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A retrospective cohort study on a novel marker to predict the severity and prognosis of acute cerebral venous thrombosis: D-dimer to fibrinogen ratio

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Abstract

Background and aim The D-dimer to fibrinogen ratio (DFR) represents an emerging and significant clinical biomarker. However, its correlation with cerebral venous thrombosis (CVT) remains underexplored. This retrospective cohort study aims to elucidate the association between DFR values and the severity and prognosis of CVT.

Methods Severe CVT was defined as the presence of at least 1 of the following risk factors: mental status disorder, coma state, intracranial cerebral hemorrhage, or thrombosis of the deep cerebral venous system. The modified Rankin Scale was utilized to assess functional outcomes. DFR measurements were obtained within 24 h of hospital admission. Logistic regression analysis was employed to determine the prognostic significance of DFR. After Bonferroni correction, a two-tailed P value < 0.017 (0.05/3) was considered statistically significant.

Result A total of 196 patients were included in the study, among whom 85 patients were diagnosed with severe CVT, and 35 and 14 patients experienced short-term and long-term adverse outcomes, respectively. Receiver operating characteristic curve analysis demonstrated that DFR has predictive value for severe CVT, poor short-term and long-term outcomes, with area under the curve values of 0.690 [95% CI: 0.617–0.764, $P < .001$], 0.773 [95% CI: 0.701–0.845, $P < .001$], and 0.754 [95% CI: 0.619–0.886, $P = .002$], respectively. DFR ≥ 0.253 was identified as a significant predictor of severe CVT [adjusted odds ratio (aOR) (95% CI): 2.03 (1.10–3.75), $P = .024$]. Additionally, DFR ≥ 0.322 and DFR ≥ 0.754 were significantly associated with poor short-term outcomes at discharge [aOR (95% CI): 2.63 (1.43–4.76), $P = .002$] and poor long-term outcomes at 12 months [aOR (95% CI): 2.86 (1.32–6.25), $P = .008$], respectively.

Conclusion Elevated DFR is associated with increased severity of CVT. Additionally, higher DFR levels can predict poorer clinical outcomes in CVT.

Keywords Cerebral venous thrombosis, Marker, Severity, Prognosis, D-dimer to fibrinogen ratio

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Introduction

Cerebral venous thrombosis (CVT) is an uncommon, but life-threatening subtype of stroke [1, 2]. Due to its non-specific clinical manifestations and complex imaging presentations, accurate determination of the severity of CVT and diagnosis are often challenging, resulting in significant morbidity and mortality [3]. Therefore, it is important to find relevant methods to effectively predict the severity and outcome of CVT patients and timely intervene to reduce the risk of adverse events and improve the prognosis of patients. Previous studies have explored indicators related to the severity and prognosis of CVT, including inflammatory markers (such as neuron-specific enolase and c-reactive protein) and imaging markers (such as the extent of thrombosis) [4–6]. The results demonstrated that active inflammatory response and extensive thrombosis are significantly associated with the severity and poor prognosis of CVT.

Fibrinogen is a glycoprotein produced mainly by liver cells, which is an important coagulation factor and contributes to the regulation of blood coagulation pathways. Moreover, fibrinogen is also involved in the inflammatory process when brain damage occurs [7, 8]. D-dimer is a fibrin degradation product and has been specifically associated with secondary fibrinolysis. The D-dimer to fibrinogen ratio (DFR) is a derived indicator of fibrinogen and D-dimer. Therefore, DFR is regarded as a composite indicator which was correlated with coagulation and fibrinolysis status and inflammation levels. DFR may reflect both the inflammatory response and thrombosis status of patients, both of which are crucial for assessing the severity and prognosis of CVT.

DFR is a novel coagulation parameter indicates the balance of fibrinolysis and coagulation processes and has clinical value in patients with acute coronary syndrome, acute ischemic stroke and cerebral hemorrhage [9–12]. Previous studies have shown that the DFR can predict the occurrence of thrombotic events [13–18], distinguish the severity of disease [11, 19, 20] and predict the clinical prognosis [11, 12, 21–23]. However, there is no relevant report on the severity and the prognosis of patients with CVT.

Based on the above results, we designed this study to investigate the relationship between DFR value and the severity of CVT and to evaluate the prognostic value of DFR level in CVT.

Methods

A total of 579 patients were reviewed in this retrospective study from September 2010 through July 2023 in Xuanwu Hospital, after identified the diagnosis of CVT by magnetic resonance venography (MRV), computed tomographic venography (CTV), or catheter angiography (DSA). The inclusion and exclusion criteria for the patients are as follows.

Inclusion Criteria:

1. Confirmed diagnosis of CVT.
2. Age > 17 years.
3. Duration from symptom onset to blood sampling within 14 days.

Exclusion Criteria:

1. Presence of conditions potentially affecting D-dimer and fibrinogen levels (including but not limited to malignancies, infectious diseases, deep vein thrombosis, and coronary artery disease).
2. Treatment with anticoagulants (such as low molecular weight heparin or oral anticoagulants) or fibrinolytic agents (e.g., batroxobin) preceding the blood draw.
3. Prior administration of anti-inflammatory or immunosuppressive medications before the collection of blood samples.
4. Lack of comprehensive clinical data encompassing hospitalization and follow-up periods.

