Thromboelastography-derived parameters for the prediction of acute thromboembolism following non-steroidal anti-inflammatory drug-induced gastrointestinal bleeding: A retrospective study

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Abstract. Efficacy of thromboelastography (TEG)-derived parameters for the prediction of acute thromboembolism (AT) in patients with non-steroidal anti-inflammatory drug (NSAID)-induced gastrointestinal bleeding (GIB) remains to be determined. A retrospective propensity score matching (PSM) study was performed to evaluate this efficacy. Patients with NSAID-induced GIB (98 with AT; 830 without AT) were matched for age, sex and history of cardiovascular and cerebrovascular diseases using PSM. Multivariate logistic regression was used to determine the efficacy of TEG-derived predictors of AT. Mean Decrease Gini (MDG) coefficients were used to rank the importance of the variables from random forest algorithm results. Univariate analysis indicated that the following indexes were significantly different between the two groups: Reaction time (R value), coagulation forming time, solidification angle, maximum amplitude (MA), coagulation index (CI), hemoglobin levels, D-dimer levels, platelet aggregation test (pAgt) results, fibrinogen levels and Acute Physiology and Chronic Health Evaluation II score (all P<0.001). Multifactor logistic regression analysis indicated that the R value (P=0.010), solidification angle (P=0.004), MA (P=0.038), D-dimer levels (P=0.012) and pAgt results (P=0.015) were independent predictors of AT in patients with NSAID-induced GIB, achieving an area under the curve of 0.999 in receiver operating characteristic curve analyses. The five most important parameters according to the MDG scores (MDGS) were: Solidification angle (MDGS=58.14), R value (MDGS=20.42), pAgt results (MDGS=15.61), D-dimer levels (MDGS=12.78) and CI (MDGS=12.61). The results of the present study indicated that TEG-derived parameters including the R value, solidification angle, MA and CI, as well as D-dimer levels and pAgt score were significant predictors of AT in patients with NSAID-induced GIB.

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Introduction

It has been established that acute thromboembolic (AT) events, including acute coronary syndrome (ACS) (1), cerebral arterial thrombosis, pulmonary embolism and deep venous thrombosis are among the most common causes of morbidity and mortality worldwide, particularly in elderly patients (2). AT events may disturb the blood supply for vital organs and subsequent ischemia of the organs may cause systemic dysfunction or even mortality (3). Numerous factors contribute to the complex pathogenesis of AT, including endothelial injury and dysfunction, platelet activation, over-activation of the coagulation system, blood stasis, and hypercoagulability (4,5).

Imbalance of coagulation and hemorrhage may also be an underlying cause of AT. Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of medications that provide analgesic and antipyretic effects, and exhibit anti-inflammatory effects when administered at higher doses (6). NSAIDs are widely used for the treatment of various conditions, primarily cardiovascular events and rheumatic disorders (7). Gastrointestinal bleeding (GIB) is an adverse side effect that is common to all classes of NSAIDs (8). In clinical practice, cases of AT have been observed among patients with NSAID-induced GIB (3). Previous studies have indicated that patients with NSAID-induced GIB, particularly those with ACS or stroke comorbidities who frequently take aspirin, are at a higher risk of developing AT (9,10). Furthermore, patients with ACS who suffered from GIB are at a significantly increased risk of fatal myocardial infarction (11). The incidence of NSAID-induced GIB has been reported to be increasing progressively, likely due to an increasing number of prescriptions for anti-platelet medications, including aspirin, for the primary and secondary prevention of cardiovascular and cerebrovascular diseases (12). Therefore, it may be hypothesized that the frequency of AT in patients with NSAID-induced GIB is likely to also increase, which could make it challenging to balance

hemostatic and anticoagulant therapy. Furthermore, patients with NSAID-induced GIB who have also suffered from an AT event tend to have worse prognosis (3), which highlights the importance of AT prevention in patients with NSAID-induced GIB.

Early identification of patients with NSAID-induced GIB who are at a higher risk of AT is of clinical significance for the prevention of fatal cardiovascular events. Although certain previous studies have been performed to assess AT in patients with NSAID-induced GIB (13,14), recent studies with parameters derived from novel hemostatic and anticoagulant testing are rare. Thromboelastography (TEG) is a novel tool used to monitor the hemostatic and anticoagulant condition of the body in real time, which may also serve as a guide for the adjustment of the dose of anti-thrombosis medications. The present study aimed to evaluate the clinical parameters to predict the occurrence of AT in a cohort of patients with NSAID-induced GIB, with an emphasis on TEG-derived parameters. The results of the present study may provide novel evidence to aid in the prevention of AT events in patients with NSAID-induced GIB.

