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Clinical features and predictors of early neurological deterioration in patients with Trousseau syndrome-related cerebral infarction

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Abstract

Objective: This study aimed to explore the clinical features of Trousseau syndrome (TS)-related cerebral infarction and determine predictors of early neurological deterioration (END). *Methods:* A retrospective study was conducted on patients with TS-related cerebral infarction admitted to the Zhongshan Hospital Affiliated with Xiamen University, from December 2015 to December 2023. Patients were categorized into groups with and without END. The laboratory findings and imaging data were compared, and receiver operating characteristic (ROC) curves were constructed to determine the best predictors of END. *Results:* The study included 30 patients with TS-related cerebral infarction, comprising 17 males and 13 females with an average age of 70.93 ± 8.7 years. Five patients experienced END. Lung cancer was the most common primary malignancy (n=13, 43.33%), with most patients (n=22, 73.33%) having stage IV disease with extensive metastasis. The primary neurological symptom was hemiplegia (n=17, 56.67%). The mean NIHSS score at admission was 9.33 ± 5.83. Imaging revealed varying stages of cerebral infarction in 10 patients (38.46%). Within three months, 25 patients (83.33%) died, 8 of whom (32%) succumbed to tumor-related complications. The incidence of END in TS-related cerebral infarction patients was 16.67% (5/30). Patients in the END group had significantly greater D-dimer levels and lower fibrinogen (Fib) levels upon admission ($P < 0.001$, $P = 0.042$). Comparisons of ROC curves revealed that D-dimer (AUC 0.916, optimal cutoff 17.86, sensitivity 1.000, specificity 0.840) and Fib (AUC 0.788, optimal cutoff 2.54, sensitivity 1.000, specificity 0.740) significantly predicted END ($P = 0.004$, $P = 0.045$). The combined use of these markers improved the AUC to 0.952, with a sensitivity of 1.00 and specificity of 0.920, surpassing those of the individual markers ($P = 0.002$). *Conclusion:* TS-related cerebral infarction most commonly occurs in patients with advanced-stage lung cancer with widespread metastasis and is associated with poor long-term prognosis. Elevated D-dimer and decreased fibrinogen levels are significant predictors of END in patients with TS-related cerebral infarction.

Keywords: Trousseau syndrome, acute cerebral infarction, Trousseau syndrome-related cerebral infarction, D-dimer, fibrinogen

INTRODUCTION

Trousseau syndrome (TS) is a paraneoplastic thromboembolic disorder that often preceds or coincids with the diagnosis of occult visceral malignancies and is potentially related to tumor-induced dysregulation of coagulation and fibrinolytic processes.[1] The clinical manifestations of TS are diverse and include deep vein thrombosis, pulmonary embolism, and arterial thromboembolism.[2] Acute cerebral infarction (ACI) is a common clinical presentation of TS, affecting approximately 15% of patients with malignant tumors.[3] However, large-scale clinical studies on the features of TS-related cerebral infarction are scarce.

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Early neurological deterioration (END) is a critical prognostic factor in ACI patients and is associated with extended hospital stays, worsened functional outcomes, and increased mortality.[4] While previous research has identified predictors of END from clinical and laboratory features in patients with conventional ischemic strokes[5], the risk factors for END in TS-related cerebral infarction remain underexplored. This study aimed to analyze the characteristics of patients with TS-related cerebral infarction and to preliminarily investigate the risk factors for END associated with this condition, thereby enhancing the understanding of this syndrome.

METHODS

Study population

This retrospective analysis was conducted on clinical data from 30 patients with ACI and concurrent malignancies admitted to Zhongshan Hospital Affiliated with Xiamen University between December 2015 and December 2023. The inclusion criteria were as follows: (1) diagnosis of a malignancy for the first time within six months prior to the ACI event or during hospitalization or showing evidence of cancer recurrence, metastasis, or progression[6]; (2) diagnosis of ACI confirmed by magnetic resonance diffusion-weighted imaging (DWI), with lesions affecting both the anterior and posterior circulations simultaneously; and (3) elevated levels of the coagulation biomarker D-dimer. Patients potentially suffering from ACI due to large artery atherosclerosis, small artery occlusion, or cardioembolic sources were excluded. Five patients with END were identified for comparison with patients who did not experience early neurological deterioration (nonearly neurological deterioration, NEND) to analyze differences in clinical characteristics between the two groups.

