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Thromboelastography predicts dual antiplatelet therapy-related hemorrhage in patients with acute ischemic stroke

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ABSTRACT

Background Stratification of the risk of hemorrhage in patients with acute ischemic stroke following dual antiplatelet therapy (DAPT) is challenging. It remains unclear whether thromboelastography (TEG) can be used to predict DAPT-related hemorrhagic events.

Objective The present study aims to discover predictors for hemorrhage events after DAPT based on parameters such as TEG.

Methods A total of 859 patients with acute ischemic stroke who received DAPT were recruited consecutively. Demographic, clinical, and neuroimaging characteristics were evaluated at baseline; TEG parameters were obtained 7 days later after DAPT. Hemorrhagic events were monitored about 1 month after the stroke.

Results Of the patients, 61 (7.1%) had hemorrhagic events. Patients in the hemorrhage group had a lower adenosine diphosphate (ADP)-induced platelet-fibrin clot maximum amplitude and a higher ADP inhibition rate (ADP%) than those in the non-hemorrhage group ($p < 0.05$). ADP% was confirmed as an independent predictor of hemorrhagic events with an optimal cut-off point of 83.3% (area under the curve (AUC) = 0.665, 95% CI 0.573 to 0.767, $p < 0.01$). We constructed a logistic model based on D-dimer, National Institutes of Health Stroke Scale scores, and ADP% to predict hemorrhagic events in patients with acute ischemic stroke during DAPT (AUC = 0.720, 95% CI 0.625 to 0.858, $p < 0.01$), with a sensitivity of 72.1% and a specificity of 76.5%.

Conclusions Monitoring changes of TEG parameters helps to guide personalized DAPT for patients with ischemic stroke. A 30–82.3% range of ADP% is recommended for DAPT treatment.

INTRODUCTION

Clinical guidelines recommend dual antiplatelet therapy (DAPT) for patients presenting with a minor stroke or a high risk of transient ischemic attack (TIA), and for those with ischemic stroke attributable to severe vascular stenosis.¹ However, DAPT is accompanied by an increased risk for hemorrhage. A multicenter study showed that DAPT-related hemorrhage in patients with cerebral infarction within 1 year was 5.02%.² Standard DAPT therapy is associated with the highest rates of bleeding in the early ischemic stage. The incidence of hemorrhagic transformation (HT) within 1 month was found to be 12% while that of major hemorrhagic events

was 5.8%, which was significantly higher than that at 31–90 days.³ Hemorrhagic events after cerebral infarction affect antiplatelet therapy compliance and also increase the incidence of poor prognosis.⁴ Therefore, there is an urgent need to predict and identify populations at high risk of hemorrhage and to provide timely interventions.

Thromboelastography (TEG) can be used to reflect the coagulation function of a whole-blood sample dynamically. By measuring the viscoelastic changes that occur during the hemostatic process, TEG gives a real-time functional evaluation of the coagulation cascades, beginning with initial platelet–fibrin interaction, through platelet aggregation, clot strengthening, fibrin cross-linkage, and eventually, clot lysis.⁵ In recent years, TEG has been shown to be a useful tool for detecting abnormal hemorrhage and vascular occlusion.⁶ Compared with the properties of traditional coagulation function tests, TEG can directly respond to changes in platelet function⁷ and can detect the efficacies of antiplatelet drugs,⁸ thereby guiding individualized antiplatelet therapy for ischemic cerebrovascular diseases. Studies have found that TEG can detect coagulopathy after acute cerebral infarction,⁹ which can be used to predict the risk of recurrent ischemic events. However, the value of TEG in predicting hemorrhagic events during the treatment of ischemic stroke remains unclear.

The aims of our study were to investigate the value of TEG in predicting the risk of hemorrhage in patients with acute ischemic stroke receiving DAPT and to establish an effective hemorrhage prediction model, which might provide new monitoring tools for decision-making and risk assessments during clinical antiplatelet treatments.