Patients and methods

Study design, setting and participants. A retrospective propensity score matching (PSM) study was conducted to evaluate the incidence of AT events and associated risk factors in patients with NSAID-induced GIB. Patients were included if the following criteria were met: i) Age ≥60 years; ii) Chinese nationality; iii) taking NSAIDs; iv) outpatients with onset of GIB and patients hospitalized with GIB; and v) clinically and/or endoscopically verified GIB. Patients were excluded if they were: i) <60 years old; ii) not taking NSAIDs; iii) bleeding from varicose veins, gastrointestinal tumors, vascular malformations or diverticula; iv) taking a combination of anticoagulants and other antiplatelet drugs (including Rivaroxaban); v) unable to consent to participation. The study participants included 928 patients >60 years of age who were diagnosed with NSAID-associated GIB at the Xuanwu Hospital in Beijing from January 2007 to January 2017. Patients were further grouped according to whether they developed AT during hospitalization, including 98 patients with AT and 930 patients without AT. Events of AT were diagnosed as ACS, cerebral embolism and venous thrombosis. Seven types of NSAIDs were used in the present study, including aspirin, ibuprofen, indomethacin, diclofenac, loxoprofen, meloxicam and celecoxib. However, aspirin, also known as the acetylsalicylic acid, accounted for 90% of all NSAIDs used. Since aspirin serves an important role in the primary and secondary prevention of cardiovascular and cerebrovascular diseases, it has become the most widely used NSAID (15). Data were collected from electronic case systems. This study was approved by the Ethics Committee of Xuanwu Hospital. The patients signed informed consent to be included.

Data sources and assessment. The diagnosis of GIB was defined as a gastric, duodenal, peptic or gastrojejunal ulcer with hemorrhage or perforation [International Classification of Diseases (ICD)-10 category codes K250, K251, K252, K254, K255, K256, K260, K261, K262, K264, K265, K266, K270, K271, K272, K274, K275, K276, K280, K281, K282, K284, K285, K286], acute hemorrhagic gastritis (K290), hematemesis (K920), melena (K921) or unspecified GI hemorrhage (K922). AT events were defined as ACS [including acute myocardial infarction (AMI; ICD-10 I21) and unstable angina (UA; ICD-10 I20)], cerebral infarction (I63) or venous thrombosis (I26, I80.2). Information was collected regarding the following potentially relevant factors: Age, sex, history of cardiovascular and cerebrovascular diseases (including coronary heart disease, myocardial infarction, cerebral hemorrhage and cerebral thrombosis), Acute Physiology and Chronic Health Evaluation (APACHE) II score, hemoglobin, D-dimer, fibrinogen (Fib) and platelet (PLT) levels, PLT aggregation test (pAgt) results, and blood coagulation values [including reaction time (R value), coagulation forming time (K value), solidification angle, maximum amplitude (MA) and coagulation index (CI)]. Incidence of AT was the primary outcome, including the incidence of ACS, cerebral infarction or venous thrombosis.

TEG measurement. Venous blood samples (2-3 ml) were obtained from all participants in a fasted state for routine blood, coagulation and platelet aggregation tests, and TEG detection. All tests were completed within 2 h after blood collection. The TEG test was performed in a blinded fashion by an experienced technician in the Department of Clinical Laboratory of Xuanwu Hospital using a Thrombelastograph® Hemostasis Analyzer System and its supporting reagents (Kaolin, Calcium Chloride, Rapid TEG™ Reagent and Heparinase; Haemonetics Corporation, Braintree, MA, USA) according to the manufacturer's protocol. The parameters derived from TEG were presented as follows: The abscissa represented time (min) and the ordinate represented the amplitude (mm). TEG results provided data that reflected the *ex vivo* coagulation function, including the five parameters (R value, K value, Solidification angle, MA value and CI value) described below. The R value (min) was used to determine the time required to detect the formation of fibrin (2 mm curve) from the start of sample detection. The normal values range from 5-10 min and reflect the combined effects of all clotting factors in the coagulation process, including the endogenous and exogenous coagulation pathways. The R value increases in the presence of anticoagulant drugs, in the absence of coagulation factors or when the levels of fibrin in the blood serum are low. Conversely, the R value decreases in a state of hypercoagulability. The normal K values range from 1-3 min from the end of R to a curve amplitude of 20 mm. The K value is determined based on the interaction of Fib and PLT in the formation of blood clot. It reflects the rate of blood clot formation. Anticoagulants that affect PLT and Fib function increases the K value. Solidification angle is the angle between the horizontal line and the tangent line from the formation point of the blood clot to the maximum curve. A normal solidification angle value falls between 53-72˚ and the formation rate of blood clots is primarily affected by PLT and Fib levels. MA (mm) reflects the maximum strength and the stability of blood clots. A normal MA value is between 50-70 mm and is mainly affected by PLT and Fib levels. CI aids in evaluating the coagulation process. Normal CI values range between -3 and +3. A CI value <-3 is considered a low

Table I. Baseline patient data in the AT and the non-AT groups.

