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Evaluation of plasma d-dimer plus fibrinogen in predicting acute CVST

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Abstract

Background—Prompt diagnosis of cerebral venous sinus thrombosis is a challenge owing in part to its complex and nonspecific early clinical symptoms.

Objective—This study aims to evaluate the value of clinically useful biomarkers (D-dimer and fibrinogen) for cerebral venous sinus thrombosis prediction.

Methods—Two-hundred and thirty-three suspected cerebral venous sinus thrombosis patients were enrolled in this prospective study. Thirty-four cases confirmed as cerebral venous sinus thrombosis using imaging modalities, whereas the other 199 cases served as mimic controls. Plasma samples of 34 healthy controls were further collected from age- and gendermatched volunteers. D-dimer and fibrinogen levels of all patients and controls were measured before imaging and treatment. The dynamic D-dimer and fibrinogen levels in cerebral venous sinus thrombosis cases after anticoagulation were monitored for up to 180 consecutive days.

Results—At admission before treatment the average D-dimer and fibrinogen levels in cerebral venous sinus thrombosis group were 968.9 ± 160.1 mg/l and 6.9 ± 1.3 g/l, both of which were significantly elevated when compared with that of the controls. In cerebral venous sinus thrombosis patients, 94.1% had D-dimer elevation, 73.5% had fibrinogen elevation, and 67.6% had both elevated D-dimer and fibrinogen. During acute phase, the sensitivity and specificity of predicting cerebral venous sinus thrombosis using only D-dimer were 94.1% and 97.5%, whereas that of D-dimer in combination with fibrinogen were 67.6% and 98.9%. After administering

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anticoagulation, D-dimer levels gradually recovered; however, fibrinogen levels fluctuated with 33.3% of the patients still exhibiting elevated values up until 180 days.

Conclusions—D-dimer may serve as an important screening tool to determine the urgency of obtaining magnetic resonance imaging/magnetic resonance venography or digital subtraction angiography in patients presenting with clinical symptoms that are suspected of cerebral venous sinus thrombosis. Furthermore, D-dimer in combination with fibrinogen may increase the predictive value of acute cerebral venous sinus thrombosis.

Keywords

acute; cerebral venous sinus thrombosis; d-dimer; fibrinogen

Introduction

Cerebral venous sinus thrombosis (CVST) is an uncommon and curable sub-type of stroke that carries low mortality once properly diagnosed and treated. This condition is usually seen more in younger individuals. However, owing to its complex and nonspecific constellation of symptom presentation, especially during acute phase, it may prove lethal if misdiagnosed or if treatment delays (1). Studies have shown poor clinical outcomes in about 10% of all CVST cases (2). In fact, one particular study reported that an initial misdiagnosis of CVST could occur in up to 73% of patients. In addition, delays in reaching to a diagnosis for over 10 days can also happen in 40% of patients admitted to the hospital (3).

Magnetic resonance venography (MRV) has shown to provide high sensitivity and specificity for the diagnosis of chronic CVST (4). Magnetic resonance imaging (MRI) in combination with MRV and digital subtraction angiography (DSA) are currently considered to be the gold standard for diagnosing CVST (5). However, it should be noted that not all CVST patients can undergo MR examination in the emergency setting because of logistical constraints of the hospital setting (5). In addition, MRI is not always positive for diagnosing CVST during its acute phase (5). Furthermore, DSA is not commonly used in emergency rooms (6), and computed tomography (CT) scanning has its own limitations in diagnosing acute CVST (7).

Incidence of CVST in children and neonates has been reported to be as high as seven cases per million per year and in adults it is between three and four cases per million per year (8,9). Arriving at a prompt diagnosis is the key to decrease mortality and morbidity in addition to improving clinical outcomes. CVST can prove to be life threatening once treatment is delayed; even standard anticoagulation and/or thrombolysis would not be able to reverse or stop the deterioration of neurological function (10). Canhao P *et al.* reported an observational study of 624 CVST patients who underwent standard anticoagulation treatment of which 4.3% died during the acute phase and 3.4% died within 30 days of symptom onset (11). To augment the need for a more efficient technique to predict CVST, the potentially important role of obtaining plasma biomarkers becomes apparent. Not only can biomarkers be readily obtained and available in the emergency department but they can also stratify and subdivide patients with CVST requiring access to urgent MRI/MRV.