MATERIALS AND METHODS

Study population

We continuously recruited patients with acute ischemic stroke from Wuhan Tongji Hospital between September 2013 and May 2019. All included patients received DAPT and fulfilled the following inclusion criteria: (1) over 18 years old; (2) clinical diagnosis of acute minor ischemic stroke which was defined as a National Institutes of Health Stroke Scale (NIHSS) score ≤ 3 , high-risk TIA (defined as a ABCD2 score ≥ 4),¹⁰ or symptomatic severe stenosis (70–99%) of a major intracranial artery (middle cerebral, carotid, vertebral, or basilar arteries)^{11,12},

and (3) no evidence of cardioembolism. The exclusion criteria were as follows: (1) incomplete data, without TEG or head CT/MRI scan; (2) any medication within the past 3 months that might affect blood coagulation function, such as cilostazol, warfarin, dabigatran, heparin, or factor Xa inhibitors (such as rivaroxaban); (3) patients who received thrombolysis or thrombectomy; (4) a history of malignant tumors, digestive diseases, or severe liver/kidney/blood-related diseases; (5) history of extracranial hemorrhagic events (gastrointestinal hemorrhage, urethral hemorrhage, mouth and nose hemorrhage); and (6) patients lost to follow-up. All the patients were prescribed clopidogrel 75 mg/day plus aspirin 100 mg/day without loading dose or other antiplatelet agents (eg, ticagrelor) within 24–48 hours of symptom onset. This study was approved by the ethics board of Tongji Hospital, and no informed consent was required owing to the retrospective nature of this study.

Clinical assessments

Demographic and clinical data that were collected included the following: age, sex, smoking (defined as a history of smoking ≥ 1 cigarette per day for 1 year or more), alcohol intake (defined as weekly alcohol intake exceeding 200 g for 1 year or more), history of stroke/TIA, hypertension, diabetes mellitus, hyperlipidemia, and coronary heart disease. Variables of blood pressure and statin therapy before and after stroke onset¹³ were recorded (see online supplemental materials). NIHSS scores were also collected on admission. Laboratory tests were completed within 24 hours of admission, which included biochemical indexes, platelet indexes, glucometabolic indexes, and coagulation function.

Ischemic infarction lesions were classified as small (<1.5 cm), medium (1.5–5 cm), or large (>5 cm) according to the size of the lesion. Stroke subtypes were classified into three categories based on etiology, using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification: (1) large-artery atherosclerosis; (2) small artery occlusion; (3) stroke of other determined etiology or undetermined etiology. The distribution (anterior and/or posterior circulation) and the location (superficial and/or deep) of the infarction lesion were provided¹⁴ (see online supplemental materials).

Thromboelastography (TEG)

It is believed that the inhibition plateau of platelet aggregation appears 7 days after a regular dose of aspirin and clopidogrel.¹⁵ Therefore, peripheral venous whole blood was collected at least 7 days after the initiation and 12 hours after the last dose of DAPT in the present study. The blood samples were analyzed within 1 hour of collection using the TEG Analyzer 5000 (Haemonetics Corporation, USA). Seven TEG parameters were selected as important variables: (1) reaction time (R, min), representing the time from the activation of clotting factors to the initial clot formation; (2) coagulation time (K, min), representing the time for clot formation to reach a 20 mm amplitude; (3) angle (α , degree), representing the speed of clot formation; (4) maximum amplitude (MA), representing the maximum intensity of the clot; (5) MA_{ADP} , representing the adenosine diphosphate (ADP)-induced blood clot strength; (6) arachidonic acid (AA) inhibition rate (AA%), representing the response to aspirin; and (7) ADP inhibition rate (ADP%), representing the response to clopidogrel. The platelet inhibition rate induced by AA or ADP is calculated using computer software according to the following formula: inhibition rate (%) = $[(MA_{thrombin} - MA_{ADP} \text{ or } MA_{AA}) / (MA_{thrombin} - MA_{fibrin})] \times 100\%$.¹⁶