In this study, we focused on investigating the potential relationship between CVT and DFR. Due to the possibility of various acute factors affecting D-dimer and fibrinogen levels, thereby interfering with the study results, we excluded patients with acute factors that could significantly influence D-dimer and fibrinogen levels.

Data collection

Within 24 h of admission, patients underwent laboratory tests and imaging studies. Upon confirmation of the diagnosis, a qualified physician determined the specific anticoagulation regimen based on the patient's condition, primarily including low molecular weight heparin bridged to warfarin and novel oral anticoagulants. Some patients also received batroxobin as adjunctive therapy in addition to anticoagulation. Baseline data of age, sex, duration from onset to admission (the time of onset is defined as the time when symptoms appear), clinical manifestation (headache, focal neurological deficit, seizure, mental disorder disease, coma), imaging manifestation (site of thrombosis, number of cerebral venous involved), CVT-related complications [intracranial hemorrhage (cerebral parenchymal hemorrhage and subarachnoid hemorrhage), venous cerebral infarction and cerebral hernia], fibrinogen, and D-dimer were recorded. Baseline laboratory data were defined as those collected within 24 h after admission and before treatment was initiated. Baseline imaging data were defined as the first post-admission imaging data. The use of treatments

during hospitalization was also recorded including endovascular treatment, anticoagulation (anticoagulation alone or anticoagulation combined with batroxobin) and decompressive craniectomy. In addition, the National Institutes of Health Stroke scale (NIHSS) at admission, and modified Rankin Scale (mRS) at discharge and at 12 months were evaluated.

Determination of DFR

The D-dimer level (normal reference value: 0.01–0.5 mg/L) and fibrinogen level (normal reference value: 2–4 g/L) was determined in the coagulation function of the patient within 24 h after admission. The DFR value is the ratio of D-dimer to fibrinogen. Due to the discrepancy in units provided by the laboratory for the two measurements, the D-dimer value needs to be multiplied by 1000 in the calculation. The DFR was calculated using the following formula:

$$\mathrm{DFR} = \frac{\mathrm{D-dimer}\left(\frac{\mathrm{mg}}{\mathrm{L}}\right) \times 10^3}{\mathrm{Fibrinogen}\left(\frac{\mathrm{g}}{\mathrm{L}}\right)}$$

Clinical assessment

To evaluate the effect of baseline DFR on predicting the severity as well as clinical outcome of CVT, we assessed the severity at admission and clinical functional outcome at discharge (short-term outcome) and 12 months (long-term outcome). Severe CVT was assessed with the presence of at least 1 of the following risk factors: mental status disorder, coma state (Glasgow Coma Scale score < 9; score range: 3–15, with the highest score indicating normal consciousness), intracranial cerebral hemorrhage, or thrombosis of the deep cerebral venous system [24]. The clinical functional outcome was assessed with mRS, namely, 0–2 represents good outcome, 3 or more represents poor.

Statistical analysis

Normally distributed continuous variables were presented as mean ± standard deviation (SD) and non-normally distributed continuous variables as median (IQR). Categorical variables were described as number (percentage). The normality of distribution was visually tested with histograms and normal probability plots (Q–Q plots). Student's t or Mann–Whitney U tests were used for continuous data, meanwhile, $\chi 2$ or Fisher exact tests were chosen for categorical data, whichever was appropriate. Binary logistic regression was used to evaluate the predictive power of DFR for the severity and outcome of CVT patient. The effective of baseline DFR for identifying severe CVT and poor outcome were analyzed using receiver operating characteristic curve (ROC) and by calculating the area under the curve (AUC). ROC curve was also applied to determine the optical cut-oof point of DFR level that distinguished between severe and non-severe CVT, and between good and poor outcomes. The multicollinearity problem between DFR and other variables was tested by correlation analysis. Variables with significant collinearity with DFR were not included in the multivariate regression model of DFR's association with severe CVT and prognosis. After Bonferroni correction, a two-tailed P value < 0.017 (0.05/3) was considered statistically significant. All statistical analyses were performed using SPSS 27.0 software (IBM Corp).

Result

Demography data of patients

After screening according to inclusion and exclusion criteria, a total of 196 patients [male: 92 (46.9%); age (mean ± SD): 38.17 ± 13.64] were enrolled in this study eventually. 85 patients [male: 35 (41.2%); age: 38.07 ± 13.59] were diagnosed with severe CVT, while 35 [male: 10 (28.6%); age: 38.29 ± 13.83] and 14 patients [male: 5 (35.7%); age (mean ± SD): 43.21 ± 19.70] experienced short-term and long-term poor outcomes, respectively. The screening process of enrolled patients is shown in the flow chart (Fig. 1). More details of demographic characteristics are shown in Table 1. In this study, fibrinogen, D-dimer, and DFR values did not follow a normal distribution. Therefore, results were presented using quartiles, and all related analyses employed non-parametric tests.

