

Coagulation Activation Markers Associate with Early Neurological Function and Infarct Volume in Acute Ischemic Stroke

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Background: The state of the coagulation-fibrinolysis system plays a pivotal role in thrombosis; however, its significance in guiding early revascularization for ischemic stroke remains inadequately understood.

Objective: To explore the correlation between coagulation activation markers and early neurological function and infarction volume in acute ischemic stroke (AIS), and to evaluate their predictive value for stroke severity.

Methods: This retrospective cohort study enrolled 135 patients with acute ischemic stroke. Participants were stratified into two groups based on admission National Institutes of Health Stroke Scale (NIHSS) scores: mild stroke group (NIHSS ≤ 3, n=95) and moderate-to-severe stroke group (NIHSS > 3, n=40). Five coagulation activation markers were quantified: thrombomodulin (TM), thrombin-antithrombin complex (TAT), plasmin- α_2 plasmin inhibitor complex (PIC), tissue plasminogen activator-inhibitor complex (t-PAIC), and D-dimer. The associations between these biomarkers and stroke severity were evaluated using logistic regression models and receiver-operating characteristic (ROC) curve analyses. Infarct volume and its spatial distribution across distinct brain regions were quantified using dedicated neuroimaging software. Subsequently, the correlation between the five coagulation markers and both total infarct volume and region-specific infarction volumes were assessed.

Results: Plasma levels of TAT, t-PAIC, and D-dimer were significantly elevated in the moderate-to-severe stroke group compared to the mild stroke group ($p < 0.05$). Multivariate logistic regression analysis identified D-dimer as an independent risk factor for moderate-to-severe stroke (OR=1.002, 95% CI: 1.000–1.004). The area under the curve (AUC) values for TAT, t-PAIC, and D-dimer in predicting moderate-to-severe stroke were 0.62, 0.63, and 0.59, respectively. The combined predictive model achieved an AUC of 0.67. Furthermore, within the moderate-to-severe stroke group, TAT levels demonstrated a positive correlation with anterior circulation cortical infarction volume ($R=0.61$, $p < 0.05$). Additionally, D-dimer levels exhibited positive correlations with both total infarct volume and anterior circulation cortical infarction volume ($R=0.74$, $p < 0.05$; $R=0.79$, $p < 0.05$).

Conclusion: TAT, t-PAIC and D-dimer serve as predictors for the severity of acute ischemic stroke, and can be used as a simple and rapid auxiliary tool combined with imaging evaluation to provide synergistic guidance for clinical decision-making.

Keywords: acute ischemic stroke, coagulation activation markers, thrombin-antithrombin complex, tissue prothrombin activator-prothrombin activator inhibitor complex

Introduction

In the pathophysiology of ischemic stroke, thrombosis constitutes a pivotal pathological mechanism. This process is intimately linked to platelet activation and the interplay of the coagulation-fibrinolysis system, while also involving inflammatory responses and oxidative stress in the cascade of tissue damage.^{1,2} Current clinical practice primarily utilizes multimodal imaging to evaluate thrombus load, vascular stenosis, or occlusion sites.³ However, these assessments focus on

real-time outcome status without adequately capturing the underlying coagulation-fibrinolysis dynamics. Tracing coagulation theory, following platelet aggregation forms platelet thrombus, the coagulation cascade is activated. Thrombin is subsequently generated and accumulates on the procoagulant surface of activated platelets, forming a cross-linked fibrin network to produce a fibrin clot.⁴ In the early ischemic phase, the platelet activation and plasminogen activator inhibition axis become dysregulated. Traditional laboratory monitoring methods such as prothrombin time (PT) and activated partial thromboplastin time (APTT) involve activating coagulation pathways through appropriate addition of initiators in vitro utilizing platelet-free plasma. These methods do not reflect actual in vivo coagulation dynamics, thereby demonstrating limited utility for clinical risk stratification and therapeutic guidance.⁵ To achieve more precise monitoring of in vivo coagulation-fibrinolysis status, there is a need for more direct and effective biomarkers capable of identifying the active state of this process. Thrombomodulin (TM), expressed on vascular endothelial cells, captures thrombin to mediate the activation of protein C, thus facilitating anticoagulant pathways. Concurrently, TM binds tissue plasminogen activator inhibitor-1 (PAI-1), modulating the kinetics of fibrinolysis.⁶ The thrombin-antithrombin complex (TAT), which comprises equimolar concentrations of thrombin and antithrombin and has 3 minutes half-life, can theoretically directly quantify the thrombin generation level prior to antithrombotic drug intervention, reflecting the early stages of coagulation activation.⁷⁻⁹ The plasmin- α 2 plasmin inhibitor complex (PIC), formed by binding plasmin with α 2-fibrinolytic inhibitors, serves as a direct indicator of fibrinolytic activity and indirectly reflects fibrinolysis status. Tissue plasminogen activator-inhibitor complex (t-PAIC), generated by physiological plasminogen activator inhibitor-1 (PAI-1) and tissue-type plasminogen activator (t-PA) at a 1:1 ratio, signifies elevated circulating t-PA levels and is established as a biomarker of fibrinolytic activation or vascular endothelial damage.^{6,10} D-dimer, a degradation product of cyclically cross-linked fibrin and positioned downstream in the fibrinolytic system, serves as a biomarker for post-activation endogenous fibrinolytic activity.¹¹ Thus, five coagulation activation markers-TM, TAT, t-PAIC, PIC, and D-dimer-are intimately linked to thrombosis mechanisms. Their quantifiable clinical application facilitates the prediction of pre-thrombotic crisis states.^{7,12} In acute ischemic stroke, platelet function and coagulation activation play pivotal roles in thrombus formation, with endogenous coagulation activation substantially contributing to the pathogenesis.¹ Research confirms the critical importance of coagulation-fibrinolysis balance in ischemic stroke,⁹ which aids in etiological classification and prognosis prediction.^{13,14} However, studies integrating early coagulation-fibrinolysis status with ischemic stroke's initial neurological symptoms remain limited, impeding comprehensive assessment of their role in severity progression and thrombosis prediction. Given the dynamic pathophysiology of ischemic stroke characterized by continuously formed activated clotting factors,^{15,16} along with enzymes and inhibitors corresponding to pathological features, provide valuable diagnostic indicators.¹⁷ Therefore, it was hypothesized that early coagulation activation indicators correlate with the severity of neurological function at the onset of ischemic stroke and were associated with the final infarct volume and lesion topography.