General data collection

Data on demographic characteristics (age, sex), cerebrovascular risk factors (hypertension, diabetes, dyslipidemia, smoking status, and alcohol consumption status), oncological features (type of malignancy, stage, and systemic metastasis status), laboratory findings (complete blood count, blood chemistry, C-reactive protein, coagulation and fibrinolysis parameters), and radiological data (cranial CT, MRI, CTA, and MRA) were collected. D-dimer levels were measured at admission, 24 hours before anticoagulation therapy, and 48 hours after anticoagulation therapy. During hospitalization, the degree of neurological deficit was assessed daily by neurologists who were formally trained using the National Institutes of Health Stroke Scale (NIHSS). An END was defined as an increase in the motor component of the NIHSS score of ≥1 point or a total increase in the NIHSS score of ≥2 points within 48 hours of admission.

Neuroimaging studies

Patients underwent CT or MR imaging during hospitalization, which was evaluated by experienced radiologists who were blinded to the clinical information. The analysis included DWI and FLAIR sequences to identify cerebral infarction lesions at different stages (acute, subacute, and chronic) and categorized the findings as either single-stage or multistage lesions. Follow-up imaging assessments revealed new regional lesions, stroke volume enlargement, hemorrhagic transformation, and no significant lesion progression.

Statistical analysis

Statistical analyses for the two patient groups (END and NEND) were performed using SPSS software version 26.0. Normally distributed quantitative data are presented as the mean ± standard deviation (X±S), and comparisons between groups were made using independent samples t tests. Variables not normally distributed were described using medians (Q1, Q3). Categorical data are expressed as frequencies and percentages, with comparisons between groups conducted using chi-square tests or Fisher's exact tests, as appropriate. Variables that were significantly different between the two groups were used to plot receiver operating characteristic (ROC) curves to determine the best predictors of END. A p value of <0.05 was considered to indicate statistical significance.

RESULTS

Clinical features

This study included 30 patients with Trousseau syndrome-related cerebral infarction. The cohort consisted of 17 males (56.67%) and 13 females (43.33%), with an average age of 70.93 ± 8.7 years. The median hospital stay was 15.50 (10.00, 21.75) days.

In terms of oncological characteristics, lung cancer was the most common primary malignancy (n=13), followed by liver cancer (n=5), cholangiocarcinoma (n=2), and gastric cancer (n=2). Other tumor types included breast cancer, esophageal cancer, thyroid cancer, rectal cancer, and nasal cavity tumors, each accounting for one patient. The majority of the patients (n = 22, 73.33%) were diagnosed with stage IV cancer with widespread metastasis.

Twenty-one patients (70%) presented with ACI as the initial clinical manifestation of cancer, with no prior cancer treatment. The principal neurological symptoms included hemiplegia in 17 patients (56.67%), dysarthria in 6 (20%), consciousness disturbances in 5 (16.67%), dizziness in 1 (3.3%), and headache in 1 (3.3%). The mean NIHSS score at admission was 9.33 ± 5.83. Regarding treatment and prognosis, all patients received antiplatelet aggregation and lipid management upon admission. After contraindications were excluded, anticoagulation therapy was initiated in 20 patients (66.67%). Following timely treatment, most patients showed improvement in neurological function, with a decrease in the NIHSS score to 6.68 ± 5.23 at discharge. However, 8 patients (26.67%) died during hospitalization; during the 3-month follow-up period, a total of 25 patients (83.33%) died, including 8 (8/9) from tumor-related complications. The detailed clinical characteristics of the patients are presented in Table 1.

Laboratory data

Elevated D-dimer levels were observed in all patients, with a median value of 9.68 (7.26, 18.17) mg/L. There was significant variability in fibrinogen (Fib) concentrations among the patients; Fib levels were above the laboratory reference range in 9 patients (30%) and below in 7 patients (23.33%). Changes in D-dimer levels before and after anticoagulation therapy were closely monitored in 17 patients receiving treatment. The results indicated that D-dimer levels increased in 10 patients (58.82%) from admission to before anticoagulation therapy, whereas 11 patients (64.71%) experienced a decrease in D-dimer levels following anticoagulation therapy. Additionally, a majority of the patients exhibited elevated white blood cell counts (n=16), neutrophil counts (n=19), and C-reactive protein levels (n=21). A summary of the laboratory data is provided in Table 2.