Hemorrhagic events and grouping

Hemorrhagic events were monitored for about 1 month after the stroke, and patients were divided into a hemorrhage group and a non-hemorrhage group. Hemorrhagic events included HT, gastrointestinal hemorrhage, and other types of hemorrhage (eg, urethral hemorrhage, mouth hemorrhage, and nose hemorrhage). Brain imaging (CT or MRI) was performed within 72 hours and on day 14 ± 7 after the onset of stroke to observe HT. In order to diagnose HT in time, imaging was also performed whenever the patient's clinical condition deteriorated. Gastrointestinal hemorrhage was defined as having coffee-ground emesis, hematemesis, blood in the nasogastric tube, and melena. Urethral hemorrhage was defined as gross hematuria or positive urine occult blood without visible urethra damage. Mouth and nose hemorrhages were defined as spontaneous mouth or nose hemorrhage without any obvious causes or a history of spontaneous hemorrhage.

Statistical analysis

Statistical analysis was performed via SPSS 22.0 software. Categorical variables are reported as n (%), and continuous variables are reported as the mean \pm SE of the mean (SEM) or median (IQR). $p < 0.05$ was considered statistically significant. The X^2 test was used to analyze categorical variables. The Kolmogorov-Smirnov test was used to confirm normal distribution. Continuous variables with normal distributions were compared via two-sided t-test, while non-normally distributed continuous variables were analyzed via the Mann-Whitney U test. Univariate logistic regression analysis was used to determine the risk factors for hemorrhagic events; subsequently, multivariate logistic regression analysis was used to adjust confounding factors and to establish a prediction model. The Hosmer–Lemeshow goodness-of-fit test was used to assess the fit of the logistic model. The diagnostic values of TEG parameters and the logistic model were tested via receiver operating characteristic (ROC) curve analysis. The area under the ROC curve (AUC) was reported. The demarcation point corresponding to the maximum of the Yoden index (sensitivity + specificity – 1) was used as the boundary value.

RESULTS

Demographics and clinical characteristics

A total of 2391 patients with ischemic stroke were initially screened, among whom 859 patients remained after applying our inclusion and exclusion criteria, resulting in 798 cases in the non-hemorrhage group and 61 cases in the hemorrhage group (figure 1). Among the 859 patients, hemorrhagic events occurred in 31 (3.6%) who had HT and 1 (0.1%) who had symptomatic intracranial hemorrhage. Other common hemorrhagic events included 19 (2.2%) cases of gastrointestinal hemorrhage, 7 (0.8%) of urethral hemorrhage, 3 (0.3%) of mouth hemorrhage, and 1 (0.1%) of nose hemorrhage (online supplemental table 1).

The NIHSS score was significantly lower in the non-hemorrhage group than in the hemorrhage group (3 (1–5) vs 4 (2–9), $p < 0.05$, table 1). However, no significant differences in age, sex, risk factors, statin treatment, infarction causes, or distribution were found between the groups (table 1). Additionally, it was demonstrated that the hemorrhagic events were not associated with the infarction locations or the variables of blood pressure (online supplemental tables 2 and 3).

Hematological data associated with hemorrhagic events

Intergroup comparisons of hematological data were also carried out. Patients in the hemorrhage group had higher levels of blood