DFR and the severity of CVT

A cohort of 85 patients met the diagnostic criteria for severe CVT, manifesting mental status disorder (15.3%), deep cerebral venous thrombosis (17.6%), coma (14.1%), and cerebral hemorrhage (76.5%). Beyond the hallmarks of severe CVT, these patients also exhibited significantly elevated incidences of focal neurological deficits (38.8% vs. 25.2%, $P = .002$), seizures (44.7% vs. 24.3%, $P < .001$), venous cerebral infarction (70.6% vs. 35.1%, $P < .001$), endovascular interventions (47.1% vs. 28.8%, $P = .009$), and decompressive craniectomy (8.72% vs. 0%, $P = .007$) compared to those with non-severe CVT. Notably, severe CVT patients had significantly higher DFR values (median [IQR]: 0.38[0.20, 0.82] vs. 0.17[0.07, 0.44], $P < .001$) compared to non-severe CVT (Table 1).

Significant difference in DFR values were observed in the subgroup analysis, with all significance levels reaching below 0.001. Patients with seizures (median [IQR]: 0.42[0.22, 1.01] vs. 0.18[0.09, 0.45], $P < .001$), venous infarction (median [IQR]: 0.37[0.20, 0.75] vs. 0.15[0.07, 0.46], $P < .001$), mental status disorder (median [IQR]:0.67[0.26, 1.12] vs. 0.23[0.10, 0.54], $P < .001$), coma (median [IQR]:0.67[0.25, 1.12] vs. 0.23[0.10, 0.54], $P < .001$), and cerebral hemorrhage (median

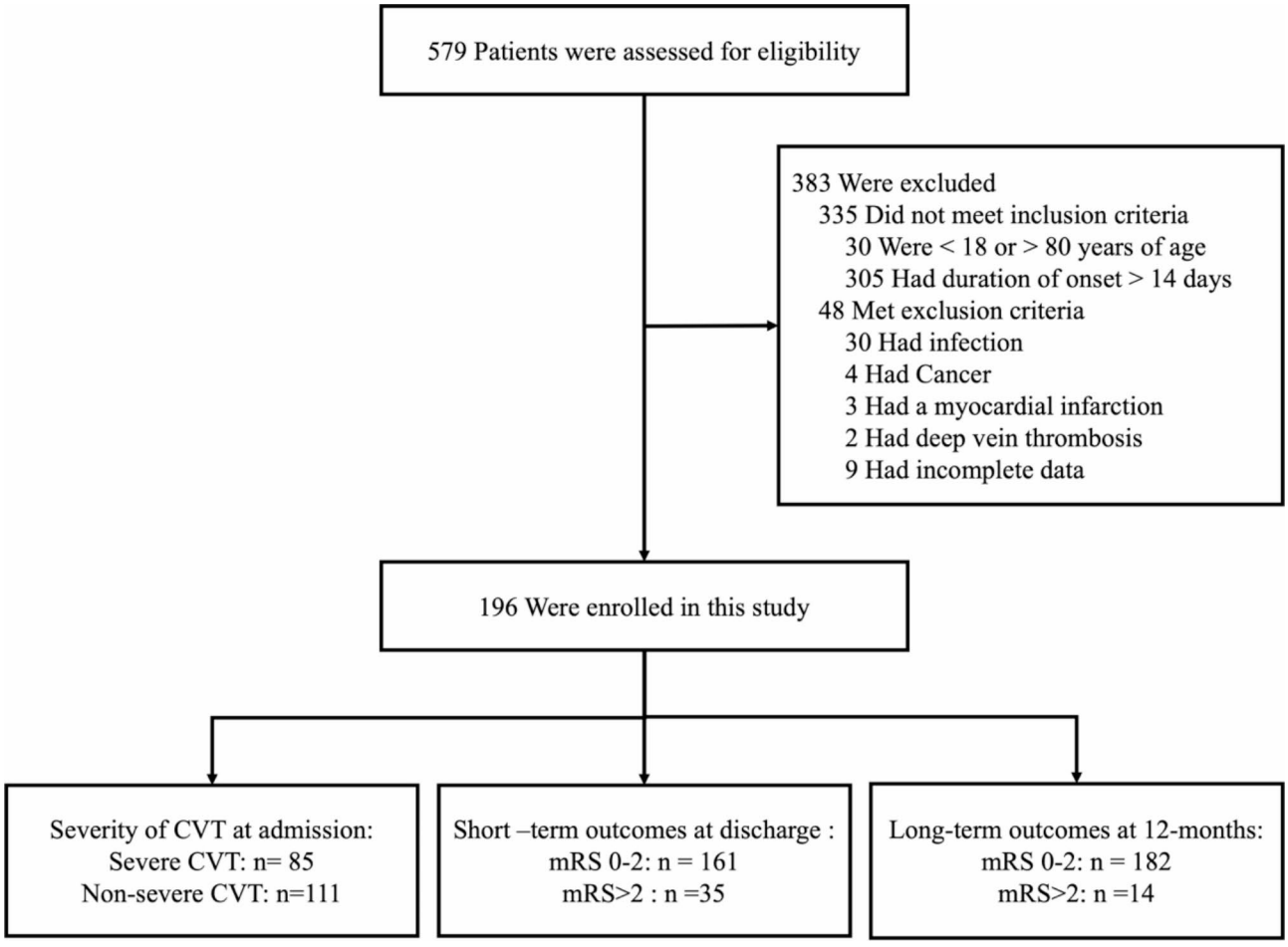

Fig. 1 Flow-chart. CVT: cerebral venous thrombosis; mRS: modified Rankin Scale

[IQR]:0.38[0.21, 0.91] vs. 0.19[0.09, 0.48], $P<.001$) have higher DFR level compared to their counterparts without these conditions (Supplementary Table 1). In other subgroups, including headache, neurological deficits, multiple venous thromboses, and deep cerebral venous thrombosis, no significant differences in DFR levels were observed.

