     | 203 (118-269)     | 209 (101-328)     | 181 (109-278)                     | 222 (131-295)            | 218 (127-297)            | 204 (118-287)                        | 212 (110-271)                     |
| Velocity <sub>1pM</sub> (nM/min) | 55.3 (27.0-95.0)  | 51.6 (24.3-85.5)  | 63.0 (21.2-131.1) | 44.3 (22.1-84.2)                  | 56.2 (29.6-104.1)        | 70 (31.1-112.0)          | 54.5 (25.7-86.6)                     | 53.9 (23.9-96.2)                  |
| Thrombin generation assay 5 pM   |                   |                   |                   |                                   |                          |                          |                                      |                                   |
| Lagtime <sub>5pM</sub> (min)     | 4.1 (3.3-5.0)     | 4.0 (3.3-4.9)     | 4.2 (3.9-5.0)     | 3.9 (3.3-4.6)                     | 4.3 (3.5-5.4)            | 4.1 (3.8-5.2)            | 4.1 (3.3-4.8)                        | 4.2 (3.8-5.8)                     |
| TTP <sub>5pM</sub> (min)         | 7.5 (5.8-8.5)     | 7.1 (6.3-8.5)     | 7.5 (6.7-7.8)     | 7.1 (6.0-7.7)                     | 7.5 (6.5-9.0)            | 7.2 (6.2-8.4)            | 7.1 (6.3-8.3)                        | 7.4 (6.4-9.7)                     |
| ETP <sub>5pM</sub> (nM min)      | 1645 (1349-2109)  | 1739 (1417-2107)  | 1491 (1205-1959)  | 1652 (1365-2030)                  | 1695 (1422-2255)         | 1510 (1364-1736)         | 1743 (1391-2105)                     | 1551 (1316-1782)                  |
| Peak <sub>5pM</sub> (nM)         | 283 (198-373)     | 293 (229-389)     | 278 (209-353)     | 283 (222-370)                     | 298 (207-411)            | 279 (238-361)            | 298 (218-383)                        | 260 (221-347)                     |
| Velocity <sub>5pM</sub> (nM/min) | 92.2 (50.8-146)   | 97.2 (59.6-145.7) | 83.7 (66.4-129.6) | 91.5 (58.6-141)                   | 97.1 (55.4-148.3)        | 96.7 (71.8-137.2)        | 97.0 (57.6-145.9)                    | 80.0 (60.2-124)                   |

Results are expressed as median (IQR).

Statistical analysis was performed using the Mann–Whitney U-test or Kruskal–Wallis test completed with 2-stage step-up method of Benjamini, Krieger, and Yekutieli for multiple comparisons.  $\alpha$ : ICHT vs Focal syndrome  $P$  value = .039;  $\beta$ : ICHT vs Diffuse encephalopathy  $P$  value = .0045;  $\gamma$ : No initial consciousness disturbance vs initial consciousness disturbance  $P$  value = .0086;  $\delta$ : No initial consciousness disturbance vs initial consciousness disturbance  $P$  value = .012. N was the number of Thrombin generation assay without anticoagulant treatment at D<sub>0</sub> sampling.

ETP, endogenous thrombin potential; hs-CRP, high-sensitivity C-reactive protein; ICHT, intracranial hypertension; NLR, neutrophil-to-lymphocyte ratio; TTP, time to peak.