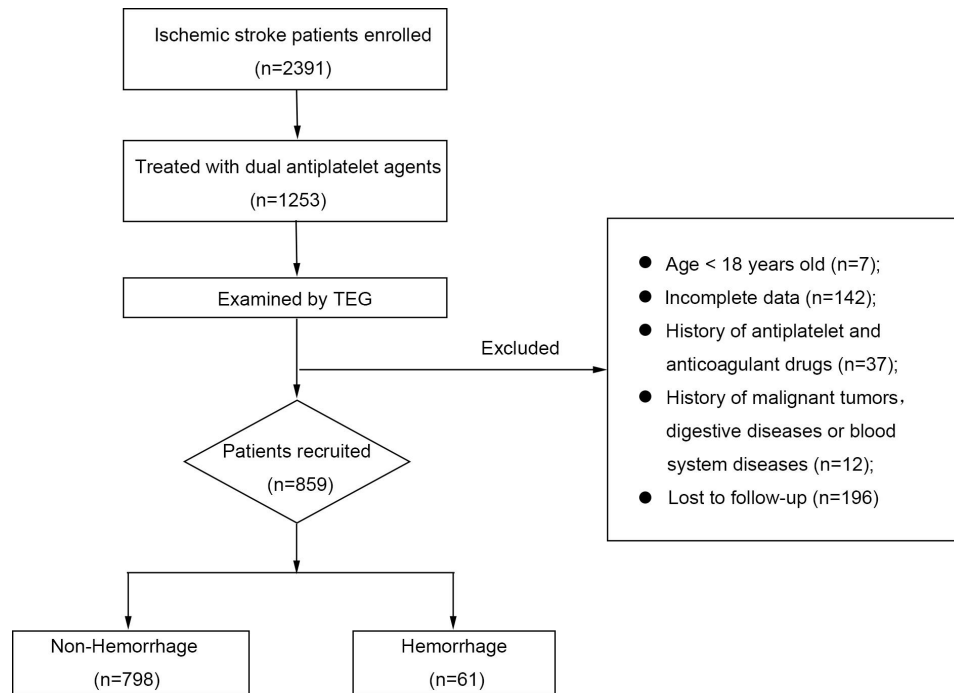


Figure 1 Flowchart of patient selection. TEG, thromboelastography.

glucose (Glu), fibrinogen (FIB), and D-dimers than those in the non-hemorrhage group ($p < 0.05$). After adjusting for NIHSS scores, D-dimer levels were still significantly higher in the hemorrhage group than in the non-hemorrhage group ($p < 0.05$). No significant difference was found in the biochemical indexes or platelet indexes between the two groups (online supplemental table 4).

Associations of TEG parameters with early hemorrhagic events

The association of TEG parameters with early hemorrhagic events was evaluated (online supplemental table 5). The MA_{ADP} was significantly higher (32.2 (18.9–42.3) vs 22 (12.9–41.4), $p < 0.05$) and the ADP% was significantly lower (58.7 (38.7–81.6) vs 78.6 (45.5–93.9), $p < 0.05$) in the non-hemorrhage group than in the hemorrhage group. The result remained the same even if the baseline data (NIHSS score, FIB, and D-dimer) were adjusted.

After grouping the MA_{ADP} by quartiles, more hemorrhagic events appeared in the lowest quartile than in the highest quartile (12.7% vs 4.1%, $p < 0.05$, online supplemental figure 1A); conversely, more patients with hemorrhagic events were found in the highest quartile than in the lowest quartile of ADP% (11.5% vs 3.7%, $p < 0.05$, online supplemental figure 1B).

All 315 patients who had symptomatic cerebral vascular stenosis were reanalyzed. Among these cases, 217 (68.9%) had anterior circulation stenosis and 95 (30.2%) had stenosis located in the posterior circulation (online supplemental table 6). This finding demonstrated that ADP% was independently associated with hemorrhagic events in patients with stenosis (online supplemental table 7), especially those with anterior circulation vascular stenosis (online supplemental tables 8 and 9).

Risk factors for hemorrhagic events in patients who received DAPT

Univariate analysis was performed on preliminarily filtered risk factors for hemorrhagic events in patients. The hemorrhagic

events were associated with FIB (OR=1.369; 95% CI 1.055 to 1.778), D-dimers (OR=1.400; 95% CI 1.020 to 1.923), NIHSS scores (OR=1.173; 95% CI 1.066 to 1.290), MA_{ADP} (OR=0.981; 95% CI 0.963 to 0.999), and ADP% (OR=1.013; 95% CI 1.002 to 1.024) ($p < 0.05$, table 2).

To identify the independent risk factors for early hemorrhagic events, variables with $p < 0.05$ in the univariate analysis were further examined by a stepwise multivariate logistic regression analysis. As a result, D-dimers, NIHSS scores, and ADP% were independently and significantly associated with hemorrhagic events, with ORs of 1.731 (95% CI 1.188 to 2.573), 1.181 (95% CI 1.064 to 1.311), and 1.020 (95% CI 1.001 to 1.039), respectively ($p < 0.05$, table 2).