ROC curve analysis underscored DFR's predictive capability for severe CVT, achieving an AUC of 0.690 (95% CI: 0.617–0.764, $P<.001$) with an optimal cut-off value of 0.253 (sensitivity 68.2% [95%CI: 64.9–71.6], specificity 64.0% [95%CI: 60.9–67.3]). (Fig. 2.a). DFR was included in the regression analysis as a categorical variable (≥0.253 or <0.253).

Univariate logistic regression analysis showed that DFR≥0.253 was significant predictor of severe CVT [odds ratio (OR) (95% CI): 2.89 (1.57–5.34), $P<.001$] (Supplementary Table 2). After adjusting all variables, multivariate logistic regression analysis showed that DFR≥0.253 was also significant predictor of severe CVT [adjusted OR (95% CI): 1.95 (1.05–3.61), $P=.033$]. This association persisted even after adjusting for variables demonstrating a clear correlation in the univariate analysis [adjusted OR (95% CI): 2.03 (1.10–3.75), $P=.024$]. (Fig. 3).

DFR and short-term outcome of CVT

A cohort of 196 patients was stratified into two groups based on their mRS scores at discharge, delineating good versus poor short-term outcomes. Notably, the frequency of male patients in the poor prognosis group was significantly diminished compared to the good outcome cohort (28.6% vs. 50.9%, $P<.001$). Patients with poor short-term outcomes demonstrated a higher DFR (median [IQR]: 0.71[0.35, 1.10] vs. 0.20[0.10, 0.47], $P<.001$), a shorter interval from symptom onset to hospital admission (mean±SD: 7.46±5.90 days vs. 10.08±5.78 days, $P=.020$), and an increased prevalence of focal neurological deficits (62.9% vs. 24.2%, $P<.001$), seizures (68.6% vs. 25.5%, $P<.001$), venous infarctions (85.7% vs. 42.9%, $P<.001$), mental status alterations (28.6% vs. 1.9%, $P<.001$), coma (28.6% vs. 1.2%, $P<.001$), cerebral hemorrhages (71.4% vs. 24.8%, $P<.001$), and severe CVT (82.9% vs. 34.8%, $P<.001$). Additionally, interventions such as

Table 1 Baseline characteristics

Variables	Total patients ($n=196$)	Severe CVT ($n=85$)	Non-severe CVT ($n=111$)	*P* value
Male, n (%)	92 (46.9%)	35 (41.2%)	57 (51.4%)	0.157
Age, years (mean ± SD)	38.17 ± 13.64	38.07 ± 13.59	38.24 ± 13.73	0.930
Duration from onset to admission, days	9.61 ± 6.07	8.07 ± 5.84	10.79 ± 6.00	0.002
Etiology				
Pregnancy	22 (11.2%)	10 (11.8%)	12 (10.8%)	0.834
Oral contraceptives	14 (7.1%)	6 (7.1%)	8 (7.2%)	0.968
Hyper-homocysteinemia	17 (8.7%)	8 (9.4%)	9 (8.1%)	0.748
Systemic diseases	16 (8.2%)	6 (7.1%)	10 (9.0%)	0.621
Clinical manifestation				
Headache	171 (87.2%)	75 (88.2%)	96 (86.5%)	0.716
Focal neurological deficit	61 (31.1%)	33 (38.8%)	28 (25.2%)	0.042
Seizure	65 (33.2%)	38 (44.7%)	27 (24.3%)	< 0.001
Coma	12 (6.1%)	12 (14.1%)	0 (0%)	< 0.001
NIHSS scores at admission	1 (0, 2)	2 (0–3)	0 (0,0)	0.002
Imaging manifestation				
More than two venous thrombosis	135 (68.9%)	56 (65.9%)	79 (71.2%)	0.428
Venous cerebral infarction	99 (50.5%)	60 (70.6%)	39 (35.1%)	< 0.001
Markers of sever CVT				
Mental status disorder	13 (6.6%)	13 (15.3%)	0 (0%)	< 0.001
Deep cerebral venous thrombosis	15 (7.7%)	15 (17.6%)	0 (0%)	< 0.001
Cerebral hemorrhage	65 (33.2%)	65 (76.5%)	0 (0%)	< 0.001
Treatment				
Endovascular treatment	72 (36.7%)	40 (47.1%)	32 (28.8%)	0.009
Anticoagulation				0.970
Anticoagulation alone	115 (58.7%)	50 (58.8%)	65 (58.6%)	
Anticoagulation combined with batroxobin	81 (41.3%)	35 (43.2%)	46 (41.4%)	
Decompressive craniectomy	7 (3.6%)	7 (8.2%)	0	0.007
DFR$\times 10^{-3}$, median (IQR)	0.25(0.11, 0.63)	0.38 (0.20, 0.85)	0.17 (0.07, 0.44)	< 0.001
mRS (0–2) at admission	140 (71.4%)	48 (56.5%)	92 (82.9%)	< 0.001