Early neurological deterioration

The incidence of END in patients with Trousseau syndrome-related cerebral infarction was 16.67% (5/30). There were no significant differences between the END and NEND groups in terms of age, sex, cerebrovascular risk factors, tumor stage, systolic blood pressure, NIHSS score at admission, or laboratory markers, including white blood cells, neutrophils, lymphocytes, and triglycerides ($P > 0.05$). However, significant differences were observed between the END and NEND groups in the D-dimer and Fib levels ($P < 0.05$). The detailed baseline characteristics and risk factors for both groups are presented in Table 3.

The inclusion of Fib and D-dimer levels in the ROC curve analysis revealed that D-dimer had an area under the curve (AUC) of 0.916 (95% *CI*: 0.812, 1.000), with an optimal cutoff value of 17.86, a sensitivity of 1.000, and a specificity of 0.840. Fib had an AUC of 0.788 (95% *CI*: 0.622, 0.954), with an optimal cutoff value of 2.54, a sensitivity of 1.000, and a specificity of 0.840. The difference in the AUC between the two markers was statistically significant ($P < 0.05$). When Fib and D-dimer were used in combination, the AUC for predicting END in Trousseau syndrome-related cerebral infarction increased to 0.952 (95% CI: 0.876, 1.000), with a sensitivity of 1.000 and a specificity of 0.920, significantly outperforming the individual markers.

Radiological characteristics

All patients' DWI confirmed the diagnosis of ACI, with lesions affecting both the anterior and posterior circulatory territories. Different stages of cerebral infarction lesions were identified in 10 patients (38.46%) (Figure 1). According to the follow-up imaging analysis of 16 patients, lesions showed no progression in 9 patients (56.25%), while new regional lesions developed in 6 patients (37.5%). Two of these patients also experienced hemorrhagic transformation and stroke volume enlargement. One patient (6.25%) exhibited both hemorrhagic transformation and an increase in stroke volume. Comparing the imaging outcomes between the two groups, lesion progression was observed in 3 patients (25%) in the NEND group and all 3 patients (100%) in the END group via follow-up imaging.

DISCUSSION

This study provides an in-depth exploration of the clinical features of TS-related cerebral

Table 1: Clinical features of the patients

No.	Age/ Sex	Tumour site	Stage	Symptom	AC therapy	Prognosis	Cause of Death
1	70/M	Liver	IV	Dysarthria	Yes	improve	Liver failure
2	58/F	Lung	IV	Hemiplegia	Yes	improve	Recurrent stroke
3	65/M	Lung	III	Hemiplegia	No	improve	Respiratory failure
4	78/F	Lung	I	Hemiplegia	Yes	improve	Survival
5	71/F	Breast	IV	Hemiplegia	Yes	dead	Recurrent stroke
6	81/F	Lung	IV	Hemiplegia	Yes	improve	Respiratory failure
7	72/F	Lung	IV	Hemiplegia	Yes	improve	Unclear
8	71/M	Bile ducts	IV	Hemiplegia	Yes	dead	Unclear
9	91/M	Pancreatic	IV	Hemiplegia	Yes	dead	Pulmonary infection
10	57/F	Lung	IV	Dysarthria	Yes	dead	Brain herniation
11	69/M	Bile ducts	IV	Headache	No	improve	Unclear
12	63/M	pancreas	IV	Dysarthria	Yes	improve	Unclear
13	61/F	Uterine	IV	Hemiplegia	Yes	improve	Malignant tumor
14	67/F	Lung	IV	Hemiplegia	Yes	improve	Unclear
15	73/M	Lung	IV	Dizziness	Yes	worse	Unclear
16	78/M	Lung	IV	Dysarthria	Yes	improve	Unclear
18	78/F	Lung	IV	Dysarthria	Yes	improve	Unclear
19	75/M	Lung	III	Hemiplegia	No	dead	Pulmonary infection
20	61/F	Rectum	IV	Hemiplegia	No	dead	Sepsis
21	68/M	esophagus	IV	Dysarthria	No	improve	Unclear
24	69/F	Liver	NA	Hemiplegia	Yes	improve	Unclear
25	56/M	Lung	IV	Hemiplegia	No	improve	Survival
26	67/M	Liver	III	Hemiplegia	No	improve	Survival
27	76/M	Liver	NA	Hemiplegia	No	improve	Unclear
30	77/M	Nasal	I	Hemiplegia	No	improve	Survival
28	85/F	Thyroid	IV	Consciousness disturbance	Yes	dead	Unclear
29	57/M	Lung	IV	Consciousness disturbance	Yes	improve	Survival
17	78/F	Stomach	I	Consciousness disturbance	No	improve	Unclear
22	81/M	Stomach	IV	Consciousness disturbance	Yes	dead	Unclear
23	75/M	Liver	IV	Consciousness disturbance	Yes	improve	Unclear