For more accurate prediction, a logistic model was established as follows: $p = 1 / (1 + e^{-[-5.009 + 0.693 \times X1 + 0.177 \times X2 + 0.029 \times X3]})$. P is the predicted probability of the model, ranging from 0 to 1, e is the natural logarithm ($e = 2.718$), and $X1$, $X2$, and $X3$ represent D-dimers, NIHSS scores, and ADP% values, respectively. The Hosmer–Lemeshow goodness-of-fit test yielded the following results: $\chi^2 = 4.076$, $df = 8$, $p > 0.05$.

ROC curve analysis of predictors of hemorrhagic events and a logistic model

ROC curve analysis demonstrated that D-dimers, NIHSS scores, and ADP% provided good predictive values for hemorrhagic events, detailed as follows: D-dimers: AUC=0.682 (95% CI 0.574 to 0.820), $p < 0.01$; NIHSS scores: AUC=0.664 (95% CI 0.552 to 0.786), $p < 0.01$; ADP%: AUC=0.665 (95% CI 0.573 to 0.767), $p < 0.01$, (figure 2A). The optimal cut-off points of risk predictors were selected via ROC curves based on the maximal Youden index (sensitivity + specificity – 1). A cut-off point of an ADP% of 82.3% was identified with a sensitivity of 71.7% and a specificity of 78.6%. The ROC curve of the logistic model showed that AUC=0.720 (95% CI 0.625 to 0.858, $p < 0.01$, figure 2B), and a cut-off point of 0.15 was identified with a sensitivity of 72.1% and a specificity of 76.5%.

Table 1 Demographics and clinical characteristics of patients

	Non-hemorrhage	Hemorrhage	P value
	(n=798)	(n=61)	
Age (years)	57 (50–65)	56 (48–65)	0.478*
Male, n (%)	572/798 (71.7)	47/61 (77.0)	0.368†
Risk factor, n (%)			
Smoking	378/798 (47.4)	33/61 (54.1)	0.310†
Alcohol intake	326/798 (40.9)	29/61 (47.5)	0.307†
History of stroke/TIA	144/798 (18.0)	13/61 (21.3)	0.525†
Hypertension	522/798 (65.4)	42/61 (68.9)	0.586†
Diabetes mellitus	180/798 (22.6)	20/61 (32.8)	0.068†
Hyperlipidemia	88/798 (11.0)	8/61 (13.1)	0.631†
Coronary heart disease	66/798 (8.3)	7/61 (11.5)	0.387†
Statin therapy, n (%)			
Prior statin	90/798 (11.3)	8/61 (13.1)	0.679†
Present intensive statin	289/798 (36.2)	28/61 (45.9)	0.126†
Scale score			
NIHSS	3 (1–5)	4 (2–9)	0.009*
Infarction cause, n (%)			
LAA	201/720 (27.9)	24/61 (39.3)	0.081†
SAO	322/720 (44.7)	19/61 (31.1)	
SOE and SUE	197/720 (27.4)	18/61 (29.5)	
Infarction distribution, n (%)			
Anterior circulation	196/720 (27.2)	24/61 (39.3)	0.060†
Posterior circulation	327/720 (45.4)	19/61 (31.1)	
Anterior and posterior circulation	197/720 (27.4)	18/61 (29.5)	

Categorical variables are presented as n (%), and continuous variables are presented as the median (IQR); p<0.05 was considered statistically significant.
*P value obtained by Mann–Whitney U test.
†P value obtained by χ^2 test.
SOE stroke of other determined etiology; LAA, large artery atherosclerosis; NIHSS, National Institutes of Health Stroke Scale; SAO, small artery occlusion; SUE, stroke of undetermined etiology; TIA, transient ischemic attack.