CVT: cerebral venous thrombosis; DFR: D-dimer to fibrinogen ratio; NIHSS: National Institutes of Health Stroke scale; mRS: modified Rankin Scale

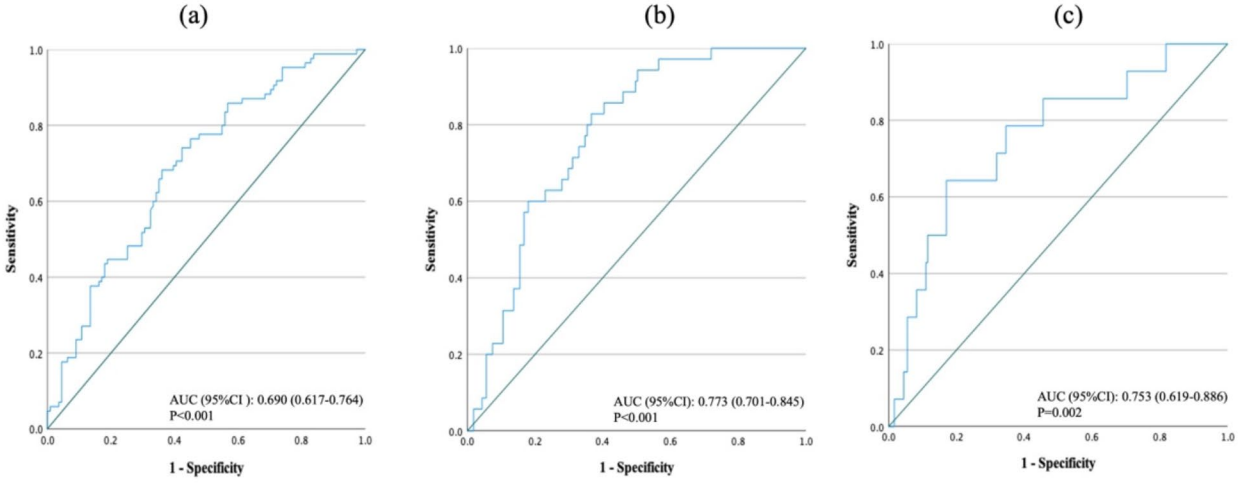

Fig. 2 Receiver operating characteristic curve for DFR on predicting severe CVT (**a**), poor short-term outcome (**b**) and poor long-term outcome (**c**). AUC: area under the curve, CI: confidence interval

Variables, n (%) / mean ± SD	Non-severe CVT	Severe CVT	aOR (95% CI)
Model 1			
DFR≥0.253	0.64 ± 0.64	0.35 ± 0.45	1.95 (1.05, 3.61)*
Sex	35 (41.2%)	57 (51.4%)	0.68 (0.35, 1.33)
Age	38.07 ± 13.59	38.24 ± 13.73	1.01 (0.98, 1.03)
Duration from onset to admission	8.07 ± 5.84	10.79 ± 6.00	0.93(0.88, 0.98)*
Focal neurological deficit	33 (38.8%)	28 (25.2%)	0.92 (0.43, 1.99)
Seizure	38 (44.7%)	27 (24.3%)	0.91 (0.42, 2.00)
Venous cerebral infarction	60 (70.6%)	39 (35.1%)	0.25 (0.12, 0.52)**
Model 2			
DFR≥0.253	0.64 ± 0.64	0.35 ± 0.45	2.03 (1.10, 3.75)*
Duration from onset to admission	8.07 ± 5.84	10.79 ± 6.00	0.94 (0.88, 0.99)*
Focal neurological deficit	33 (38.8%)	28 (25.2%)	0.92 (0.44, 1.93)
Seizure	38 (44.7%)	27 (24.3%)	0.91 (0.42, 1.98)
Venous cerebral infarction	60 (70.6%)	39 (35.1%)	0.25 (0.12, 0.51)**

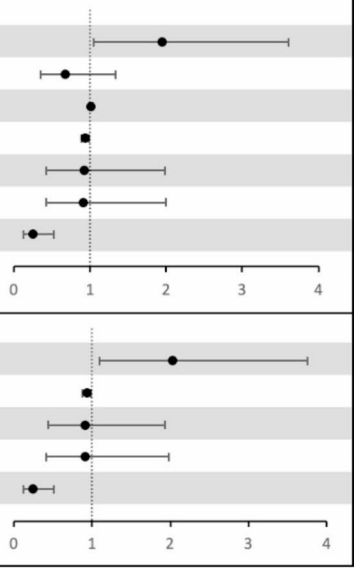

Fig. 3 Multivariate logistic regression analyses for association of variables with severe CVT. DFR: D-dimer to fibrinogen ratio; aOR: adjusted odds ratio; CI: Confidence interval. Model 1: Multivariate regression models constructed for all variables. Model 2: The multivariate regression model is constructed in the univariate regression analysis of variables with significant correlation with DFR. * $P < .05$; ** $P < .017$

endovascular treatments (60.0% vs. 31.7%, $P<.001$) and decompressive craniectomy (20.0% vs. 0%, $P<.001$) were markedly higher in the poor outcome group. These findings are detailed in supplementary Table 3.