**TABLE 3** Laboratory markers on day 0 were associated with initial imaging results.

| Biomarkers                       | Cerebral parenchymal lesions |                          | Parenchymal lesion severity |                           |                    | Type of lesion            |                           |                  |
|----------------------------------|------------------------------|--------------------------|-----------------------------|---------------------------|--------------------|---------------------------|---------------------------|------------------|
|                                  | Absence of a lesion          | Presence of a lesion     | Minor                       | Moderate                  | Severe             | Ischemic                  | Hemorrhagic               | Both             |
| hs-CRP (mg/L)                    | 9.5 (2.6-23.2) $\alpha$      | 15.3 (5.4-31.8) $\alpha$ | 13.4 (5.7-28.5)             | 18.3 (4.0-52.6)           | 68.3 (19.8-134.4)  | 16.1 (7.8-27.5)           | 10.8 (5.4-30.3)           | 19.9 (3.6-55.8)  |
| NLR                              | 3.25 (2.08-6.07) $\beta$     | 4.32 (2.70-6.42) $\beta$ | 4.32 (2.7-5.9)              | 4.3 (3.2-10.8)            | 5.1 (4.1-9.5)      | 4.0 (2.7-6.0)             | 5.4 (2.5-6.8)             | 4.2 (2.8-7.3)    |
| D-dimer ( $\mu$ g/L)             | 930 (530-1660)               | 1240 (645-2423)          | 1070 (543-2175) $\gamma$    | 2220 (1108-3885) $\gamma$ | 1760 (900-2620)    | 1640 (575-2990)           | 1430 (640-2425)           | 1050 (733-2313)  |
| Fibrinogen (g/L)                 | 3.8 (3.3-4.7)                | 4.3 (3.6-4.7)            | 4.3 (3.6-4.7)               | 4.3 (3.6-5.2)             | 4.2 (3.8-4.6)      | 4.5 (3.7-4.9)             | 4.1 (3.6-4.6)             | 4.4 (3.6-5.2)    |
| Thrombin generation assay 1 pM   |                              |                          |                             |                           |                    |                           |                           |                  |
| N                                | 123                          | 74                       | 40                          | 18                        | 4                  | 25                        | 26                        | 22               |
| Lagtime <sub>1pM</sub> (min)     | 7.8 (5.8-9.0)                | 7.9 (6.7-9.3)            | 8.0 (7.3-9.4)               | 7.5 (5.0-9.1)             | 7.1 (5.6-10.0)     | 8.1 (7.3-9.4)             | 7.8 (6.4-8.7)             | 7.5 (5.0-9.2)    |
| TTP <sub>1pM</sub> (min)         | 11.8 (9.9-13.5)              | 11.9 (10.2-13.4)         | 12.3 (10.7-13.7)            | 11.0 (8.3-13.1)           | 10.0 (8.3-13.3)    | 12.3 (10.6-13.8)          | 11.9 (10.1-13.7)          | 11.0 (8.3-12.9)  |
| ETP <sub>1pM</sub> (nM min)      | 1269 (938-1701)              | 1442 (1090-1835)         | 1442 (1092-1836)            | 1454 (1081-1833)          | 1835 (1349-2176)   | 1448 (1180-1854)          | 1406 (1081-1555)          | 1280 (913-2042)  |
| Peak <sub>1pM</sub> (nM)         | 185 (109-279)                | 221 (139-304)            | 222 (136-308)               | 218 (118-292)             | 336 (217-392)      | 228 (145-291)             | 215 (139-284)             | 218 (89.7-359)   |
| Velocity <sub>1pM</sub> (nM/min) | 44.4 (22.06-84.2)            | 57.3 (31.4-110.6)        | 54.3 (27.8-102.4)           | 56.0 (31.5-110.6)         | 121.5 (65.2-146)   | 55.3 (32.2-84.1)          | 52.5 (31.9-114.8)         | 67 (20.0-125.7)  |
| Thrombin generation assay 5 pM   |                              |                          |                             |                           |                    |                           |                           |                  |
| Lagtime <sub>5pM</sub> (min)     | 3.96 (3.3-4.8)               | 4.17 (3.54-5.00)         | 4.2 (3.4-5.0)               | 4.2 (3.5-5.4)             | 4.6 (3.6-5.8)      | 3.9 (3.5-4.6)             | 4.2 (3.8-6.0)             | 4.2 (3.2-5.6)    |
| TTP <sub>5pM</sub> (min)         | 7.1 (6.0-8.5)                | 7.3 (6.5-8.1)            | 7.3 (6.6-8)                 | 7.3 (6.0-9.0)             | 7.1 (5.8-9.4)      | 7.2 (6.5-7.9)             | 7.5 (6.8-9.4)             | 7.3 (6.0-9.1)    |
| ETP <sub>5pM</sub> (nM min)      | 1627 (1348-2000)             | 1716 (1422-2163)         | 1844 (1424-2155)            | 1477 (1356-2185)          | 2373 (1469-2450)   | 2025 (1646-2441) $\delta$ | 1629 (1433-1797) $\delta$ | 1663 (1080-2124) |
| Peak <sub>5pM</sub> (nM)         | 278 (206-366)                | 311 (228-419)            | 337 (237-425)               | 269 (191-411)             | 421 (231-485)      | 361 (264-428)             | 268 (196-356)             | 299 (178-427)    |
| Velocity <sub>5pM</sub> (nM/min) | 89.8 (54.7-139)              | 101.1 (66.0-150.8)       | 109.2 (70.0-149.0)          | 92.1 (50.8-173.9)         | 168.5 (65.4-214.7) | 124 (80.6-150.1)          | 84.9 (50.0-131.3)         | 85.0 (51.1-185)  |