DISCUSSION

Although DAPT has great value in reducing stroke progression and recurrence in patients with ischemic stroke, the reduction of coagulative function by DAPT increases the risk of hemorrhage. The most common hemorrhagic events are gastrointestinal

Table 2 Risk factors for hemorrhagic events

	Univariate logistic regression				Multivariate logistic regression			
	OR	95% CI		P value	OR	95% CI		P value
		Lower	Upper			Lower	Upper	
Glu	1.091	0.984	1.209	0.097	–	–	–	–
FIB	1.369	1.055	1.778	0.018	–	–	–	–
D-dimer	1.400	1.020	1.923	0.037	1.731	1.188	2.573	0.016
NIHSS	1.173	1.066	1.290	0.001	1.181	1.064	1.311	0.002
MA _{ADP}	0.981	0.963	0.999	0.042	–	–	–	–
ADP%	1.013	1.002	1.024	0.019	1.020	1.001	1.039	0.036

Variables with a p value<0.05 in the univariate analysis were entered into the multivariate logistic regression model.
ADP%, adenosine diphosphate inhibition rate; DAPT, dual antiplatelet therapy; FIB, fibrinogen; Glu, blood glucose; MA_{ADP}, ADP-induced platelet-fibrin clot maximum amplitude; NIHSS, National Institutes of Health Stroke Scale.

hemorrhage and HT. It is estimated that gastrointestinal hemorrhage accounts for 0.1–8.0% of such cases,¹⁷ the incidence of cerebral-infarction HT fluctuates between 13% and 43%, and the incidence of symptomatic HT is between 0.6% and 20%.¹⁸ In the present study, the incidences of hemorrhagic events, HT, and gastrointestinal hemorrhage were 7.1%, 3.6%, and 2.2%, respectively.

Once a hemorrhagic event occurs in a patient with ischemic stroke, the treatment protocol should be adjusted in a timely manner to reduce the occurrence of adverse prognoses brought by DAPT. In recent years, TEG has been widely used to monitor personal reactivity to antiplatelet drugs in order to guide the prevention of stroke recurrence. However, few studies have investigated the value of TEG in predicting hemorrhagic complications in patients following DAPT.

In this study, TEG parameters were compared between the hemorrhage and non-hemorrhage groups. The quartile analysis indicated that patients falling into lower MA_{ADP} quartiles or higher ADP% quartiles had an increased incidence of hemorrhagic events. Moreover, ADP% had a greater predictive value for hemorrhagic events in people with vascular stenosis in the anterior circulation. Previous studies have shown that individual responsiveness to clopidogrel varies greatly. ADP% <30% indicates that clopidogrel becomes ineffective,¹⁹ but ADP% >92.5% is a predictor of major bleeding in cardiovascular disease.²⁰ Combined with the present findings, this suggests that an ADP% of 30–82.3% is the preferential effective range of DAPT to recommend in patients with ischemic stroke. However, the relationship between ADP% and the severity of bleeding events is still unclear. We also evaluated patients’ response to aspirin. The arachidonic acid inhibition rate was distributed across a narrow range, which made it difficult to correlate with the risk of hemorrhagic events.

According to our demographic and clinical data, the NIHSS scores were higher in the hemorrhage group than in the non-hemorrhage group, which was consistent with a previous study.²¹ Higher NIHSS scores indicate severe neurological dysfunction that is related to a large infarct size and/or poor collateral circulation, indicating severe ischemic necrosis of local brain tissue and increased risk of hemorrhage.²² Therefore, treatment plans should be adjusted according to the severity of the disease to reduce the risk of hemorrhagic events.

Blood Glu, FIB, and D-dimer levels were high in patients of the hemorrhage group. A study showed that hyperglycemia can induce a 25-fold increase of the infarct size and a fivefold increase in the risk of hemorrhage.²³ Elevated blood Glu is known to affect endothelial cell function and the blood–brain barrier, leading to increased vascular permeability, extravasation of blood cells, and risk of HT.²⁴ Increased fibrinogen often indicates increased blood viscosity, which may seriously damage microcirculation, leading to functional and structural small blood vessel wall damage.²⁵ D-dimers represent a biomarker for fibrin formation and degradation. High levels of D-dimers also suggest increased subclinical fibrinolytic activity, which might account for the reduced efficiency of hemostatic function in vascular disease and might contribute to hemorrhagic events.²⁶ However, previous studies have shown that the above indicators are positively correlated with NIHSS scores.^{27–29} Therefore, in the present study, we specifically adjusted for NIHSS scores and found that there was no significant difference in blood Glu or FIB between the hemorrhage and non-hemorrhage groups, whereas significant differences were found in D-dimers between these two groups after adjusting for NIHSS scores. Previous studies have revealed that D-dimers are associated with disease