Variables exhibiting significant collinearity with DFR are detailed in supplementary Table 4, including duration from onset to admission (correlation coefficient: -0.26, $P=.000$), seizure (0.22, $P=.000$), mental status disorder (0.17, $P=.018$), coma (0.19, $P=.007$), venous cerebral infarction (0.17, $P=.018$), cerebral hemorrhage (0.23, $P=.001$), and deep cerebral venous thrombosis (0.14, $P=.049$). These variables were not included as confounding factors in the multivariate logistic regression analysis examining the correlation between DFR and prognosis.

The ROC curve for baseline DFR underscored its predictive utility for discerning poor short-term outcomes, with an AUC of 0.773 (95% CI: 0.701–0.845, $P<.001$). An optimal DFR cutoff of 0.322 was identified, exhibiting a sensitivity of 82.9% (95%CI: 78.6–87.1) and a specificity of 63.4% (95%CI: 59.4–67.6) (Fig. 2.b). DFR was included in the regression analysis as a categorical variable (≥0.322 or <0.322).

Univariate logistic regression analysis identified DFR≥0.322 as a significant forecaster of adverse short-term outcomes [OR (95% CI): 2.70 (1.51–4.76), $P<.001$] (Supplementary Table 5). Multivariable logistic regression, refined to exclude variables showing significant collinearity with DFR, reaffirmed the predictive value of DFR≥0.322 for poor short-term prognosis [adjusted OR (95% CI): 2.63 (1.47–5.88), $P=.003$], even after adjusting for factors closely associated in univariate analysis [adjusted OR (95% CI): 2.63 (1.43–4.76), $P=.002$] (Fig. 4).

DFR and long-term outcome of CVT

A total of 196 patients were stratified into two cohorts based on their 12-month mRS scores, delineating groups with either good or poor long-term outcomes. Baseline demographics and clinical characteristics are detailed in supplementary Table 6. Analysis revealed that patients categorized within the poor long-term outcome group exhibited significantly elevated DFR levels (median [IQR]: 0.89[0.36, 1.43] vs. 0.24[0.11, 0.57], $P=.002$) compared to their counterparts with good outcomes. Furthermore, the poor outcome group was characterized by a notably shorter median interval from symptom onset to hospital admission (4.479±5.90 vs. 9.98±6.06, $P=.020$), alongside increased incidences of seizures (71.4% vs. 28.1%, $P<.001$), venous infarctions (92.9% vs. 47.3%, $P=.001$), mental status disorders (28.6% vs. 1.9%, $P<.001$), coma (42.9% vs. 3.3%, $P<.001$), cerebral hemorrhages (64.3% vs. 30.8%, $P=.016$), and severe CVT (78.6% vs. 40.7%, $P=.006$). Additionally, the utilization of decompressive craniectomy was significantly more frequent in the poor long-term outcome group (21.4% vs. 2.2%, $P=.009$).

The ROC curve analysis for baseline DFR confirmed its predictive capability regarding poor long-term outcomes, with an AUC of 0.753 (95% CI: 0.619–0.886, $P=.002$). The optimal DFR threshold was determined to be 0.754, achieving a sensitivity of 64.3% (95%CI: 56.2–72.4) and a specificity of 83.0% (95%CI: 73.9–92.9) (Fig. 2.c). DFR

Variables , n (%) / mean ± SD	Good short-term outcome (n=161)	Poor short-term outcome (n=35)	aOR (95%CI)
Model 1			
Male	82 (50.9%)	10 (28.6%)	0.31 (0.11, 0.88)*
Age, years	38.14 ± 13.64	38.29 ± 13.83	1.00 (0.97, 1.04)
Headache	143 (88.8%)	28 (80.0%)	0.32 (0.10, 1.04)
Focal neurological deficit	39 (24.2%)	22 (62.9%)	6.20 (2.36, 16.30)**
More than two venous thrombosis	113 (70.2%)	22 (62.9%)	0.32 (0.10, 1.04)
Endovascular treatment	51 (31.7%)	21 (60.0%)	2.06 (0.79, 5.41)
Anticoagulation alone	96 (59.6%)	19 (54.3%)	0.93 (0.41, 2.86)
Anticoagulation combined with batroxobin	65 (40.4%)	16 (45.7%)	1.08 (0.41, 2.85)
DFR≥0.322	0.41 ± 0.54	0.79 ± 0.54	2.63 (1.47, 5.88)**
Model 2			
Male	82 (50.9%)	10 (28.6%)	0.36 (0.15, 0.86))*
Focal neurological deficit	39 (24.2%)	22 (62.9%)	5.91 (2.57, 13.57)**
DFR≥0.322	0.41 ± 0.54	0.79 ± 0.54	2.63 (1.43, 4.76)**

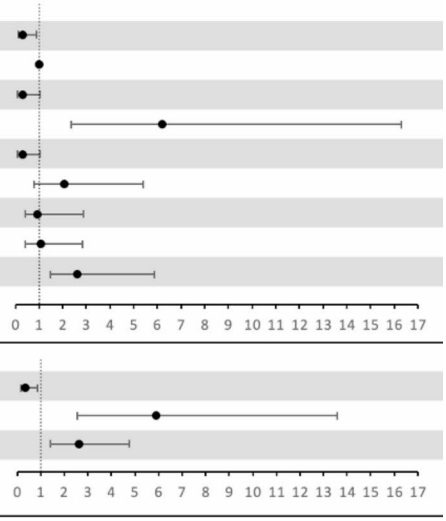

Fig. 4 Multivariate regression analyses for association of variables with poor short-term outcome at discharge. DFR: D-dimer to fibrinogen ratio; aOR: adjusted odds ratio; CI: Confidence interval. Variables with significant collinearity to DFR were not included in the multiple regression analysis model. Model 1: Multivariate regression models constructed for all variables that are not collinear with DFR. Model 2: The multivariate regression model is constructed in the univariate regression analysis of variables with significant correlation and not collinear with DFR. * $P < .05$; ** $P < .017$