Characteristic	AT group (n=98)	Non-AT group (n=830)
Age (years)	75.04±6.35	71.75±7.77
Male	66 (67.3)	497 (59.9)
History of cardiovascular and cerebrovascular diseases	91 (92.9)	665 (80.1)
APACHE II score	26 (24-28)	23 (21-24)
Hemoglobin (g/l)	72.33±9.50	79.64±8.03
D-dimer (ug/ml)	2.25 (1.29-3.13)	0.95 (0.26-1.20)
Fibrinogen (mg/dl)	3.37 (3.10-3.94)	2.68 (2.11-3.13)
PLT ($x10^9$/l)	196.49±62.13	194.97±60.74
pAgt (%)	68 (63-73)	57 (53-60)
R value (min)	5.1 (4.6-5.7)	6.4 (5.8-6.9)
K value (min)	1.6 (1.2-2.0)	2.4 (1.8-2.9)
Solidification angle (˚)	70.5 (69.0-71.6)	57.5 (53.1-61.2)
MA (mm)	64.0 (60.1-68.1)	55.2 (50.9-59.7)
CI	0.55 (0.10-1.13)	-0.84 (-1.82-0.60)

APACHE, Acute Physiology and Chronic Health Evaluation; PLT, platelet; pAgt, platelet aggregation test; R value, reaction time; MA, maximum amplitude; CI, coagulation index; K value, coagulation forming time; AT, acute thromboembolism.

Table II. Comparisons of the matching variables following propensity score matching (%).

Variable	AT group (n=98)	Non-AT group (n=294)	t-value or χ^2	P-value
Age (years)	75.04±6.35	75.04±6.78	0.000 (t)	1.000
Male	66 (67.3)	197 (67.0)	0.004 (χ^2)	0.951
Cerebrovascular disease history	91 (92.9)	273 (92.9)	0.000 (χ^2)	1.000

AT, acute thromboembolism. T, is the statistic of independent t-test; χ^2 is the statistic of chi-square test.

coagulation state, whereas a CI value >+3 is considered a high coagulation state.

Statistical analysis. Continuous variables with normal distribution were presented as the mean ± standard deviation. For continuous variables with a skewed distribution, the median and interquartile range were used. An independent t-test or Mann-Whitney U test were applied for continuous variables with normal or skewed distribution. Categorical variables were presented as the number (percentage) and a chi-square test was used for the analysis. Considering the impact of potential confounding factors and selection bias in the present study, PSM was used at a ratio of 1:3 between the AT group and the non-AT group. Age-, sex- and history of cardiovascular disease-matched PSM was applied to derive the cohort. Nonrandom package (V1.42) of R-3.3.3 (www.r-project.org) was used to implement propensity matching. Multivariate logistic regression analysis was used to extract risk factors associated with AT and the results were presented as an odds ratio (OR) with 95% confidence intervals. The Mean Decrease Gini (MDG) coefficients from a random forest algorithm were used to rank the important indexes associated with AT. MDG scores provide a method to quantify the contribution of each index to the classification accuracy. A greater MDG value indicated that the degree of impurity arising from a category could be reduced the most by a single variable, and, therefore, suggested an important associated index. Statistical analysis was performed using SPSS software (version 17.0; SPSS, Inc., Chicago, IL, USA) and the randomForest package (V4.6-12) of R software. All statistical tests were two-sided and P<0.05 was considered to indicate a statistically significant difference.

Results

Baseline patient data. Patients in the AT group were between 60 and 93 years old (75.04±6.35 years of age) with 66 males (67.3%) and 32 females (32.7%). Patients in the non-AT group were between 60 to 95 years old (71.75±7.77 years of age), with 497 males (59.9%) and 333 females (40.1%) (Table I). Among the 98 patients with AT, 30 patients were diagnosed with AMI (30.6%), 34 with UA (34.7%), 28 with cerebral infarction (28.6%) and six with venous thrombosis (6.1%). Patients in the AT group exhibited an increased prevalence of cerebrovascular disease history, as well as increased APACHE II scores, D-dimer, Fib, PLT and PLT aggregation levels, solidification angle, MA and CI, and decreased hemoglobin levels, and R and K values compared with the non-AT group.

PSM. PSM for the AT group to the non-AT group was used at a ratio of 1:3, respectively. The matched variables were age, sex and history of cerebrovascular disease. The sex was balanced (χ^2=2.048; P=0.152), while the age (χ^2=4.038; P<0.001) and history of cerebrovascular disease (χ^2=9.417; P<0.002) were not (data not shown). Following PSM, there were 98 cases in the AT group and 294 cases in the non-AT group, who were balanced in terms of age, sex and history of cerebrovascular disease (Table II).