Methods

Research Design and Ethical Review

This study performed a retrospective analysis of clinical data, biological specimens, and imaging materials obtained from ischemic stroke patients admitted to the Stroke Unit at our hospital between October 2023 and February 2025 (Figure 1). Patient inclusion was continuously screened by neurology specialists. Inclusion criteria: 1. Age ≥ 18 years; 2. Hospital admission within 48 hours of acute ischemic stroke onset; 3. Provision of informed consent. Exclusion criteria: 1. First-time stroke or history of stroke with a modified Rankin Scale (mRS) score ≤ 2 ; 2. No antithrombotic medication use in the month prior to onset; 3. Severe hepatic or renal impairment (serum alanine aminotransferase [ALT] or aspartate aminotransferase [AST] > 2 times the upper limit of normal [ULN], or serum creatinine > 1.5 times ULN) or heart failure (New York Heart Association [NYHA] class III–IV); 4. Failure to collect blood samples prior to treatment or sample hemolysis resulting in data loss. This observational cohort study was designed to provide monitoring evidence for stroke diagnosis and treatment. The study protocol conformed to the principles outlined in the Declaration of Helsinki and received approval from the Ethics Committee of the Second Affiliated Hospital of Xiamen Medical College (approval number: 20220692025133). The study involves

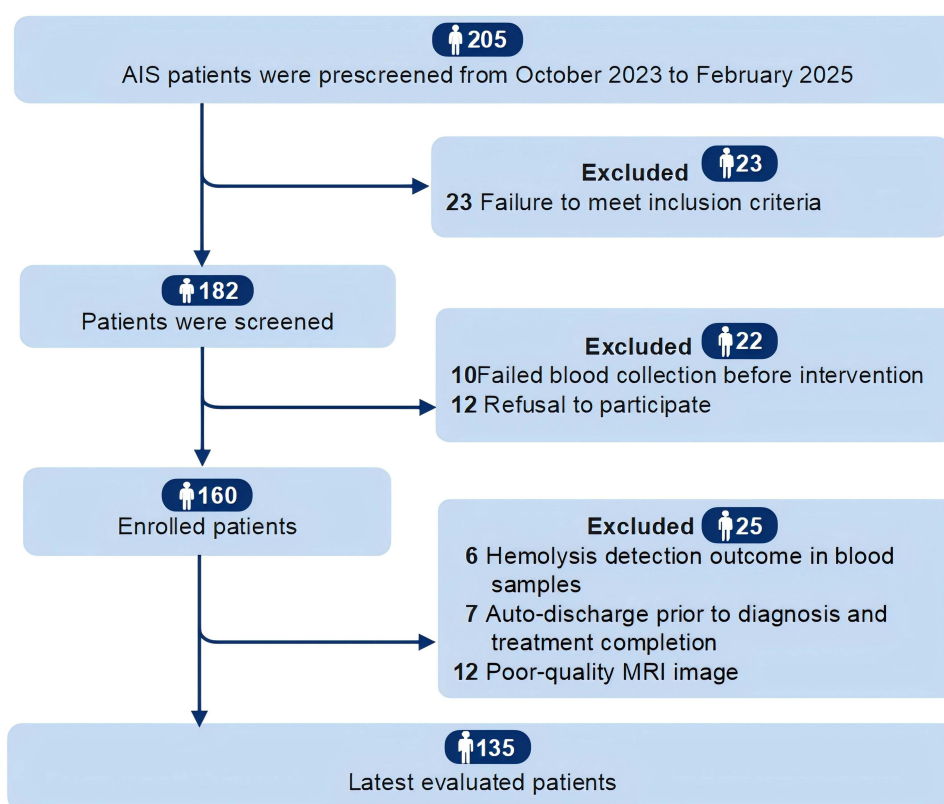


Figure 1 Flowchart of patient selection.

retrospective data analysis with all data anonymized, the ethics committee waived the requirement for individual informed consent.

Clinical Data

Clinical data included the encompassed patient age, gender, medical history (including hypertension, diabetes, hyperlipidemia, atrial fibrillation, smoking status, and alcohol consumption), time interval from hospital admission to treatment initiation, and post-admission vascular reperfusion therapy (intravenous thrombolysis and/or arterial thrombectomy) or antiplatelet therapy. Stroke severity was quantified using the standardized National Institutes of Health Stroke Scale (NIHSS).¹⁸ In reference to the classification of mild stroke proposed by J.K. Schwartz et al, cases with scores ≤ 3 were categorized as mild stroke, while those with scores > 3 were classified as moderate-to-severe stroke.¹⁹ Alberta Stroke Program Early Computed Tomography Score (ASPECTS)²⁰ was employed to evaluate cerebral Computed Tomography (CT) findings at admission, followed by comprehensive cranial magnetic resonance imaging (MRI) within 72 hours of hospitalization to assess infarction lesions and volume. Carotid plaque was assessed using color Doppler flow imaging (ProSound F75, Japan). Intimal-media thickness (IMT) > 1.5 mm was considered an indicator of carotid plaque formation. Carotid plaques were classified based on morphology and acoustic characteristics into low-echo, medium-echo, high-echo, and mixed-echo types. Medium-echo and high-echo plaques were classified as stable plaques, while low-echo and mixed-echo plaques were categorized as vulnerable plaques.²¹ Early neurological deterioration (END) is clinically defined as a dynamic NIHSS score increase of 2 points or more within 72 hours of hospital admission.^{22,23} Neurologists refer to the Trial of Org 10172 in Acute Stroke Treatment (TOAST)²⁴ for stroke etiology classification into four categories: large-artery atherosclerosis (LAA), cardioembolic (CE), small-artery occlusion (SAO), and other/undetermined etiology (OUE).