Variables , n (%) / mean ± SD	Good long-term outcome (n=182)	Poor long-term outcome (n=14)	aOR (95% CI)
Model 1			
Male	87 (47.8%)	5 (35.7%)	0.55 (0.14, 2.08)
Age, years	37.78 ± 13.06	43.21 ± 19.70	0.99 (0.94, 1.03)
Headache	161 (88.5%)	10 (71.4%)	0.28 (0.06, 1.31)
Focal neurological deficit	52 (41.1%)	9 (25.4%)	4.54 (1.21, 17.05)*
More than two venous thrombosis	126 (69.2%)	9 (64.3%)	1.68 (0.42, 6.80)
Endovascular treatment	66 (36.3%)	6 (42.9%)	0.52 (0.12, 2.21)
Anticoagulation alone	107 (58.8%)	8 (57.1%)	0.73 (0.19, 2.80)
Anticoagulation combined with batroxobin	75 (41.2%)	6 (42.9%)	1.37 (0.31, 2.78)
Decompressive craniectomy	4 (2.2%)	3 (21.4%)	15.16(1.73, 132.84)*
DFR≥0.754	0.44 ± 0.54	0.93 ± 0.64	3.22 (1.39, 7.14)**
Model 2			
Focal neurological deficit	52 (41.1%)	9 (25.4%)	3.93 (1.17, 13.14)*
Decompressive craniectomy	4 (2.2%)	3 (21.4%)	9.07 (1.53, 53.84)*
DFR ≥0.754	0.44 ± 0.54	0.93 ± 0.64	2.86 (1.32, 6.25)**

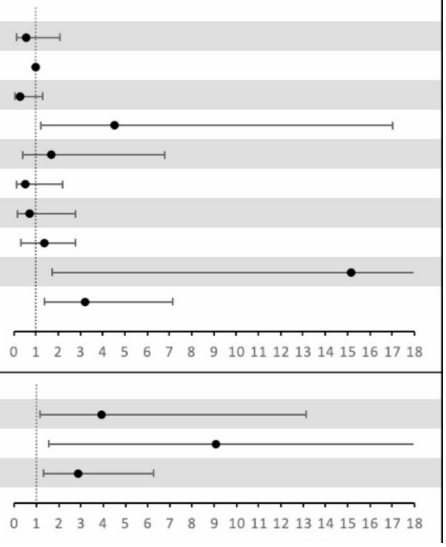

Fig. 5 Multivariate regression analyses for association of variables with poor long-term outcome at 12-months. DFR: D-dimer to fibrinogen ratio; aOR: adjusted odds ratio; CI: Confidence interval. Variables with significant collinearity to DFR were not included in the multiple regression analysis model. Model 1: Multivariate regression models constructed for all variables that are not collinear with DFR. Model 2: The multivariate regression model is constructed in the univariate regression analysis of variables with significant correlation and not collinear with DFR. * $P < .05$; ** $P < .017$

was included in the regression analysis as a categorical variable (≥0.754 or <0.754).

Univariate logistic regression analysis identified DFR≥0.754 as a significant predictor of poor long-term outcomes [OR (95% CI): 1.66 (1.39–5.56), $P=.004$] (Supplementary Table 7). In the multivariate logistic regression model, after excluding variables with significant collinearity with DFR, DFR≥0.754 remained a strong independent predictor of poor long-term outcomes [adjusted OR (95% CI): 3.22 (1.39–7.14), $P=.006$].

This association persisted even after adjusting for variables demonstrating a clear correlation in the univariate analysis [adjusted OR (95% CI): 2.86 (1.32–6.25), $P=.008$] (Fig. 5).

Discussion

This is the first study to explore the clinical association of DFR with the severity and the prognosis of CVT. The main findings of our current study were that (1) DFR was revealed to be an independent predictor for severe CVT; (2) DFR was an independent predictor for the poor short-term and long-term outcome of CVT; (3) In terms of AUC, DFR has discriminating capacity to severe CVT and poor outcome of CVT. Overall, it is possible that DFR should be able to serve as a potential parameter for discriminating "bad" patients with CVT.

Previous studies on the association D-dimer and fibrinogen with CVT were only in the stage of diagnostic research, and their sensitivity and specificity were poor [25–30]. However, DFR, a derivative indicator of D-dimer and fibrinogen, has shown good clinical value in predicting the severity and outcome of disease. Han et al. investigated that DFR was strongly predictive of progressive hemorrhagic injury in a cohort of traumatic brain injury [11]. In another study, the difference in DFR was reported to be significant between with and without acute ischemic stroke [17]. Although the predictive effect of DFR in the severity of CVT has not been examined, our results seem to be consistent with the above findings. In this study, DFR was significantly higher in the subgroup of patient with CVT secondary cerebral hemorrhage and venous cerebral infarction compared with without. It is well known that secondary brain damage is a prominent feature of severe CVT, therefore DFR was significantly associated with severe CVT in this study.