Though not concordant, previous studies have found the importance of plasma d-dimer levels in CVST prediction. In one report, almost all MRV-confirmed CVST cases had abnormally elevated d-dimer levels (12). Nevertheless, other studies have not shown such a strong link between d-dimer levels and CVST such as one where among five cases of CVST, only three cases had elevated d-dimer levels (13). The reasons underlying the discrepancy are not clear, but the small number of cases that have been reported in addition to the nonrigid method of sample collection in those studies may have affected the final result.

Fibrinogen is a protein that functions as a coagulation factor in plasma. Pathological fibrinogen elevation points to a hypercoagulable state and increases the possibility of thrombosis (14). Previous reports have shown that a high level of fibrinogen has been strongly associated with arterial stroke progression and severity (14). D-dimer, on the other hand, is a specific degradation product of the cross-linked fibrin monomers (derived from fibrinogen) after being hydrolyzed by plasmin (15–18). Generally, d-dimer elevation indicates secondary endogenous fibrinolysis (15,17). However, the course of all the thrombosis is not necessarily followed by secondary endogenous fibrinolysis. Nevertheless, abnormal fibrinogen elevation in combination with d-dimer elevation can further augment and reinforce the confirmation of new thrombus formation and secondary endogenous fibrinolysis (15–18). Hence, d-dimer and fibrinogen serve as two closely related biomarkers in stroke and other thrombotic vascular diseases (16,19). Moreover, d-dimer and fibrinogen are inexpensive and commonly used in the clinical setting and can easily be obtained and assayed with standard laboratory equipment. However, it should also be noted that d-dimer levels may rise in certain pathological states besides thrombosis such as cancer (20), liver disease (21), kidney disease (14), organ-graft rejection (22), and thrombolysis treatment (15). Therefore, to increase the effectiveness of detecting thrombosis, a combination of d-dimer with fibrinogen assay becomes necessary.

Although d-dimer elevation has been shown to be associated with CVST, its predictive value in diagnosing CVST has not been well established clinically (23,24). In this study, we aim to re-evaluate the value of plasma d-dimer and fibrinogen levels in CVST prediction with larger case numbers of patients stratified according to either an acute CVST state or mimic (suspected patient) controls as well as those in matching healthy controls.

Additional features in this study include the following: (1) all patients were enrolled during the acute phase (within seven-days of symptom onset and before imaging confirmation and anticoagulation treatment); (b) dynamic changes of d-dimer in acute CVST cases were monitored during 180 days after administering anticoagulation treatment; and (c) plasma fibrinogen in combination with d-dimer levels were also monitored synchronously. These aforementioned features were taken together and made our present study distinctly different from previous ones (23,25–27).

Subjects and methods

Patient enrollment

Our study design was approved by the local research ethics committee. All 233 emergency cases suspected with acute CVST came from two stroke service centers in Beijing, China. Patients were consecutively enrolled from August 2004 to September 2010 after obtaining a signed informed consent. The patient group was stratified into two groups according to the final MR or DSA imaging results: CVST and the non-CVST group (also known as 'mimic controls').

A total of 34 cases in the CVST group were treated with low molecular weight heparin (LMWH) subcutaneously for 10 days and then by warfarin (orally), keeping the international normalized ratio (INR) between 2 and 2.5 during the course of the study. Two cases underwent recombinant tissue plasminogen activator (rtPA) intravenous thrombolysis on day 8 and 10, respectively, after LMWH treatment because of progressive neurological deterioration and as such failed to meet the inclusion criteria of the study.

Inclusion criteria—The following were the inclusion criteria in order to qualify for the study:

- age less than 45 years;
- symptom onset within seven-days, including unexplained headaches, visual changes, seizures, and impaired consciousness with focal neurological deficit; and
- the final CVST diagnosis was to be confirmed through MRI/MRV or DSA.

Exclusion criteria—The following were the exclusion criteria:

- symptoms such as unexplained headaches, visual changes, seizures, and impaired consciousness existing for more than seven-days;
- atrial fibrillation demonstrated by electrocardiogram, or the presence of congestive heart failure;
- disseminated intravascular coagulopathy;
- deep venous thrombosis (DVT) or pulmonary embolism;
- chronic or restoration phase of CVST;
- malignancy;
- presence of other systemic disease or states with a clear etiology that affect d-dimer and fibrinogen levels such as pregnancy, rheumatoid arthritis, septicemia, and meningitis (2,28,29);
- severe hepatic and renal dysfunction;
- patients who underwent anticoagulant and/or thrombolytic treatment before enrolment;

- confounding factors, such as brain trauma, parasitic infection, and other brain damage with a clear etiology were excluded after undergoing emergent brain CT;
- patients who did not agree to enroll in this study as well as those who died within 24 h of arrival to the hospital were also excluded; and
- Patients treated with the medications that directly affect levels of plasma d-dimer and fibrinogen (i.e. rtPA) before enrollment were rejected.