Measurement of Coagulation Activation Markers

All blood sample were collected before hospital admission and prior to treatment initiation. The second venous blood sample (2.7mL) collected after puncture should be immediately transferred to a BD vacuum tube containing 0.3mL of 0.109 mol/L sodium citrate anticoagulant for testing. The laboratory performs real-time detection after centrifugation at 2000×g for 15 minutes at room temperature. TAT, TM, t-PAIC, PIC, and D-dmmer test kits are supplied by Guangzhou Wanfu Company, with detection conducted using the Shenzhen Yingkai Shine i2900 chemiluminescence platform. In-house quality control follows the manufacturer's reference quality control protocol.

Infarct Volume in Cubic Centimeters

Within 5 days after hospital admission, a 3.0T head MRI (General Electric Company Discovery MR750w) was performed, including a diffusion-weighted imaging(DWI) sequence with b-values of 0 s/mm² and 1000 s/mm² (repetition time 4500ms; echo time 90ms; field of view 240×240 mm; matrix 392×216; slice thickness 5mm; number of slices 42). To ensure data objectivity, all scanned datasets were acquired and encoded in Digital Imaging and Communications in Medicine(DICOM) format to eliminate bias, with image samples randomly coded prior to storage. Volume quantification of DWI lesions was performed using the 3D-Slicer 4.10.2 manual segmentation algorithm based on intensity changes and edge detection. 3D-Slicer is a volumetric analysis software that processes, analyzes, and visualizes various types of medical neuroimaging data through its specialized module.²⁵ For DWI lesion segmentation, the system first performs visual analysis on axially reconstructed MRI images. Researchers manually delineate regions of interest using color-coded markers, then expand the labeled pixels to define lesion boundaries. Final volumetric measurements (mm³) are derived through this procedure, performed independently by two radiology technicians under blinded conditions.

Statistical Analysis

Statistical analyses were conducted utilizing IBM SPSS Statistics version 28.0. Data visualization and graphical representations were generated employing R version 4.5.1. Quantitative data were presented as median (interquartile range[IQR]). Inter-group differences were analyzed using *t*-tests or Mann–Whitney *U*-tests. Categorical variables were expressed as percentages, with inter-group comparisons performed using Chi squared test or Fisher's exact test. Baseline data from mild versus moderate-to-severe stroke patients were compared. Variables with $p \leq 0.05$ identified in univariate analyses were incorporated into multivariate logistic regression models. To evaluate the predictive capacity of coagulation activation markers, receiver operating characteristic (ROC) curve analysis was performed, and the area under the curve (AUC) was calculated. The utility of coagulation markers in establishing risk-based models for distinguishing between mild and severe strokes at admission was determined based on AUC values. Spearman correlation coefficients were used to measure associations between coagulation markers and core infarct volume, as well as infarct volumes at distinct anatomical locations.

Results

Of the 205 patients screened, 23 were not eligible for enrollment, 10 were blood drawn after treatment, 6 were hemolyzed blood samples, 12 were rejected for enrollment, 7 were discharged without complete clinical acute treatment, and 12 were obtained for image artifacts. A total of 135 patients were included in the final evaluation analysis.

Clinical Characteristics and Coagulation Markers in Mild Versus Moderate-to-Severe Stroke Groups

Patients were divided into two groups based on NIHSS scores at admission: 95 cases in the mild stroke group with median age 58 years[IQR52.00–68.00 years], and 68 males (72%); 40 cases in the moderate-to-severe stroke group with median age 65.5 years[IQR55.50–74.75 years], and 29 males (73%) (Table 1). No statistically significant differences were observed between groups in gender, hypertension, diabetes, hyperlipidemia, smoking status, alcohol consumption, carotid plaque, or time from symptom onset to treatment initiation. However, the moderate-to-severe stroke group exhibited significantly older patients, higher prevalence of atrial fibrillation, greater admission ASPECTS scores, and

Table 1 Clinical Characteristics and Coagulation Markers in Mild Stroke and Moderate to Severe Stroke