Abbreviations: M, man; F, female; AC therapy, Anticoagulation therapy.
The cause of death refers to the reason for a patient's death during hospitalization or within three months after discharge.

infarction, revealing several key findings. Firstly, we observed that TS-related cerebral infarction is most commonly observed in patients with primary malignancies such as lung cancer, colorectal cancer, and liver cancer, with the highest incidence occurring in advanced stages of malignancy. These observations align with previous research findings.[7-9] Secondly, the clinical manifestations primarily include acute disturbances in consciousness, speech impairments, and limb paralysis, which are similar to those observed in conventional strokes.[10,11] Moreover, despite the majority of patients in our study receiving prompt treatment during the acute phase of cerebral infarction, the long-term prognosis for these patients remains poor. This unfavorable outcome may not be directly attributable to the stroke itself, but rather

Table 2: Laboratory data of the patients

No.	NIHSS		Fib	D-Dimer (mg/L)			CRP	WBC	NEUT	LYM
	Initial	48h	(g/L)	Adm.	Pre-AC	Post-AC	(mg/L)	(10^9/L)	(10^9/L)	(10^9/L)
1	7	7	5.09	1.71	1.71	1.77	135.0	6.97	5.57	0.44
2	8	3	3.25	17.9	17.9	6.08	62.6	7.63	5.68	1.39
3	7	6	2.49	6.66	NA	NA	17.1	9.61	6.54	1.91
4	7	4	3.32	0.88	1.12	0.59	1.39	5.68	3.33	1.90
5	12	9	6.66	19.55	35.2	17.54	181	12.61	10.61	1.02
6	4	4	4.09	8.41	NA	NA	9.96	7.17	4.15	1.80
7	20	20	2.85	7.11	6.29	7.45	94.9	26.30	21.8	1.08
8	3	12	2.35	24.36	27.88	14.38	63.5	5.55	4.14	0.85
9	5	5	2.98	11.48	13.72	6.95	31.9	11.24	9.82	0.71
10	2	8	1.54	24.96	35.2	NA	NA	15.00	12.62	1.20
11	1	1	1.78	2.72	NA	NA	2.56	6.14	3.75	1.37
12	8	8	4.48	17.70	20.66	9.73	39.80	13.67	11.61	0.85
13	14	20	2.59	18.02	35.2	NA	26.5	10.69	8.94	1.05
14	20	20	2.89	19.27	NA	NA	28.2	6.89	5.31	1.11
15	1	3	1.12	35.20	35.2	35.2	NA	15.13	10.27	2.38
16	4	4	1.77	8.8	10.77	1.98	NA	5.50	3.38	1.58
17	12	12	0.96	5.04	NA	NA	14.5	9.50	7.86	1.32
18	5	5	2.24	20.66	20.11	3.91	65.0	10.29	8.93	0.91
19	11	11	4.67	8.30	NA	NA	74.9	13.68	9.53	0.80
20	9	11	2.24	18.22	NA	NA	141	18.16	16.36	1.22
21	8	8	4.83	7.7	NA	NA	NA	6.81	4.54	1.63
24	9	8	1.91	35.2	35.2	35.2	61.44	9.18	7.89	0.85
25	13	13	8.69	17	NA	NA	NA	14.45	12.74	0.90
26	5	1	2.08	6.2	NA	NA	18.26	8.99	6.61	1.68
27	12	10	2.66	12.5	NA	NA	97.17	11.51	9.39	1.24
30	12	12	5.82	8.68	NA	NA	16.45	10.64	8.84	0.81
28	22	22	4.60	3.54	4.37	2.35	24.08	6.71	4.74	1.41
29	17	14	1.04	9.48	24.45	4.63	NA	15.29	13.23	1.38
17	12	12	0.96	5.04	NA	NA	14.5	9.50	7.86	1.32
22	18	18	2.75	13.48	13.48	8.03	113.3	10.10	8.36	0.95
23	4	4	2.41	9.88	NA	NA	4.58	7.68	6.10	1.12