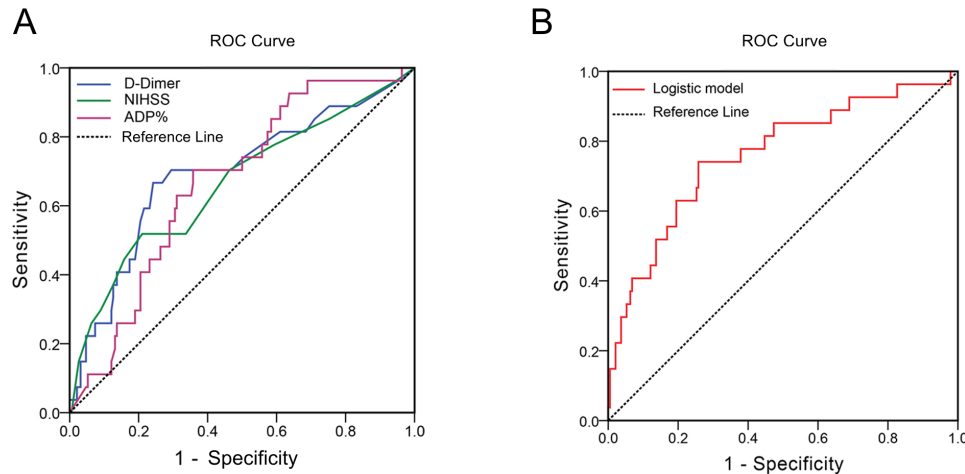


Figure 2 Receiver operating characteristic curve (ROC) analysis of risk factors and logistic model. (A) ROC curves are shown, with data as follows: D-dimers: area under the curve (AUC)=0.682 (95% CI 0.574 to 0.820, $p<0.01$); National Institute of Health Stroke Scale (NIHSS) scores: AUC=0.664 (95% CI 0.552 to 0.786, $p<0.01$); adenosine diphosphate inhibition rate (ADP%): AUC=0.665 (95% CI 0.573 to 0.767, $p<0.01$). (B) The logistic model is shown, with data as follows: AUC=0.720 (95% CI 0.625 to 0.858, $p<0.01$).

severity²⁸ and hemorrhagic stroke,²⁶ and can be used to predict the functional prognoses of ischemic stroke.

Based on these findings, a logistic regression model was established using D-dimer levels, NIHSS scores, and ADP%. ROC curve analysis showed that it yielded a good predictive value for hemorrhagic events (AUC >0.7). Currently, several assessment scales evaluate hemorrhage risk. A widely used scale is the S₂TOP-BLEED score, which is mainly based on demographics and risk factors of vascular disease.³⁰ In contrast, the present regression model incorporated some indicators of platelet function and disease severity, which may be complementary for predicting the hemorrhage risk after DAPT in ischemic patients. However, this model needs to be independently validated prospectively.

The present study has some limitations. First, biases might have appeared in this single-center retrospective study. Second, although previous reports have shown that 84% of hemorrhagic events occur in the first 2 weeks, the appearance of HT might be underestimated without consecutive scans. Third, although a one-time TEG test is reasonable in practice, it might lead to insufficient observation of the underlying dynamic changes of platelet function. Fourth, only Chinese patients were enrolled in this research, so generalizing these results to non-Asian patients may require careful interpretation and further research.

CONCLUSIONS

The TEG parameters, MA_{ADP} and ADP%, are related to hemorrhagic events in patients following DAPT. ADP%, D-dimer levels, and NIHSS scores support a logistic regression model to benefit the prediction of hemorrhagic events. Hence, these results may be useful for guiding treatment strategies in patients with ischemic stroke.

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Contributors DH, YG, YZ, and LW collected the clinical data. DH, YG, and JZ processed the statistical data. DH, ZY, and WQ drafted and revised the manuscript. XL designed and guided the study.

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Competing interests None declared.

Patient consent for publication Not required.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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