Characteristic	Minor Stroke (N=95)	Moderate-to-Severe Stroke (N=40)	χ^2/t	p
Age(years),mean(IQR)	58.00(52.00,68.00)	65.50(55.50,74.75)	-2.156	0.033
Male sex,n(%)	68(72%)	29(73%)	0.012	0.913
Medical history,n(%)				
Hypertension	80(84%)	37(93%)	1.674	0.271
Diabetes mellitus	22(23%)	13(33%)	1.279	0.286
Atrial fibrillation	6(6%)	12(30%)	13.664	<0.001
Hyperlipidaemia	29(31%)	15(38%)	0.623	0.430
Current smoker	30(32%)	8(20%)	1.866	0.211
Alcohol intake	20(21%)	6(15%)	0.663	0.482
Admission ASPECTS,median(IQR)	9.00(9.00,10.00)	9.00(8.00,10.00)	-2.914	0.004
Carotid Artery Plaque,n(%)			4.203	0.122
Non-plaque	37(39%)	9(23%)		
Stable plaque	28(30%)	12(30%)		
Vulnerable plaque	30(32%)	19(48%)		
TOAST classification,n(%)			25.359	<0.001
LAA	33(35%)	21(53%)		
CE	3(3%)	10(25%)		
SAO	37(39%)	7(18%)		
OUE	22(23%)	2(5%)		
Therapeutic regimen,n(%)			15.425	<0.001
Revascularization	18(19%)	21(53%)		
Antithrombotic therapy	77(81%)	19(48%)		
Infarct volume,median(IQR)	771.16(151.70, 2841.15)	6302.36(912.39, 23,722.45)	-4.664	<0.001
Onset-to-treatment time(h),Mean(IQR)	11.00(5.00,24.00)	6.00(2.00,10.75)	1.881	0.062
END,n(%)	16(17%)	14(35%)	5.370	0.025
Experimental index				
TM,TU/mL,median(IQR)	8.68(7.55,10.25)	8.82(6.65,11.33)	-0.504	0.615
TAT,ng/mL,median(IQR)	2.84(1.49,4.65)	3.82(2.17,7.42)	-2.229	0.026
PIC, μ g/mL,median(IQR)	0.64(0.46,0.85)	0.87(0.52,1.29)	-2.511	0.012
t-PAIC,ng/mL,median(IQR)	11.61(7.68,15.01)	12.53(10.23,18.44)	-2.036	0.042
D-dimer, μ g/mL,median(IQR)	240.0(160.0,321.0)	330.00(200.25,501.50)	-3.077	0.002
APTT,s,median(IQR)	30.80(29.50,33.80)	31.00(28.45,33.80)	-0.200	0.841
PT,s,median(IQR)	11.30(10.70,11.18)	11.25(10.70,11.58)	-0.205	0.838
FIB,g/L,median(IQR)	3.25(2.96,3.68)	3.16(2.84,3.58)	-1.137	0.255
PLT* $10^9/L$, median(IQR)	228.0(193.0,252.0)	219.50(182.00,246.75)	-1.084	0.278
WBC* 10^9 , median(IQR)	7.55(6.47,9.08)	7.81(6.19,10.32)	-0.752	0.452
RBC* 10^{12} , median(IQR)	4.80(4.42,5.23)	4.88(4.43,5.10)	-0.154	0.877
Hs-CRP, mg/L, median(IQR)	1.71(0.79,4.02)	2.56(1.10,4.47)	-0.901	0.368
PDW%, median(IQR)	16.20(16.00,16.70)	16.35(16.00,16.48)	-0.553	0.580
PLR, median(IQR)	228.0(193.0,252.0)	219.50(182.00,246.75)	-0.612	0.541

Abbreviations: IQR, interquartile range; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; LAA, Large-artery atherosclerosis; CE, Cardio embolic stroke; SAO, Small-artery occlusion; OUE, other determined etiology and undetermined etiology; END, early neurological deterioration, an increase in the NIHSS motor score of ≥ 1 or a total score of ≥ 2 within 72h of admission; TM, thrombomodulin; TAT, thrombin-antithrombin complex; PIC, plasmin- $\alpha 2$ plasmin inhibitor complex; t-PAIC, tissue plasminogen activator-inhibitor complex; APTT, Activated Partial Thromboplastin; PT, Prothrombin time; FIB, Fibrinogen; PLT, platelet; WBC, white blood cell; RBC, erythrocyte; Hs-CRP, hypersensitive c-reactive protein; PDW%, Platelet Distribution Width; PLR, Platelet-to-Lymphocyte ratio.

larger infarct volumes ($p < 0.05$). This group also exhibited a higher proportion of large atherosclerotic lesions, increased utilization of emergent endovascular recanalization therapy following admission, and lower incidence rates of early neurological deterioration. Analysis of coagulation biomarkers revealed no statistically significant difference in thrombomodulin(TM) levels ($P = 0.615$), while levels of thrombin antithrombin complex(TAT), plasmin- $\alpha 2$ plasmin inhibitor complex(PIC), tissue-type plasminogen activator inhibitor complex (t-PAIC), and D-dimer were significantly

elevated (P values: 0.026,0.012,0.042,0.002). No statistically significant differences were observed between the two groups in conventional coagulation parameters (activation partial thromboplastin time [APTT], prothrombin time [PT], fibrinogen [FIB], platelet count [PLT], red blood cell count [RBC], platelet distribution width [PDW(%)] and inflammatory markers (white blood cell count [WBC], high-sensitivity C-reactive protein [Hs-CRP], and platelet-to-lymphocyte ratio[PLR]).

Logistic Regression Analysis of Predictors of Moderate and Severe Stroke

Logistic regression analysis revealed statistically significant differences between the two groups in age, atrial fibrillation incidence, hospital admission ASPECT scores, etiological subtypes, treatment regimens, infarct volume, and early neurological deterioration. No significant statistical differences were observed between TM and PIC. Elevated plasma levels of TAT, t-PAIC, and D-dimer were identified as significant risk factors for moderate-to-severe stroke, with plasma D-dimer constituting an independent risk factor. More specifically, each 1μg/mL increase in plasma D-dimer was associated with a 1.002-fold increased likelihood of moderate-to-severe stroke (95% CI: 1.000–1.004; P=0.050) (Table 2).

ROC Curve Analysis of Risk Factors for Moderate and Severe Stroke

Univariate analysis identified elevated levels of TAT, t-PAIC, and D-dimer in moderate to severe stroke. Following adjustment for age, atrial fibrillation, admission ASPECTS, TOAST classification, therapeutic regimen, infarct volume, and END, D-dimer remained significantly associated with an increased risk of moderate to severe stroke. The area under the ROC curve(AUC) for TAT in predicting moderate to severe stroke was 0.62 (95% CI, 0.523–0.717). The AUC for D-dimer was 0.63 (95% CI, 0.537–0.731). The AUC for t-PAIC was 0.59 (95% CI, 0.494–0.690). Furthermore, the combined model incorporating TAT, t-PAIC, and D-dimer yielded an AUC of 0.67 (95% CI, 0.579–0.768) for predicting moderate to severe stroke (Figure 2).