Methods

Blood samples were collected from 233 consecutive patients. These patients showed up in the emergency room with an unexplained headache that had been ongoing for or within seven-days of symptom onset. In addition, based on the presenting symptoms, these patients were clinically suspected to have a high suspicion of CVST, before obtaining any imaging studies or treatment.

Thirty-four cases out of the consecutive 233 patients were finally confirmed with the diagnosis of acute CVST with MRI/MRV and/or DSA imaging within 72 h of admission. These 34 cases also matched the inclusion criteria for enrolment, whereas the other 199 cases were excluded from a diagnosis of CVST and instead formed the 'mimic controls' group. Furthermore, 34 healthy controls were obtained that were age-and gender-matched volunteers. This enabled us to compare plasma d-dimer and fibrinogen levels in CVST patients with the mimic and healthy controls. In the CVST group, dynamic d-dimer and fibrinogen levels during anticoagulation treatment were monitored at 7-, 15-, 30-, 90-, and 180-day interval, and the sinus recanalization status was followed up with imaging at 30 days, 90 days, and 180 days after enrollment. Characteristics and medical histories of patients in the CVST group were also collected (Table 1).

d-dimer and fibrinogen levels were measured by immunoturbidimetry assay with the coagulational laboratory autoanalyzer (ACL2000; Instrumentation Laboratory, Milan, Italy). The cut-off values were equal or greater than 500 mg/l for d-dimer and equal or greater than 4 g/l for fibrinogen, as in accordance to the normal criteria of our laboratory and the criteria of other previously used published studies (29–31). MRI/MRV imaging was performed on the 1.5 Tesla machine (Sigma GE Medical System, Chicago, WI, USA).

Statistics

Descriptive statistics were calculated for all data of samples assays. All the values in the text and tables are presented as mean standard deviation ($\bar{x} \pm s$) and analyzed with Student's t-test. The percentages of the cases with abnormally elevated d-dimer and/or fibrinogen in every group were analyzed with chi-square test. P-values less than 0.05 were considered to be statistically significant. The specificity and sensitivity of d-dimer and fibrinogen on CVST prediction were described using Receiver operating characteristic curve (ROC). All calculations were performed with the spss 13.0 statistical package (SPSS Inc. Chicago, IL 60606- 6412, USA).

Results

Characteristics of the CVST cases

Table 1 displays the clinical data of the acute CVST cases before anticoagulation treatment in which 97% of patients had severe and unexplained headache and 23.5% had focal neurological symptoms. In addition, 29.4% had a history of oral contraceptive use and 35.3% had a history of infection within two to three-weeks (gingivitis, tympanitis, and flu like symptoms with extended period of fever). However, 20.6% had no clearly confirmed etiology. The most common sinuses involved were horizontal superior sagittal sinus (H-SSS) and vertical superior sagittal sinus. Four cases involved with the H-SSS were also associated with right lateral transverse sinus. In addition, two more cases involving the H-SSS were also associated with right medial transverse sinus.

Focal brain lesions seen during imaging using MRI/MRV and DSA included: unilateral or bilateral cerebral ischemic infarction, hemorrhagic infarction, 'cord sign' in the involved sinus, and blood signal loss. However, positive imaging was not always seen in all CVST patients who presented within the acute phase (the details of the positive imaging rates were showed in Table 1).

The non-CVST 'mimic' controls were diagnosed with the following conditions: migraine in 30.7%, tension-type headaches in 44.7%, viral meningitis in 11.6%, and idiopathic intracranial hypertension in 13.1% (Table 2). Thirteen patients had coronary artery disease, and 12 cases had lacunar infarction. All five cases in the 'mimic' group with d-dimer elevation had concomitant coronary artery disease of which two also had cerebral lacunar infarction.