Statistical analysis were Mann-Whitney U test or Kruskal-Wallis test completed with two-stage step-up method of Benjamini, Krieger and Yekutieli for multiple comparisons.  $\alpha$ : Absence of lesion vs presence of lesion  $P$  value = .035;  $\beta$ : Absence of lesion vs presence of lesion  $P$  value = .0013;  $\gamma$ : Minor lesion vs moderate lesion  $P$  value = .0058;  $\delta$ : Ischemic lesion vs hemorrhagic lesion  $P$  value = .048. N was the number of Thrombin generation assay without anticoagulant treatment at D<sub>0</sub> sampling.

ETP, endogenous thrombin potential; hs-CRP, high-sensitivity C-reactive protein; ICHT, intracranial hypertension; NLR, neutrophil-to-lymphocyte ratio; TTP, time to peak.

## 4 | DISCUSSION

In our prospective study including 231 patients with CVST, we identified several biomarkers associated with clinical presentation characteristics and/or predictors of evolution. We confirmed, in a limited number of events, that hemorrhage and elevation of inflammation biomarkers, particularly hs-CRP and D-dimer, were associated with early death.

CVST is a rare thrombotic disorder caused by systemic or local imbalances in hemostasis [9]. Prognosis is usually good, with more than 80% of the patients making a complete recovery [5,6]. Despite the highly favorable prognosis, identification of patients with CVST having a possible unfavorable outcome can be challenging. For example, in a large cohort of 642 patients from the International Study on Cerebral Vein and Dural Sinus Thrombosis, clinical factors of unfavorable outcome have been identified: namely, male sex, age <37 years, coma, mental status disorder, intracranial hemorrhage on admission, thrombosis of the deep cerebral venous system, central nervous system infection, and cancer [5]. More recently, a practical clinical score was established to predict outcomes after CVST [20]. The clinical score associating parenchymal lesion size of >6 cm, bilateral Babinski signs, male sex, parenchymal hemorrhage, and level of consciousness are associated with unfavorable outcomes. However, no laboratory marker had been evaluated in these 2 studies. We confirmed that age >52 years and hemorrhagic parenchymal lesions were associated with unfavorable outcomes. We also found that dyslipidemia was associated with unfavorable outcomes; this abnormality has never been reported before. However, the confidence interval of the odds ratio is very wide, and this result deserves to be cautiously interpreted.

The association of inflammation biomarkers with diagnosis, severity, and poor prognosis of cerebrovascular events has already been reported, especially in patients with CVST [15,20–25]. Recently, a multicenter prospective observational study was conducted in Portugal: the Pathophysiology of Venous Infarction – Prediction of Infarction and Recanalization in CVT (PRIORITY-CVT) study, including 62 patients, demonstrated that biomarkers associated with inflammation predicted poor prognosis in cerebral vein thrombosis (CVT) [15]. In this study, patients had more unfavorable outcomes than the FPCCVT cohort (21% vs 3% of deaths, respectively). Three biomarkers, namely NLR, CRP, and interleukin (IL)-6, were evaluated as predictors of evolution. As reported in our study, NLR was associated with initial parenchymal brain lesions [16]. A higher baseline NLR, CRP, and IL-6 levels were predictors of unfavorable functional outcome at 90 days [16,24]. We demonstrated in our cohort that baseline systemic inflammation biomarkers were also associated with poor outcomes during hospitalization. Finally, we reported a non-significant fibrinogen increase associated with parenchymal lesions and an increasing number of sinus veins with thrombosis, as well as a lower baseline NLR in patients with improvement in imaging findings at 3 months. Noteworthy, in the PRIORITY-CVT, higher NLR, CRP, and IL-6 levels at admission were not associated with the early evolution of brain lesions or early recanalization. In a recent study including 52 CVST, the hs-CRP level was significantly higher in patients with acute or

subacute CVT than in patients with chronic CVT [25]. However, in our study, including a much higher number of patients, we did not find a significant difference.