Differences in Coagulation Activation Markers with Infarction Volume

The study quantitatively assessed infarct volume and location in cranial MRI scans, revealing 46 cases (27.5%) of anterior circulation cortical infarction, 78 cases (46.7%) of anterior circulation deep infarction, and 27 cases (16.2%) of posterior circulation infarction. Within this cohort, 15 cases encompassed both cortical and deep infarctions in the anterior circulation, while 1 case exhibited infarctions in involving both anterior and posterior circulations. The correlation

Table 2 Logistic Regression Analysis of Predictors of Moderate and Severe Stroke

Characteristic	Univariate Analysis			Multivariate Analysis		
	B	OR (95% CI)	p	B	OR (95% CI)	p
Age(years)	0.034	1.034(1.002,1.068)	0.036	0.018	1.018(0.972,1.066)	0.451
Atrial fibrillation	1.850	6.357(2.185,18.497)	<0.001	−1.781	0.168(0.010,2.838)	0.216
Admission ASPECTS	−0.551	0.576(0.409,0.812)	0.002	−0.228	0.796(0.446,1.421)	0.440
TOAST classification	−0.604	0.547(0.383,0.781)	<0.001			0.027
Therapeutic regimen	1.554	4.728(2.113,10.578)	<0.001	−1.938	0.144(0.046,0.450)	<0.001
Infarct volume	0.000	1.000(1.000,1.000)	0.004	0.000	1.000(1.000,1.000)	0.168
END	0.978	2.659(1.144,6.178)	0.023	−1.610	0.200(0.058,0.690)	0.011
TM,TU/mL	0.070	1.073(0.943,1.221)	0.285			
TAT,ng/mL	0.092	1.096(1.008,1.192)	0.032	0.128	1.137(0.982,1.315)	0.085
PIC,μg/mL	−0.008	0.992(0.882,1.115)	0.888			
t-PAIC,ng/mL	0.071	1.074(1.014,1.138)	0.016	0.031	1.031(0.956,1.112)	0.426
D-dimer,μg/mL	0.003	1.003(1.001,1.005)	0.006	0.002	1.002(1.000,1.004)	0.050

Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; END, early neurological deterioration, an increase in the NIHSS motor score of ≥1 or a total score of ≥2 within 72h of admission; TM, thrombomodulin; TAT, thrombin-antithrombin complex; PIC, plasmin-α2 plasmin inhibitor complex; t-PAIC, tissue plasminogen activator-inhibitor complex;

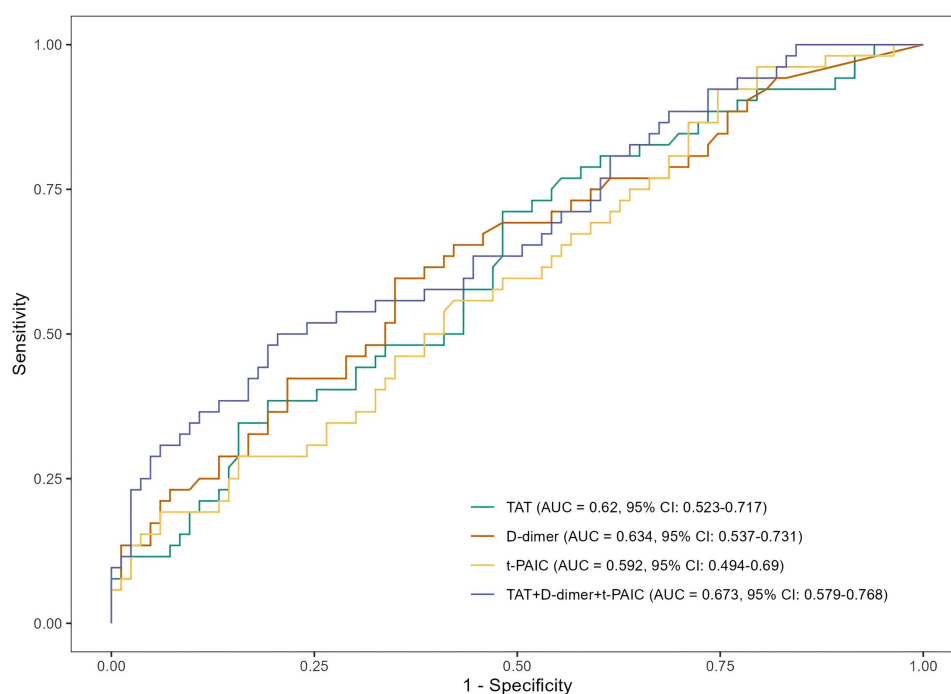


Figure 2 Receiver operator characteristic curve analyses for coagulation markers to predict moderate to severe stroke.

between infarct volume and five coagulation activation markers was investigated (Figure 3). In the mild stroke group, TM levels exhibited significant inverse correlations with both total cerebral infarction volume and posterior circulation infarction volume ($R=0.17$, $p<0.05$; $R=0.49$, $p<0.05$). Conversely, in the moderate-to-severe stroke group, TM levels demonstrated no significant correlations with total infarction volume, anterior circulation cortical infarction volume, anterior circulation deep infarction volume, or posterior circulation infarction volume ($p>0.05$ for all comparisons). Similarly, TAT levels showed no statistically significant associations with total infarction volume, anterior circulation deep infarction volume, or posterior circulation infarction volume. Notably, in the moderate-to-severe group, TAT levels increased with the enlargement of anterior circulation cortical infarction volume ($R=0.61$, $p<0.05$). Levels of t-PAIC and PIC demonstrated no significant correlation with total infarct volume or regional infarction volumes, nor were clear associations observed in stratified analyses comparing mild versus moderate-to-severe patient groups. D-dimer levels showed no significant correlation with anterior circulation deep infarction volume or posterior circulation infarction volume. However, D-dimer levels increased markedly with total infarct volume and anterior circulation cortical infarction volume, particularly showing a significant upward trend in the moderate-to-severe group ($R=0.74$, $p<0.05$; $R=0.79$, $p<0.05$) (Figure 3).