The value of D-dimer and fibrinogen in acute CVST prediction

Baseline levels of d-dimer and fibrinogen in the CVST group were compared with the two control groups (Figs 1 and 2 and Table 2). The average plasma d-dimer level in the CVST group ($987.7 \pm 324 \mu\text{g/l}$) was significantly higher than either the mimic ($343.23 \pm 102 \mu\text{g/l}$) or healthy control ($320.22 \pm 98 \mu\text{g/l}$) groups (Fig. 1). The average plasma fibrinogen level in the CVST group ($6.87 \pm 1.25 \text{ g/l}$) was also significantly higher than mimic ($3.22 \pm 0.55 \text{ g/l}$) and healthy controls ($2.93 \pm 0.68 \text{ g/l}$) (Fig. 2).

Among the CVST group, the average d-dimer levels in cases with positive radiological signs (including ischemic infarct, hemorrhagic infarct, and brain edema) was $1016.7 \pm 211 \text{ mg/l}$ as opposed to $765.7 \pm 143 \text{ mg/l}$ in those CVST cases without radiological signs of the aforementioned pathologies. In addition, the average duration of d-dimer elevation was 16.5 ± 4.5 days in those CVST cases with positive radiological signs vs. 7.5 ± 2.5 days in those CVST cases without radiological signs ($P < 0.01$ for all observations).

Among the CVST patients, 94.1% (32/34) had d-dimer elevation, 73.5% (25/34) had fibrinogen elevation, and 67.6% (23/34) had both d-dimer and fibrinogen elevation. In addition, 26.5% (9/34) had d-dimer elevation but normal fibrinogen, and 5.9% (2/34) had normal d-dimer levels but elevated fibrinogen (6.8 g/l and 7.2 g/l). There was no CVST patient with normal d-dimer and fibrinogen.

In the ‘mimic’ control cases, only 2.5% (5/199) had d-dimer elevation, 16.1% (32/199) had fibrinogen elevation, 1% (2/199) had both d-dimer and fibrinogen elevation, and 83.9% (167/199) had the normal levels of d-dimer and fibrinogen. In healthy control cases, 8.8% (3/34) had mild fibrinogen elevation, and no cases had d-dimer elevation. On comparing the ‘mimic’ with healthy controls with respect to the elevation rates of d-dimer, fibrinogen and both, the percentages were 2.5%, 16.1%, 1% in the mimic group vs. 0, 8.8%, and 0 in the healthy controls, respectively ($P < 0.05$ for all observations).

The sensitivity and specificity of d-dimer and fibrinogen levels in acute phase are displayed in Table 3. The sensitivity (94.1%), specificity (97.5%), positive predicting value (86.5%) and negative predicting value (98.9%) of d-dimer support its usefulness in CVST prediction. However, the sensitivity (73.5%), specificity (83.9%), and positive predicting value (43.9%) of fibrinogen were lower than that of d-dimer, although its negative predicting value was 94.9%. The sensitivity (67.7%), specificity (98.9%), and positive predicting value (92.0%) and negative predicting value (94.7%) of both d-dimer and fibrinogen elevation were also noted.

Dynamic D-dimer and fibrinogen levels in 180 days of anticoagulation

The area under the ROC curves of d-dimer and fibrinogen at acute phase (within seven-days), sub-acute phase (30 days), and late phase (90 days) were analyzed (Figs 3 and 4). The analysis revealed that both d-dimer and fibrinogen had a large area under the ROC curves during acute phase (Figs 3a and 4a). However, at 30 days, the area under the curve narrowed (Figs 3b and 4b); and at the 90-day mark, the area of d-dimer further shrank, but the shrinking of fibrinogen was not as dramatic compared with the d-dimer over the time course (Figs 3c and 4c). This trend indicated that d-dimer was more sensitive and specific than fibrinogen in CVST prediction during acute phase but not in sub-acute and late phase.

By analyzing the dynamic values of plasma d-dimer and fibrinogen at 0, 7, 15, 30, 90, and 180 days after symptom onset in CVST patients, we found that the majority (94.1%) of CVST cases had d-dimer elevation in acute phase, especially within sevendays of symptom onset, but this trend was found to decrease gradually after initiating anticoagulation treatment. MRI/MRV imaging follow-up associated with d-dimer assay revealed that sinus recanalization was negatively correlated with d-dimer decreasing with the correlation coefficient being -99.3 (Table 4). At 30 days of MRI/MRV imaging follow-up, 84.4% of the CVST cases attained sinus recanalization either partially or completely with corresponding clinical symptom improvement (mRS = 0–1). It should be noted that 100% of the cases obtained complete sinus recanalization after 90 days of treatment.