Fibrinogen is an important biomarker which associated with both inflammation and coagulopathy [7, 8]. D-dimer, which is produced by the breakdown of fibrin by plasmin, is another biomarker closely related to thrombotic and fibrinolytic processes and inflammation. In addition, some studies have reported that a high D-dimer level is a highly nonspecific marker of VTE and may be a sign of inflammation rather than thrombosis [31, 32]. Given these findings, DFR may also be an indicator of inflammation levels. Hu et al. found that there is increasing evidence suggesting that an inflammatory response is closely associated with the pathophysiology of severe CVT by reviewing previous literature [33]. This may be one of the theoretical underpinnings of our findings which the difference in DFR was significant between severe and non-severe patients with CVT in a different subgroup.

A group of studies reported the predictive effect of DFR on clinical functional outcomes. Bai et al. and Liu et al. indicates that DFR is an independent and novel predictor of long-term and short-term prognosis of patients with acute myocardial infarction [10, 34]. Luo et al. reported that DFR can provide prognostic information about patients with acute intracerebral hemorrhage patients [12]. Another study demonstrated the value of the DFR is positively correlated with NIHSS score in acute cerebral infarction patients [35]. In this study, we demonstrate for the first time that DFR was an independent risk factor for poor clinical outcome in patients with CVT by logistic regression analysis after adjusting for all risk factors. Therefore, it is worthy of clinical application.

The formation of newly developed thromboses consumes a significant amount of fibrinogen, and the presence of multiple thrombi activates the fibrinolytic system, leading to the production of large amounts of fibrin degradation products (D-dimer). Both of these mechanisms can contribute to an elevated DFR. Therefore, an increased DFR may reflect active thrombus formation, which can lead to widespread CVT. Extensive CVT can cause secondary brain tissue damage, such as venous infarction and hemorrhagic transformation post-infarction, which may also lead to elevated DFR [12, 35]. These factors may elucidate the mechanisms linking DFR values with CVT severity. Widespread thrombosis, venous infarction, and hemorrhagic transformation of infarcts, which are secondary to CVT, are significantly associated with poor prognosis in CVT patients, thereby explaining the potential mechanism by which DFR predicts adverse outcomes in CVT patients.

In this study, the AUC were found to be 0.690, 0.773 and 0.753 for the ROC of DFR at admission, which are considered predictors of severe CVT, poor short-term outcome and poor long-term outcome. The optimal DFR cut-off value of 0.253, 0.322 and 0.754 provided sensitivity and specificity for the prediction of severe CVT and poor outcome. The NIHSS is significant in assessing the severity of acute ischemic stroke, but currently, there is a lack of effective scales for evaluating the severity and prognosis of CVT in clinical practice, despite some studies attempting to apply the NIHSS to CVT evaluation. Therefore, it is crucial to actively explore clinical predictive indicators related to CVT severity and prognosis. DFR, with its easily accessible clinical data and direct association with thrombosis, has emerged as a potential clinical predictor. The main finding of this study is that DFR is significantly associated with CVT severity and can predict potential secondary brain damage from CVT, assisting in clinical decision-making regarding treatment strategies, such as whether to proceed with anticoagulation alone or to consider aggressive endovascular treatment. We recommend using DFR as an adjunctive clinical assessment tool for all CVT patients to guide treatment decisions, as coagulation function tests are routine for

every CVT patient and do not waste medical resources. However, due to the current lack of high-evidence-level studies to confirm this conclusion, DFR cannot yet serve as a primary reference indicator for clinical diagnosis and treatment. We look forward to validating these findings through subsequent large-scale prospective clinical trials and plan to explore the clinical application value of DFR in guiding CVT treatment methods and advancing its clinical use.

Limitations

The present study has several limitations. First, it is a retrospective, observational study. The biases associated with selection, information, and confounding in retrospective studies may impact the research results. Second, to ensure the rigor of the study, this research excluded patients with conditions such as tumors and inflammation that could induce abnormalities in D-dimer and fibrinogen levels. However, these conditions themselves also represent risk factors for adverse outcomes in CVT, which may affect the real-world applicability of our findings. Further studies are needed to confirm these findings.

Conclusion

Elevated DFR is associated with increased severity of CVT. Additionally, higher DFR levels can predict poorer clinical outcomes in CVT.

Abbreviations

CVT Cerebral venous thrombosis
DFR D-dimer to fibrinogen ratio

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Author contributions

DL wrote the first draft of the manuscript; MW, XZ, XH, NL, XR, KF and DZ performed the material preparation, data collection and statistical analysis, RM wrote sections of the manuscript and contributed to manuscript revision; RM takes full responsibility for the data, the analyses and interpretation, and the conduct of the research. All authors read and approved the submitted version.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval

The study was approved by the Institutional Ethic Committee of Xuanwu Hospital, Capital Medical University, and was conducted according to the guidelines laid down in the Declaration of Helsinki. Prior to any study procedure, written informed consent was obtained from all participants.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Competing interests

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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