Comparison of important indexes between groups. The R and K values of the AT group were significantly lower compared with the non-AT group (both P<0.001), while the solidification angle, MA and CI significantly increased compared with the non-AT group (all P<0.001). In the AT group, the D-dimer levels, pAgt results, Fib levels and APACHE II scores were significantly increased (all P<0.001), while hemoglobin levels were significantly lower compared with the non-AT group (P<0.001). There was no difference in the number of PLTs between the two groups (P=0.898; Table III). The comparison of the solidification angle, R value, D-dimer levels and pAgt results between the two groups was presented in Fig. 1.

Predictors of AT events in patients with NSAID-induced GIB. Results of the multivariate logistic regression analysis indicated

Table III. Index comparisons between the AT and non-AT groups.

Index	AT group (n=98)	Non-AT (n=294)	Z or t-vlaue	P-value
R value (min)	5.1 (4.6-5.7)	6.5 (5.9-6.9)	11.829 (Z)	<0.001
K value (min)	1.6 (1.2-2.0)	2.4 (1.7-2.9)	7.428 (Z)	<0.001
Solidification angle (˚)	70.5 (69.0-71.6)	57.2 (53.1-61.2)	13.427 (Z)	<0.001
MA (mm)	64.0 (60.1-68.1)	52.9 (50.5-59.6)	10.165 (Z)	<0.001
CI	0.55 (0.10-1.13)	-1.30 (-1.84-0.60)	8.154 (Z)	<0.001
D-dimer (ug/ml)	2.25 (1.29-3.13)	0.47 (0.23-1.30)	10.198 (Z)	<0.001
pAgt (%)	68 (63-73)	56 (53-60)	10.942 (Z)	<0.001
Fibrinogen (g/l)	3.37 (3.10-3.94)	2.44 (2.11-3.16)	8.703 (Z)	<0.001
APACHE II	26 (24-28)	22 (21-24)	10.119 (Z)	<0.001
Hemoglobin (g/l)	72.33±9.50	79.79±8.11	6.932 (t)	<0.001
PLT ($x10^9$/l)	196.49±62.13	195.57±61.18	0.128 (t)	0.898

APACHE, Acute Physiology and Chronic Health Evaluation; PLT, platelet; pAgt, platelet aggregation test; R value, reaction time; MA, maximum amplitude; CI, coagulation index; K value, coagulation forming time; AT, acute thromboembolism. t is the statistic of independent t-test; Z is the statistic of Mann-Whitney U test.