In contrast, plasma fibrinogen elevation can be seen in both acute phase and late phase (73.5% elevation in acute phase and 33.3% elevation in convalescence phase). However, the majority (67.6%) of CVST cases in acute phase had both d-dimer and fibrinogen elevation.

Discussion

Immediate diagnosis and proper treatment would reduce the incidence of death and long-term disability in CVST (32–35). Therefore, establishing a rapid yet clinically applicable

blood test would be of essence, keeping in mind that CVST patients will die from diagnosis and treatment delay.

The following highlights the important findings of our study: in the CVST cases, 94.1% patients were found to have d-dimer elevation, 73.5% have fibrinogen elevation, and 67.6% had both d-dimer and fibrinogen elevation. In contrast, dual elevation of d-dimer and fibrinogen were found only in 1% of mimic controls and were not found at all in healthy controls. Only a few of the 'mimic' cases had d-dimer elevation, whereas fibrinogen elevation was found in some 'mimic' cases and healthy controls.

This finding suggests the potentially important role that d-dimer may have by serving as a useful biomarker for CVST prediction. d-dimer in combination with fibrinogen elevation may also increase the positive predicting value for acute CVST.

Features of this study that differed from the previous research are as follows: first, we reevaluated values of d-dimer in combination with fibrinogen using a larger acute CVST case cohort (34 cases, symptoms onset within seven-days). In addition, our results were also compared with both 'mimic' (the subsequent 199 suspected patient with CVST) and matched healthy controls (34 cases).

Second, our study noted that d-dimer elevation can only be detected in acute phase (94.1% within seven-days) and sub-acute phase (15.6% from 7 to 30 days after symptom onset) but not during the chronic phase. This indicates that only newly formed thrombi can undergo endogenous fibrinolysis and would consequently result in d-dimer elevation that is shown in, as mentioned previously, the acute and sub-acute phases of CVST. By establishing a temporal effect, we were able to highlight the exact time window of the two biomarkers on CVST prediction.

Third, we observed the relation between the dynamic d-dimer in combination with fibrinogen and the MRI outcomes of CVST at the 30 days and 90 days of anticoagulation treatment. By doing so, we were able to reveal the significance of d-dimer and fibrinogen assay during the CVST. Results reveal that recanalization negatively correlated with the decreasing levels of d-dimers.

Taking all of the aforementioned points together, our study distinctly differs from previous ones. Our results strongly point to the presence of d-dimer elevation during acute CVST (23,25–27).

It should be noted that fibrinogen reflects both a hypercoagulable status and that of thrombosis (15,32,33). By virtue of this, fibrinogen elevation may exist in both acute (with newly formed thrombus) and recanalization state (phase of hypercoagulability but not of thrombosis) of CVST. However, at the 30th day, plasma fibrinogen levels were low compared with 15th and 90th day (Table 4). The reason for this discrepancy in plasma fibrinogen levels is not clear but can potentially be attributed to their 'fluctuating levels' during the whole anticoagulation treatment. The fluctuating levels may be due to a number of factors, one being secondary to a mismatch caused by adjusting the dosage of anticoagulant as per the required INR level during treatment. In addition, the plasma

fibrinogen levels can also be affected by how compliant the patient is with regard to taking anticoagulant medications.

In this study, both positive and negative predictive values of d-dimer for acute CVST were very high (Table 3). In contrast, studies focusing on peripheral DVT have reported a relatively low positive predictive value of the d-dimer (33.3% and 8.3%), although negative predictive value was still very high (100% and 97.5%) (33,34). The reason for this discrepancy remains unclear and may be attributed in part because of different mechanisms of origination and progression seen when peripheral DVTs are compared with that of thrombi found in CVST. Additional factors such as differences in age and systemic disease conditions in the patients can also explain the aforementioned discrepancy, among other unexplained factors (35,36).

Though d-dimer elevation is associated with most thrombotic vascular diseases, it should be noted that it stands to be a highly sensitive yet very non-specific thrombus localization test (36). Moreover, plasma d-dimer levels may also vary with a number of factors such as age, gender, the population group, medications as well as the type of assay method used (37,38). Considering the potential confounding factors that may affect the plasma d-dimer levels in our study, we designed two controls (mimic and healthy) and limited the enrollment age to less than 45 years. By doing so, the healthy controls removed any potential interference to the results caused by factors other than thrombotic vascular diseases. The 'mimic' controls would verify the practicality of using plasma d-dimer and fibrinogen levels in a clinical setting.