Abbreviations: Adm., admission; Pre-AC, Pre-anticoagulation; Post-AC, post-anticoagulation; CRP, C-reactive protein; WBC, White Blood Cell; NEUT, Neutrophil; LYM , Lymphocyte.
Reference ranges: D-dimer: 0–0.55 mg/L; Fibrinogen: 2.0–4.0 g/L; CRP: 0–6 mg/L; WBC: 3.5–9.5 × 10^9/L; Neutrophils: 1.8–6.3 × 10^9/L; Lymphocytes: 1.1–3.2 × 10^9/L.

more closely associated with cancer-related complications such as pulmonary infections, sepsis, and organ failure.

END is a critical prognostic indicator in patients with TS-related cerebral infarction.[4] In our study, we observed significantly elevated D-dimer levels in patients with TS-related cerebral infarction who experienced END compared to those NEND group, which is consistent with previous findings.[12] As D-dimer is a key molecular marker of a hypercoagulable state and Fib system activation, elevated D-dimer levels are considered a prominent feature of malignancy-associated cerebral infarction.[13,14] Seok *et al*. conducted Doppler ultrasonography on the bilateral internal carotid arteries of patients with malignancies and acute cerebral infarction and reported a positive correlation between plasma D-dimer levels and the quantity of microembolic signals in the bloodstream.[15] This observation directly

Table 3: Baseline characteristics and laboratory data of Without END and END patients

Variable	Without END (n = 25, 83.33%)	END (N = 5, 13.67%)	P-value
Age, year [SD]	72.20 ± 8.64	64.60 ± 6.99	0.076
Sex, male n(%)	15 (60.00)	2 (40.00)	0.628
Hypertension, n(%)	17 (68.00)	1 (20.00)	0.128
Diabetes, n(%)	6 (24.00)	2 (40.00)	0.589
Dyslipidemia status, n(%)	3 (12.00)	1 (20.00)	0.538
Smoking, n(%)	4 (16.00)	0 (0.00)	0.304
Alcohol, n(%)	7 (28.00)	0 (0.00)	1.000
Cancer stage IV, n(%)	17 (73.91)	5 (100.00)	0.533
Systolic blood pressure, [SD]	150.78 ± 21.60	131.20 ± 16.53	0.069
Initial NIHSS, [SD]	10.04 ± 5.73	5.80 ± 5.54	0.140
C-reactive protein, [IQR]	31.95 (16.45, 74.97)	63.45 (44.98, 102.22)	0.354
White Blood Cell, [IQR]	9.50 (6.97, 11.51)	15.00 (10.69, 15.13)	0.169
Neutrophil, [IQR]	7.86 (5.31, 9.53)	10.27 (8.94, 12.62)	0.208
Lymphocyte, [SD]	1.21 ± 0.39	1.34 ± 0.60	0.531
NLR, [SD]	7.81 ± 4.85	8.33 ± 3.83	0.824
Triglycerides, [IQR]	1.10 (0.89, 1.35)	1.71 (1.13, 1.89)	0.083
HDLC, [SD]	1.19 ± 0.35	1.11 ± 0.10	0.640
LDL-C, [SD]	2.90 ± 0.79	3.10 ± 1.11	0.629
D-Dimer, [IQR]	8.74 (6.66, 13.48)	24.36 (18.22, 24.96)	**0.004**
Fibrinogen, [IQR]	2.89 (2.24, 4.60)	2.24 (1.54, 2.35)	**0.042**

Abbreviations: END, early neurological deterioration; NIHSS, National Institutes of Health Stroke Scale; NLR, Neutrophil-to-Lymphocyte Ratio; HDLC, High-Density Lipoprotein Cholesterol; LDL-C, Low-Density Lipoprotein Cholesterol.