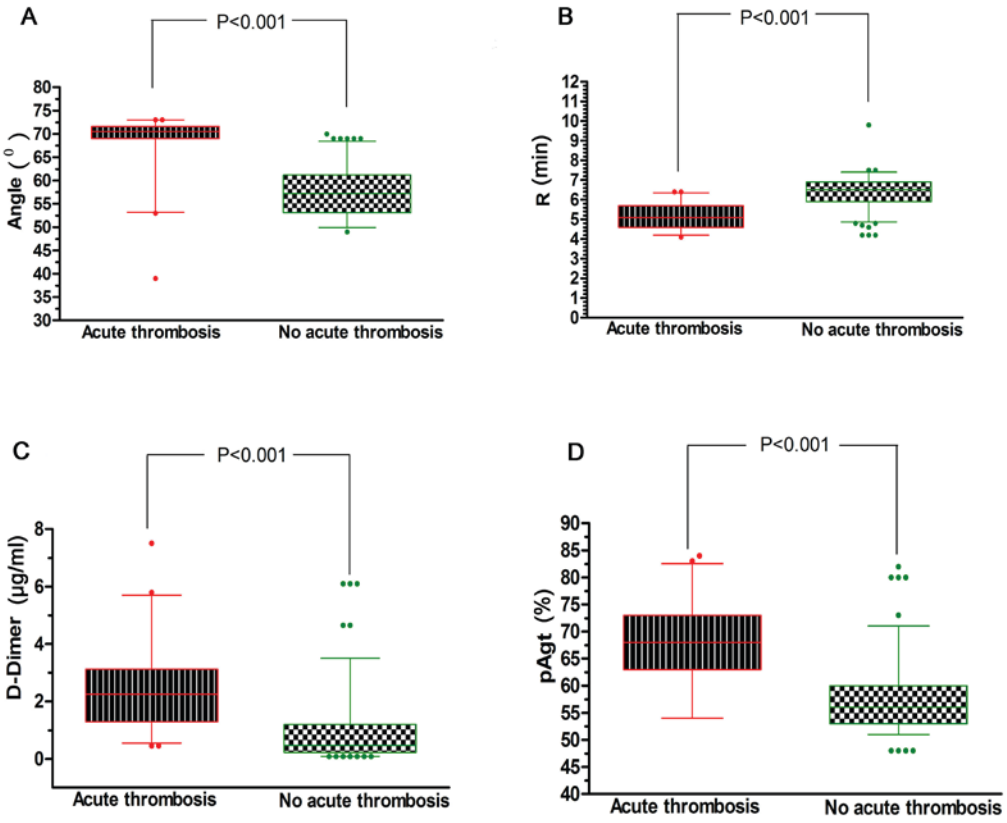

Figure 1. Comparison of TEG indexes and coagulation function between AT and non-AT groups. (A) The TEG solidification angle of the AT group was 70.5 (69.0-71.6), significantly higher compared with the non-AT group 57.2 (53.1-61.2), which indicated a rapid formation of blood clots in the AT group. (B) The TEG R value of the AT group was 5.1 (4.6-5.7), significantly lower compared with the non-AT group 6.5 (5.9-6.9), which reflected the short time required for the formation of fibrin in the blood sample and a high coagulation state compared with the non-AT group. (C) The D-dimer value of the AT group was 2.25 (1.29-3.13), significantly higher compared with the non-AT group (0.47; 0.23-1.30), indicating that the AT group was more vulnerable to thrombosis compared with the non-AT group. (D) The pAgt value of the AT group was 68 (63-73), significantly increased compared with the non-AT group at 56 (53-60), indicating that the AT group was more likely to exhibit platelet aggregation promoting the formation of blood clots. TEG, thromboelastography; AT, acute thromboembolism; R value, reaction time; pAgt, platelet aggregation test; angle, solidification angle.

that the thrombus elastic figure.index values (including the following five indicators: R value, K value, solidification angle, MA and CI), Fib, hemoglobin and D-dimer levels, pAgt results, and APACHE II scores were all potential independent predictors of AT events in patients with NSAID-induced GIB (Table IV). The overall predictive efficacy using these

Table IV. Multivariate logistic regression analysis evaluating the predictive efficacy of clinical parameters for AT in patients with NSAIDs-induced GIB.

Index	Regression coefficient	Standard error	Wald	P-value	OR value	95% CI
R value (min)	-2.536	0.983	6.651	0.010	0.079	0.012-0.544
K value (min)	-1.640	0.947	3.002	0.083	0.194	0.030-1.240
Solidification angle (˚)	0.296	0.102	8.376	0.004	1.345	1.100-1.644
MA (mm)	0.228	0.110	4.319	0.038	1.256	1.013-1.558
CI	1.034	0.633	2.668	0.102	2.812	0.813-9.721
D-dimer (ug/ml)	1.360	0.540	6.330	0.012	3.895	1.350-11.231
pAgt (%)	0.270	0.110	5.973	0.015	1.310	1.055-1.626
Fibrinogen (g/l)	1.464	0.850	2.970	0.085	4.325	0.818-22.869
APACHE II	0.444	0.290	2.349	0.125	1.559	0.884-2.750
Hemoglobin (g/l)	-0.088	0.067	1.699	0.192	0.916	0.803-1.045

APACHE, Acute Physiology and Chronic Health Evaluation; pAgt, platelet aggregation test; R value, reaction time; MA, maximum amplitude; CI, coagulation index; K value, coagulation forming time; AT, acute thromboembolism.

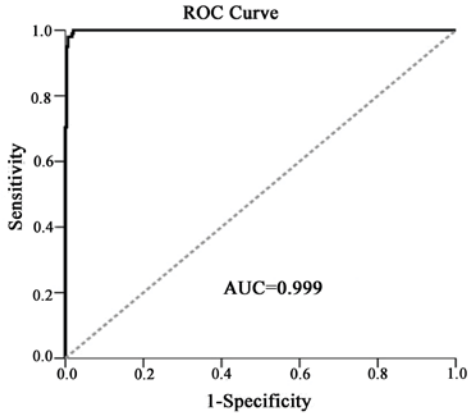

Figure 2. Area under the ROC curve to assess the predictive value of clinically-derived parameters for the prediction of AT events in patients with NSAID-induced GIB. The logistic regression model was adopted to assess the predictive efficacy of clinical variables on AT. An AUC of 0.999 (95% confidence interval: 0.996-1.001) indicated a good predictive value. ROC, receiver operating characteristic; AUC, area under the curve; AT, acute thromboembolism; NSAID, non-steroidal anti-inflammatory drug; GIB, gastrointestinal bleeding.

parameters was good and the area under the curve (AUC) of the receiver operating characteristic curve was 0.999 (95% confidence interval: 0.996-1.001; Fig. 2). However, the entire cohort of participants was used to construct and validate the logistic regression model, which may have resulted in over-fitting. Therefore, the present study additionally adopted a 5-fold cross validation to re-analyze the data. During the analysis, the data were divided into five sets. For each analysis, one set was considered the testing data to validate the classification performance of the logistic regression model whereas the remaining sets were considered training data to construct the logistic regression model. The classification accuracy rates and AUC for the testing data were presented in Fig. 3.