In this study, five cases in the 'mimic' group with elevated d-dimer levels were also found to have coronary artery disease. In addition, two of the five cases that had both elevated d-dimer and fibrinogen levels experienced cerebral lacunar infarction. Although diagnosis of CVST in the aforementioned five patients cannot be completely eliminated, nevertheless evidence of spontaneous recanalization was never seen.

Though not to be used as a sole and definitive diagnostic tool, plasma d-dimer and fibrinogen levels may help in augmenting and providing an initial screening tool to help decide which patients should undergo emergent MRI/MRV to confirm the diagnoses of CVST in time.

Conclusions

Our study suggests that d-dimer may help to predict which patient should undergo urgent MRI/MRV or DSA when a clinically suspected CVST patient comes to the hospital to expedite the diagnosis of CVST. d-dimer in combination with fibrinogen may increase the predictive value of acute CVST. However, suspected patients with normal plasma d-dimer or fibrinogen should not be excluded from the diagnoses of CVST. A large multicentered trial with higher statistical power is needed to reinforce our findings.

Limitations

We are aware that our study has limitations. First, one of the reasons for high positive predictive value of d-dimer for acute CVST in this study might be due to the exclusion of all the other common risk factors that elevate plasma d-dimer and fibrinogen levels. Second, we were unable to exclude the possibility of external, confounding variables that may affect the readings of plasma d-dimer and fibrinogen before the patients were admitted to the hospital. However, a few factors that were accounted for included age, anticoagulation or thrombolysis medication used, and systematic disease status. Third, besides plasma d-dimer and fibrinogen, which are commonly assessed biomarkers in the clinical setting, other plasma biomarkers may have the same if not a higher predictive value for CVST as well, such as thrombin-antithrombin complexes and soluble fibrin. A large multicenter trial addressing all the limitations and expanding on our study would provide further answers and would potentially reinforce the concept of using plasma d-dimer and fibrinogen to predict the presence of acute CVST.

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Fig. 1.

Plasma D-dimer levels in acute phase of CVST. Within seven-days after symptom onset, plasma D-dimer levels were measured and compared. $**P < 0.001$, CVST vs. mimic control, and CVST vs. healthy control. $n = 34$ for CVST group, $n = 199$ for mimic controls, and $n = 34$ for healthy controls. CVST, cerebral venous sinus thrombosis.

Fig. 2.

Plasma fibrinogen levels in acute phase of CVST. Within seven-days after symptom onset, plasma fibrinogen levels were measured and compared. $**P < 0.001$, CVST vs. mimic controls, and CVST vs. healthy controls. $n = 34$ for CVST group, $n = 199$ for mimic controls, and $n = 34$ for healthy controls. CVST, cerebral venous sinus thrombosis.

Fig. 3.

ROC curves of D-dimer within seven-days, at 30 days, and 90 days after symptom onset. The specificity and sensitivity of D-dimer on CVST prediction were described with ROC curves, $n = 34$ within seven-days, $n = 32$ at 30 days and 90 days after symptom onset. The area under the ROC curves for within seven-days vs. the area under the ROC curves for 30 days and 90 days, all $P < 0.001$. The blue line is the ROC (receiver operating characteristic curve), the green line is the standard curve. CVST, cerebral venous sinus thrombosis.

Fig. 4.

ROC curves of fibrinogen within seven-days, at 30 days, and 90 days. The specificity and sensitivity of fibrinogen on CVST prediction were described with ROC curves, $n = 34$ within seven-days, $n = 32$ at 30 days and 90 days. The area under the ROC curves for within seven-days vs. the area under the ROC curves for 30 days and 90 days, all $P < 0.001$. The blue line is the ROC (receiver operating characteristic curve), the green line is the standard curve. CVST, cerebral venous sinus thrombosis.