Furthermore, correlation analysis was performed to assess the relationships between biomarkers and clinical symptoms and functional outcomes. A heat map visualizing correlations among admission NIHSS scores, infarct volume, early neurological deterioration, and five coagulation activation markers (Figure 4). The severity of neurological impairment at admission and total infarct volume demonstrated statistically significant correlations with coagulation activation markers; with the strongest association was observed with D-dimer levels ($R=0.7$, $p<0.05$) (Figure 4).

Discussion

The secondary prevention of stroke fundamentally presents a crucial challenge related to the equilibrium between thrombotic risk and hemorrhagic burden. Clinically, there has been a long-standing discussion regarding monotherapy, dual - therapy antiplatelet regimens, and anticoagulation therapies. At present, the OCEANIC-STROKE trial has shown that for patients with non-cardiogenic ischemic stroke within 72 hours of onset, adding 50 mg of Asundexian once daily to antiplatelet therapy significantly decreases the risk of ischemic stroke recurrence compared to placebo, without

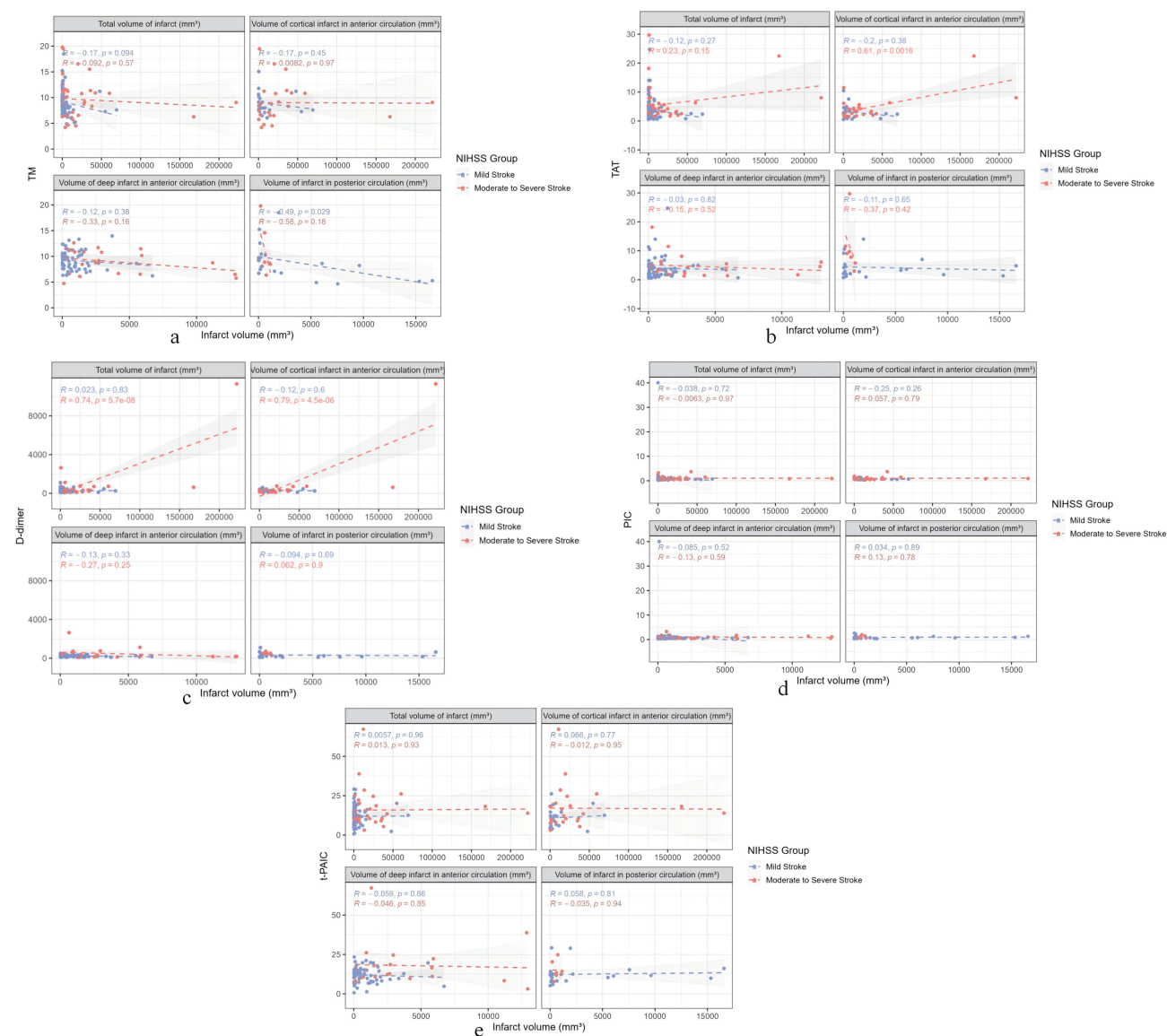


Figure 3 The correlation between coagulation markers and infarct volume, infarct location.

elevating the risk of major bleeding.²⁶ This phenomenon reveals deeper pathophysiological differences, suggesting that cerebral thrombosis may rely more heavily on platelet activation and endogenous contact activation pathways. In this exploratory observational study, we conducted an initial investigation of coagulation activation markers at the time of admission for 135 ischemic stroke patients with varying neurological severity. The results demonstrated that, compared to patients with mild stroke, those presenting with moderate-to-severe stroke demonstrated significantly elevated plasma levels of TAT, t-PAIC, and D-dimer, indicating more activated coagulation-fibrinolysis status. Incorporating these coagulation activation markers into risk factor-based models may enhance clinical assessment of neurological severity in ischemic stroke patients.