AT-associated indicators evaluated by the random forest algorithm. The random forest algorithm was used to rank the significant indexes in single factor comparisons. The analysis included parameters of thrombus elastic figure. index values (including R value, K value, solidification angle, MA and CI), Fib, hemoglobin and D-dimer levels, and pAgt and APACHE II scores. The most important indicators extracted according to the MDG scores (MDGS) were the solidification angle, R value, pAgt results, D-dimer levels and CI (Table V; Fig. 4). A two-dimensional classification graph of samples was constructed based on the random forest classification algorithm of the neighboring matrix, providing a multidimensional scaling lattice diagram (Fig. 5). The samples could be well classified by the above-mentioned indicators.

Discussion

Previous studies indicated that elderly patients are at an increased risk of developing NSAID-induced gastrointestinal injuries (16,17). Patients with a history of previous peptic ulcer bleeding are 13 times more at risk (18-20). The digestive tract bleeding associated with the use of NSAID has been reported since 1934, when Aschenbrenner had published case reports of AMI associated with GIB (21). In the present study, patients with GIB, especially those with NSAID-associated GIB, tended to be at a higher risk of thromboembolic events, including cerebrovascular and cardiovascular events, which was consistent the results of a recent report (3). The present study indicated that among patients with NSAID-associated GIB, 10.6% experienced AT events, which was similar to previous reports (13,22). AT events may affect the prognosis of patients with GIB, leading to an increased risk of morbidity and mortality (23). A previous study has suggested that patients with ACS with severe GIB and even those with minor bleeding events are at a higher risk of MI and 30-day mortality (24). Among patients with ACS in the Acute Catheterization and Urgent Intervention Triage Strategy trial, GIB was associated with reduced 1-year survival rates [hazard ratio (HR): 4.0] and increased incidences of MI (HR: 2.9), composite ischemia (HR: 1.9), stroke (HR: 4.2) and mortality (HR: 2.6) (9,11). Among 6,853 patients with ischemic disease, GIB significantly increased the mortality

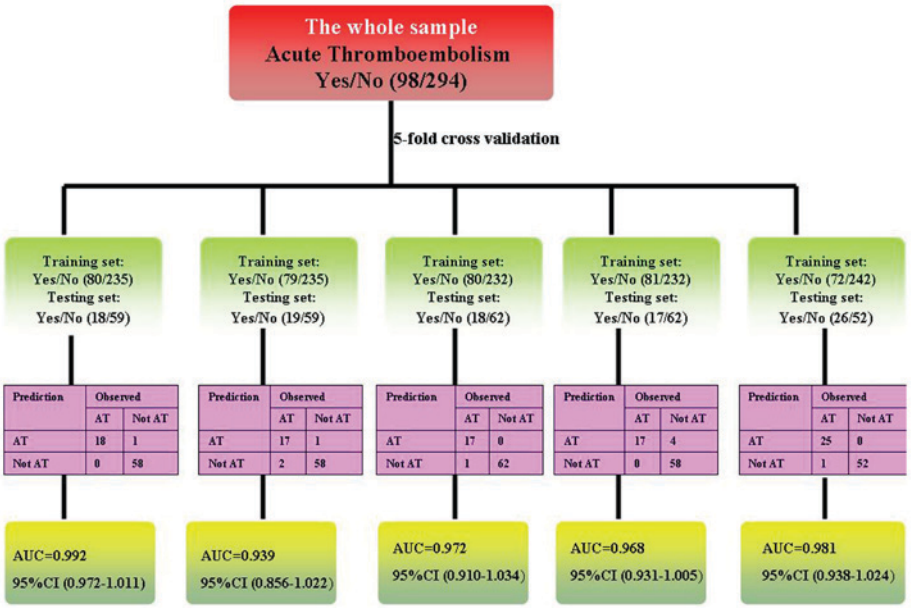

Figure 3. Five-fold cross validation process to validate the classification performance of the logistic regression model. The samples were divided into five sets. For each analysis, one set was considered testing data to validate the classification performance of the logistic regression model whereas the remaining sets were considered as training data to construct the logistic regression model. The AUC values were 0.992 (95% CI: 0.972-1.011), 0.939 (95% CI: 0.856-1.022), 0.972 (95% CI: 0.910-1.034), 0.968 (95% CI: 0.931-1.005), and 0.981 (95% CI: 0.938-1.024), respectively. CI, confidence interval; AT, acute thromboembolism; AUC, area under the curve.

of patients [odds ratio (OR): 3.3], as well as incidence of recurrent cerebral infarction (OR: 3.7) and MI (OR: 2.8) (25).