Table 1

Demographic and clinical data of patients in CVST group

Patients characteristics (<i>n</i> = 34)	Data
Age (years)	28 ± 9.5 (15–39)
Female/male	25/9
Mean of symptoms' duration (Days)	4.5 ± 2.3 (1–7)
Presenting symptoms, <i>n</i> (%)	
Headaches	33 (97)
Disturbed consciousness	12 (35.3)
Seizures	8 (23.5)
Papilledema	19 (55.9)
Blurred vision	9 (26.5)
Brain imaging lesions <i>n</i> (%)	
Focal neurological signs	8 (23.5)
Ischemic infarction	6 (17.6)
Hemorrhagic infarction	2 (5.9)
Cerebral hemorrhage	0
Cord sign	2 (5.9)
Brain edema	11 (32.3)
History <i>n</i> (%)	
Oral contraceptive	10 (29.4)
Spontaneous abortion	3 (8.8)
Infection (meningitis, cold, otitis, naso sinusitis)	12 (35.3)
Nonspecial history	9 (26.5)
Normal pregnancy	0
Hypercoagulable status <i>n</i> (%)	
APS	2 (5.9)
Antithrombin III deficiency	1 (2.9)
Protein C deficiency	3 (8.8)
Protein S deficiency	4 (11.8)
Dehydration	1 (2.9)
Affected sinus segment, <i>n</i> (%)	
H-SSS	9 (26.5)
V-SSS	7 (20.6)
SC	2 (5.9)
Straight sinus	2 (5.9)
Right-LTS	7 (20.6)
Right -MTS	6 (17.6)
Right -SS	2 (5.9)
Left-LTS	2 (5.9)
Left-MTS	2 (5.9)
Left-SS	1 (2.9)

Note: CVST in four cases involves H-SSS associated with right-LTS and in two cases involves H-SSS associated with right-MTS. H-SSS, horizontal superior sagittal sinus; V-SSS, vertical superior sagittal sinus; MTS, medial transverse sinus; LTS, lateral transverse sinus; SS, sigmoid sinus; SC, sinus confluence; APS, antiphospholipid syndrome; CVST, cerebral venous sinus thrombosis.

Table 2

D-dimer and fibrinogen in CVST, mimic and healthy controls

Disease abnormal items	CVST % (abnormal/total)	Mimic control % (abnormal/total number)					Total	Healthy control
		Migraine	Tension-type headache	Viral meningitis	IIH			
D-dimer	94.1 (32/34)	3.2 (2/61)	1.1 (1/89)	3.8 (1/23)	3.8 (1/26)	2.5 (5/199)	0% (0/34)	
Fibrinogen	73.5 (25/34)	18.0 (11/61)	14.6 (13/89)	19.2 (5/26)	11.5 (3/26)	16.1 (32/199)	8.8 (3/34)	

Note: The ratio of cases with elevated fibrinogen: CVST vs. mimic control, $\chi^2 = 51.864$, and CVST vs. healthy control, $\chi^2 = 26.138$, all $P < 0.001$. The ratio of cases with elevated D-dimer: CVST vs. mimic control, $\chi^2 = 165.766$, and CVST vs. healthy control, $\chi^2 = 60.444$, all $P < 0.001$. CVST, cerebral venous sinus thrombosis; IIH, idiopathic intracranial hypertension.

Table 3

Sensitivity and specificity of D-dimer and fibrinogen on predicting CVST

Items	CVST	Mimic control	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
D-dimer						
(+)	32 ^a	5 ^b	94.1	97.5	86.5	98.9
(-)	2 ^c	194 ^d				
Fibrinogen						
(+)	25 ^a	32 ^b	73.5	83.9	43.9	94.9
(-)	9 ^c	167 ^d				
D-dimer + Fibrinogen						
(+)	23 ^a	2 ^b	67.6	98.9	92.0	94.7
(-)	11 ^c	197 ^d				

Note:

^a positive;

^b false positive;

^c false negative;

^d true negative.

CVST, cerebral venous sinus thrombosis.

Table 4

Dynamic changes of percentages of cases for elevated D-dimer, fibrinogen, and the sinus recanalization at 180 days after symptom onset

Follow-up days	Total cases (n)	Fibrinogen elevation % (n)	D-dimer elevation % (n)	Sinus recanalization % (n)
0	34	73.5 (25)	94.1 (32)	0
7	34	64.7 (22)	100 (34)	5.9 (2)
15	32	56.3 (18)	31.3 (10)	62.5 (20)
30	32	40.6 (13)	15.6 (5)	84.4 (27)
90	32	50 (16)	3.1 (1)	100 (32)
180	30	33.3 (10)	0	100 (30)

Note: Two patients were rejected from at the 8th and 10th days after the rtPA use. Two patients lost at the 180 days follow-up. rtPA, recombinant tissue plasminogen activator.