This study revealed that patients with moderate-to-severe stroke are older, exhibit a higher prevalence of atrial fibrillation, present with higher ASPECTS scores at admission, larger infarct volumes, and lower rates of early neurological deterioration. These findings are consistent with previous research.^{27–29} Notably, the highly effective reperfusion therapy (HERMES) achieved functional independence (defined as a modified Rankin Scale[mRS] score ≤ 2 at 90 days) in only 48% of patients with acute ischemic stroke.³⁰ Multiple randomized controlled trials, including CHANCE, CHANCE-2, POINT, and START, have consistently demonstrated the critical importance of precise

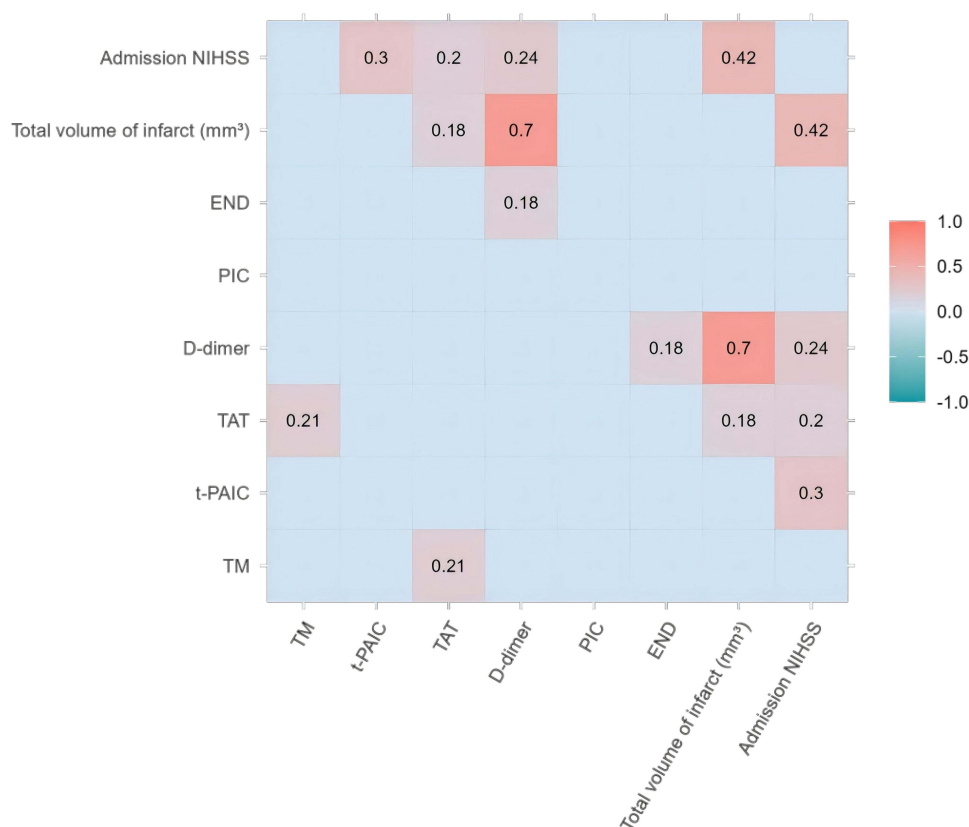


Figure 4 The correlation between coagulation markers and admission INHSS, Total volume of infarct and END.

antithrombotic therapy in preventing thrombosis in ischemic stroke.^{31,32} Monitoring disease progression via stroke-associated biomarkers provides new directions for precision treatment and identifying novel therapeutic targets.³³ In this study, early-onset coagulation activation marker analysis revealed no significant difference in TM levels between mild and moderate-to-severe stroke groups ($P=0.615$). However, Xin Xu et al found that both systemic and local TM levels were negatively correlated with admission NIHSS scores.³⁴ Conversely, Yonge Liu et al observed no dynamic alterations in TM levels during quantitative monitoring of intravenous thrombolysis in stroke patients.³⁵ This discrepancy may indicate a potential association between elevated TM and more severe endothelial dysfunction in the cohort of large-vessel occlusion severe stroke patients (median admission NIHSS=15) investigated by Xin Xu et al. Previously, Naifang Ye et al reported elevated levels of TAT and D-dimer were higher in patients with moderate to severe stroke than those with mild stroke, but there was no assessment of TM, t-PAIC, and PIC levels.³⁶ A prospective clinical study by Xiaoxia Zhao et al demonstrated that malignant cerebral artery infarction(MCAI) patients exhibited significantly higher admission levels of TAT, PIC, and t-PAIC (median plasma concentrations 12.25ng/mL, 1.67 μ g/mL, and 13.85 ng/mL) compared to non-malignant cerebral artery infarction(NMCAI) patients (median plasma concentrations 4.6ng/mL, 1.07 μ g/mL, and 8.70 ng/mL).³⁷ Similarly, the current study revealed significantly increased levels of TAT, PIC, and t-PAIC (median plasma concentrations: 3.82ng/mL, 0.87 μ g/mL, and 12.53ng/mL) in the moderate-to-severe stroke group relative to the mild stroke group (median plasma concentrations: 2.84ng/mL, 0.64 μ g/mL, and 11.61ng/mL). Notably, Xiaoxia Zhao et al postulated that heightened coagulation activation levels may be associated with larger baseline infarct volumes (≥ 70 mL) in their patient cohort. Previous studies have confirmed the diagnostic value of coagulation activation markers in predicting thrombosis,^{38–40} Furthermore, investigations have demonstrated that coagulation-fibrinolysis markers—specifically TAT, PIC, D-dimer—serve as indicators of tissue damage and activators of the coagulation cascade, thereby facilitating disease diagnosis.⁴¹ Our findings reveal that plasma levels of TAT, t-PAIC, and D-dimer levels show significant predictive value for moderate-to-severe ischemic stroke. ROC analysis confirmed their predictive efficacy, yielding area under the curve (AUC) values of 0.62, 0.59, and 0.63, respectively. Notably, D-dimer demonstrated superior