Additionally, a study of patients with GIB who were taking anticoagulant drugs indicated that suspension of anticoagulants lead to an increased incidence of thromboembolism in 90 days (HR: 14-20), as well as an increased overall mortality (HR: 3.3) (26). The exact mechanisms underlying the pathogenesis of GIB complicated by AT remain to be elucidated, although possible explanations have been suggested. For instance, a large amount of blood loss occurring shortly after GIB (>20% of circulating blood volume) may lead to insufficient perfusion of the coronary artery and brain (22). Subsequently, a sudden decrease of blood flow in the heart reduces the flow within the coronary artery, causing an atheromatous plaque rupture, followed by ischemia in the coronary artery (27). Furthermore, the sympathetic nervous system and the adrenal medullary system may be activated as a response to the rapid decrease in the blood volume, which leads to constriction of the vessels and aggravation of artery stenosis, if it is already present (28). If patients experienced a previous cerebral infarction and MI, the endogenous coagulation system could be activated, resulting in acute thrombus formation (29). In response to the aforementioned events, the bone marrow may increase platelet production, followed by a release of the platelet factors including thrombin and catecholamine, making patients more vulnerable to blood clots and ischemic events (29,30). Furthermore, antithrombotic drugs may be discontinued due to concerns of bleeding (26,31), and the incidence of AT may also increase.

Predictors for AT events in NSAID-induced GIB have not been well evaluated previously. Bhatti *et al* (13) demonstrated that patients with GIB-related MI had significantly more cardiac risk factors (2.4+/-0.2 vs. 1.6+/-0.1), lower presenting hematocrits (26.0+/-1.3 vs. 30.5+/-0.8), and lower hematocrit in the first 48 h (22.3+/-0.9 vs. 25.1+/-0.6) than those without MI. Emenike *et al* (14) found that elderly patients with high APACHE II scores on admission to intensive care units and presenting additional risk factors for coronary artery disease are more likely to experience AT events. The study also found that age and low levels of hemoglobin were risk factors for AT (14). The above results were confirmed by the present study, which also demonstrated that high APACHE II scores and low hemoglobin levels were associated with an increased risk of AT in patients with NSAID-induced GIB. The novelty of the present study directly pertains to the inclusion of TEG-derived parameters for evaluation of the risk of AT in patients with NSAID-induced GIB, to complement the conventional clinical parameters. Compared with the traditional coagulation detection, TEG could comprehensively analyze the plasma composition and its influence on blood coagulation, which may better reflect the precise blood coagulation parameters of patients (32). TEG graphically demonstrates the process of coagulation, including the initiation, formation of blood clots and fibrinolysis using 20 standard parameters (33). TEG accurately reflects the presence of the hypercoagulable state in the blood (33). Compared with the conventional methods, TEG is more rapid and accurate, and is a sensitive test for the overall evaluation of coagulation function (34).

Traditional coagulation test parameters, including activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time and Fib levels, only examine a part of the plasma and blood coagulation cascade, rather than the whole body blood coagulation reaction condition, and, therefore, cannot determine whether PLT function and fibrinolytic system are normal (35). A number of patients with normal PLT, PT and APTT exhibit active bleeding and abnormal

Table V. Ranking of important indexes associated with AT based on MDG.

Index	MDG
Solidification angle (˚)	58.14
R value (min)	20.42
pAgt (%)	15.61
D-Dimer (ug/ml)	12.78
CI	12.61
MA (mm)	9.77
APACHE II	7.33
Fibrinogen (g/l)	4.86
Hemoglobin (g/l)	2.95
K value (min)	2.72

APACHE, Acute Physiology and Chronic Health Evaluation; pAgt, platelet aggregation test; R value, reaction time; MA, maximum amplitude; CI, coagulation index; K value, coagulation forming time; AT, acute thromboembolism; MDG, Mean Decrease Gini.