In addition, we studied D-dimer levels. The D-dimer increase at diagnosis was associated with neurological deficit [22]. In our FPCCVT cohort, the initial D-dimer levels were associated with initial consciousness disturbance, early death occurrence, and the severity of parenchymal lesions. Together with hs-CRP, D-dimer measured at D<sub>5</sub> predicted early death. The association between inflammatory biomarkers and clinical outcomes has been reported in different studies [16,26]. Interestingly, a previous study demonstrated that the D-dimer decrease between D<sub>0</sub> and day 180 was associated with complete sinus recanalization in MRI findings at 6 months [21]. In a study evaluating fibrin clot properties, an increase in D-dimer was observed in patients who had developed recurrent CVST [27]. An altered fibrin clot and fibrinogen increase were observed in patients with recurrent CVST [28] and in patients with CVST-related pregnancy [29]. The combined activation of inflammatory and hemostatic responses after infection or tissue injury is a defense mechanism. This process is referred to as immunothrombosis: within this novel concept, inflammatory cells such as leukocytes and platelets directly drive the progression of venous thrombosis [30]. Under pathological conditions, an increase in tissue factor expression and increased levels of the plasminogen activation inhibitor 1, blocking fibrinolysis, amplify coagulation [31]. The elevation of D-dimer in our patients at baseline in parallel to that of other inflammation biomarkers shows that D-dimer is an acute phase reactant [32,33]. Once anticoagulant treatment had been initiated, the subsequent D-dimer decrease makes the interpretation of D-dimer more complex, although D-dimer measured on D<sub>5</sub> still predicted early death.

Finally, in our cohort, TG parameters measured on D<sub>0</sub>, namely, ETP and velocity, were predictive of the presence of ischemic parenchymal lesions and a greater number of thrombosed sinuses. In the literature, to our knowledge, no study had previously evaluated TG as a predictor of CVST evolution. TG assay is a global coagulation assay that may be altered in hypercoagulable states [12,33] or different types of endothelial injury [34–36]. In our study, lower ETP<sub>5PM</sub> was associated only with hemorrhagic parenchymal lesion development.

The strengths of our study were a prospective study design, with a prolonged follow-up, together with clinical and imaging evaluation at similar time points, including the evolution of parenchymal brain lesions and functional outcomes. However, our study has some limitations. Whereas inflammation markers and D-dimer are routinely performed, TG assay is performed only in some laboratories, and the calibrated automated thrombogram system is poorly standardized. We had a few severe clinical presentations. However, Coutinho et al. [37] showed an improvement over time in initial CVT presentations due to improved diagnostic methods. We have demonstrated that the FPCCVT cohort had similar clinical, radiological, biological, and etiological characteristics to the historical International Study on Cerebral Vein and Dural Sinus Thrombosis cohort, suggesting the generalizability of our results. Contrarily, clinical prediction of CVST outcomes is likely complicated, involving several patient characteristics,

especially underlying comorbid conditions. Also, we could not assess race or ethnicity as a social determinant related to our findings for regulatory reasons. The power was limited in that we only had 5 deaths and therefore could not perform age-adjusted or multivariable analysis.

In conclusion, we reported here that 2 widely available biomarkers, namely hs-CRP and D-dimer, could help predict early death in CVST in addition to patient characteristics. These results need to be validated in external cohorts.

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## ETHICS STATEMENT

The study was performed in accordance with the Declaration of Helsinki. The institutional review board (person committee protection of Rouen University Hospital) and a national ethical committee approved the study. An informed consent was obtained from all subjects.

## AUTHOR CONTRIBUTIONS

P.B., V.S. and E.M.F. performed analysis, drafted manuscript. A.T.B. and V.L.C.D. are the principal investigators of this research program and revised the manuscript for important intellectual content, and are accountable for all aspects of the work. All other authors are investigators from the different centers. They are listed in order of the number of inclusions and participated in the proofreading of the manuscript. All authors contributed to the article and approved the submitted version.

## RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

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#### SUPPLEMENTARY MATERIAL

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