predictive performance compared to the other biomarkers examined. Our study also observed differential expression of coagulation activation markers distinct cerebral vascular distribution sites. Such distinct anatomical regions of cerebral vessels exhibit unique hemodynamic shear forces and vascular wall structures that are sensitive to hemodynamic changes, thereby directly influencing coagulation marker profiles.⁴² Cerebral vasculature is conventionally classified into the anterior and posterior circulation systems, with arterial branches divided into cortical and deep regions. Consequently, infarction sites were further categorized into anterior-cortical, anterior-deep, and posterior-circulation territories. Results demonstrated a negative correlation between TM levels and infarct volume, with minimal regional variations. This phenomenon can be explained by TM's function as an anticoagulant cofactor: following vascular endothelial injury, TM detaches from endothelial cells into the circulation. Its multiple domains exhibit high-affinity binding to thrombin substrates, effectively generating anticoagulant effects. Decreased TM levels may increase individual thrombosis risks.⁴³ As previously established, TAT functions as a sensitive indicator of thrombin generation. During coagulation, thrombin acts as a pivotal enzyme: it activates platelets through proteolysis of PAR1 and PAR4 receptors,⁴⁴ and modulates fibrin network formation via its concentration gradient.⁴⁵ High thrombin concentrations generate highly branched fibrin dense nets, creating clots that exhibit relative resistance to fibrinolysis.⁴⁶ Previous studies by Zhao Xiaoxia et al have identified that elevated TAT and t-PAIC levels as risk factors for extensive infarct volumes; however, stratified analyses based on distinct vascular distributions of infarction remain unaddressed. Our study found that TAT levels correlate positively with infarct volume, particularly in anterior circulation cortical infarction regions. Systematic studies indicate that plasma TAT levels increase in ischemic stroke patients, especially in acute stroke of cardiac embolism.⁹ However, due to TAT's short half-life, previous studies involving real-time monitoring of TAT levels for prognosis comparison suffered from temporal mismatches, necessitating further research to reveal dynamic coagulation activation states. Additionally, our study demonstrated that D-dimer levels correlate positively with total infarct volume, with more significant increases observed in anterior circulation cortical regions. In contrast, t-PAIC and PIC exhibited no significant correlation with either total infarct volume or site-stratified infarct volumes. Within established coagulation theory, t-PAIC corresponds to the exogenous activation pathway of the fibrinolytic system, while PIC represents the activation of plasmin, both indicating the initiation of fibrinolysis. D-dimer, being a downstream fibrinolysis marker, constitutes a degradation product of cross-linked fibrin.^{6,47} Therefore, t-PAIC, PIC, and D-dimer all serve as reliable markers of fibrinolytic status.⁴⁸ This study demonstrated that early D-dimer levels correlated with changes in infarct volume, but early t-PAIC and PIC levels exhibited no significant differences in infarct volume, which may reflect that t-PAIC and PIC may reflect a more immediate fibrinolytic state, whereas D-dimer levels correspond to a relatively delayed phase of fibrinolysis.

Furthermore, the incidence of early neurological deterioration (END) in ischemic stroke reached 40%.^{49,50} Evidence indicates that this may be associated with the in situ extension of primary thrombi, which could result from increased abnormal coagulation activity and resistance to fibrinolysis, or from collateral failure activating the coagulation cascade adjacent to the primary thrombus, or from endogenous coagulation activation producing inflammatory factors that exacerbate thrombosis.^{15,16} Zhao Yifei et al established a prognostic risk nomogram utilizing LASSO regression models to incorporate coagulation activation indicators, including PIC and t-PAIC.⁵¹ Our study identified significant correlations between coagulation activation markers and admission NIHSS scores, infarct volume, and early neurological deterioration. Further analysis revealed associations between admission NIHSS scores, infarct volume, and five coagulation activation indicators with baseline neurological severity and infarct volume, with D-dimer exhibiting the strongest correlation ($R=0.7$). The findings indicate that real-time monitoring of the coagulation-fibrinolysis status during neurological symptom changes demonstrates greater clinical significance for therapeutic guidance.

While this study demonstrates notable strengths, its limitations must be acknowledged. Firstly, as a prospective observational study with limited sample size, it may suffer from selection bias. The research lacks age stratification and dynamic evaluation of post-intervention coagulation activation marker changes in clinical practice. Future studies should incorporate more multicenter samples to compare dynamic changes in these markers across different intervention types, assess their predictive value for disease progression and prognosis, and establish more accurate models to guide clinical antithrombotic therapy. Despite these constraints, the study achieves clear objectives: using simple coagulation markers

to differentiate the severity of ischemic stroke neurological deficits, providing valuable evidence for early antithrombotic treatment decisions, particularly in guiding management of disabling strokes.

Conclusion

The use of simple coagulation activation markers to distinguish the severity of early neurological symptoms in emergency admission for ischemic stroke may have potential as adjunctive biomarkers for assess the real-time coagulation and fibrinolysis status of ischemic stroke to guide treatment.

Data Sharing Statement

The authors affirm that the original data are available from the corresponding author without undue reservation.

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Disclosure

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