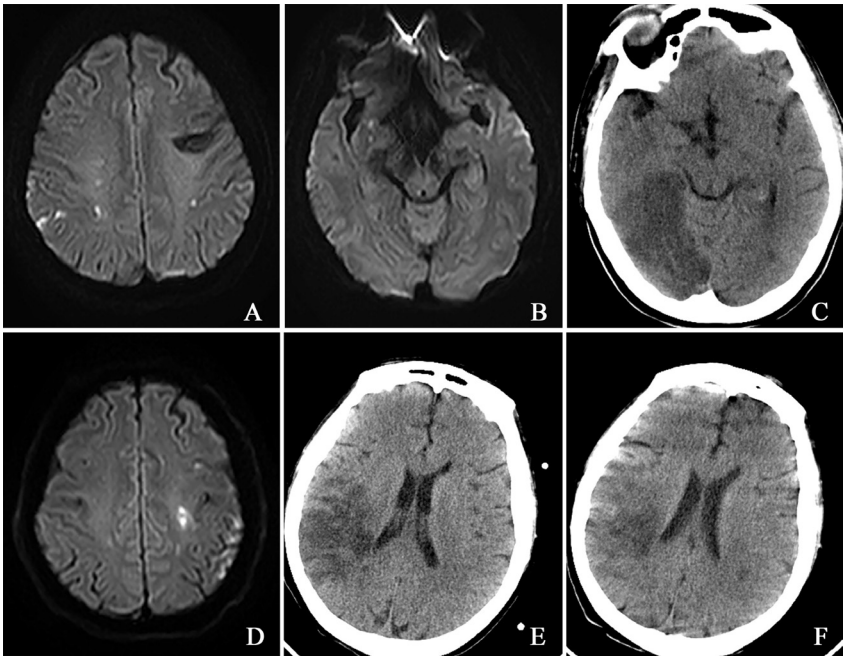

Figure 1. Image data of patient**.** A and D display cerebral infarcts at different stages (acute and subacute). Images B and C are from Diffusion Weighted Imaging (DWI) and cranial CT scans taken on the second and fifth days of hospitalization, respectively, showing new infarct lesions in the right temporal lobe. Images E and F are from cranial CT scans on the third and eighth days after admission, depicting new acute cerebral infarct lesions in the left centrum semiovale of the parietal lobe.

supports the hypothesis that a hypercoagulable state may contribute to malignancy-associated cerebral infarction by facilitating the formation of intravascular microemboli. Further research revealed a positive correlation between D-dimer levels and the secretion of extracellular vesicles by malignant tumor cells. These extracellular vesicles may activate platelet aggregation and promote the formation of neutrophil extracellular traps through both tissue factor-dependent and tissue factor-independent pathways, thus driving the thrombosis process.[16,17]

Our study also revealed that patients with early neurological deterioration frequently exhibit decreased Fib levels, which may indicate the presence of cancer-associated chronic disseminated intravascular coagulation (CDIC). Unlike disseminated intravascular coagulation triggered by sepsis or trauma, cancer-associated CDIC typically progresses slowly and involves extensive consumption of platelets and coagulation factors. This leads to persistent dysregulation of the coagulation system and subsequently increases the risk of thrombosis.[18] Although there are currently no unified diagnostic criteria for cancer-associated CDIC, most studies have identified reductions in Fib levels and elevations in D-dimer levels as key markers for assessing this condition.[19,20]

By analyzing radiological data for Trousseau syndrome-related cerebral infarction, we found that 38% of the patients presented with cerebral infarction lesions at various stages. Follow-up imaging revealed that patients in the END group often developed new regional lesions. This observation aligns with findings by Nam *et al*., who also noted an increased incidence of new local lesions in magnetic resonance imaging of patients with occult cerebral infarction and active cancer, particularly those experiencing END.[12] This suggests that elevated levels of D-dimer and fibrinogen may contribute to the risk of recurrent embolism or thrombosis, thereby leading to END. Additionally, we observed that most patients with TS-related cerebral infarction exhibited a continual increase in D-dimer levels from onset until the initiation of anticoagulation therapy, with most responding well to anticoagulation treatment. Therefore, the potential benefits of initiating anticoagulation therapy early in these patients, after ruling out contraindications, to reduce the risk of further embolism or thrombosis and thus decrease the incidence of END merit further exploration.

A major limitation of this study is the small sample size, which constrains our ability to accurately analyze the clinical characteristics of TS-related cerebral infarction and the risk factors for END. Although some markers did not reach statistical significance, observable differences were noted, which could largely be attributed to the limited sample size leading to potential biases. Additionally, the varying intervals between the onset of symptoms and the administration of anticoagulant medications among our patients may have affected the accuracy of our assessments of the trends in D-dimer levels.

DISCLOSURE

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Conflicts of interest: None

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