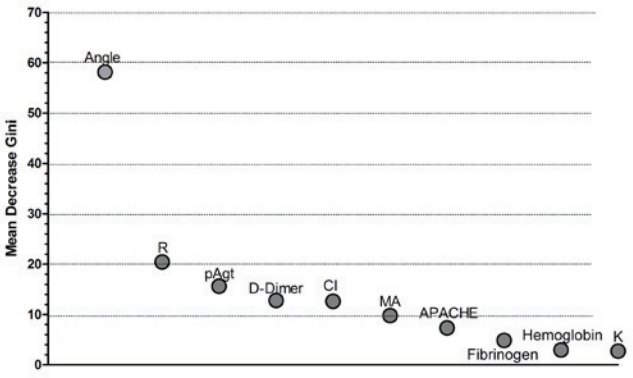

Figure 4. MDG plot for important indexes associated with AT. AT-associated indicators evaluated by the random forest algorithm. The random forest algorithm was used to rank significant indexes in single factor comparisons, including the R and K values, solidification angle, MA, CI, and hemoglobin, D-dimer and Fib levels, and pAgt and APACHE II scores. The most important indicators according to the MDG scores were solidification angle, R value, pAgt score, D-dimer levels and CI. MDG, Mean Decrease Gini; APACHE, Acute Physiology and Chronic Health Evaluation; pAgt, platelet aggregation test; R value, reaction time; MA, maximum amplitude; CI, coagulation index; K value, coagulation forming time; AT, acute thromboembolism.

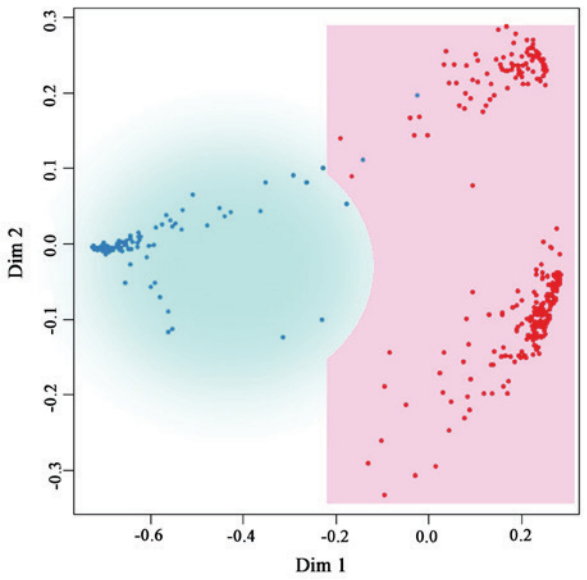

Figure 5. MDS plot for indexes used in the random forest algorithm. The MDS plot projects a high-dimensional influence measure to a 2D surface presenting similarities among samples and their respective groups. In this plot, the AT group (blue circles) and the non-AT group (red circles) were well separated. MDS, multidimensional scaling; Dim, dimension; AT, acute thromboembolism.

coagulation (36,37). Blood coagulation and an increase in PLT adhesion serve roles in the occurrence and development of acute thrombosis (27). TEG can accurately determine whether the blood is in a state of high coagulation (38). Previous studies have indicated that MA can be used to predict bleeding following heart surgery, deep venous thrombosis following severe trauma, as well as stroke events, stent thrombosis and post-traumatic mortality (39-43). For vein embolization, TEG has been shown to directly indicate if patients are prone to developing a thrombotic disease when the high coagulation state changes (R value decreases and MA value increases) (40). It has been reported that the MA value in TEG can be used to predict an increased risk of venous thromboembolism in patients with severe lower limb trauma (40). The MA value of rapid TEG is also an independent predictor of pulmonary embolism (44,45). Other studies have reported that CI had a predictive value for deep venous thrombosis and thrombosis in prostate cancer (46,47). Furthermore, the TEG method simulates the entire process of venous thrombosis *ex vivo*, and, therefore, the CI value can reflect a composite index of venous thrombosis formation. Usually, when the blood is in a state of high coagulation, TEG is exhibits decreased R and K values, and an increased solidification angle, MA value and CI value (48). The present study indicated that the average R value in the 98 patients of the AT group was lower compared with the non-AT group, and the solidification angle, MA and CI increased compared with the non-AT group. The results indicated that the R value, MA, solidification angle and CI were sensitive indicators of high coagulation in TEG, and coagulation increased in the AT group compared with non-AT patients. These results require confirmation by future studies with a larger cohort.

APACHE II scores, and hemoglobin and Fib levels differed between patients with or without AT events, however, the results of the multivariate analysis suggested that none were independent risk factors for AT in patients with NSAID-induced GIB. D-dimer, is a well characterized sensitive marker of thrombosis with fiber dissolving activity (49), which had a predictive value for AT in patients with NSAID-induced GIB in the present study. D-dimer is a degradation product produced during the hydrolysis of fibrinolytic enzymes and is a specific indicator of hypercoagulability and secondary fibrinolysis (49). Secondary fibrinolytic activity was primarily enhanced in patients with AT, who typically present with reduced levels of plasminogen and increased levels of D-dimer (50). However, conventional coagulation monitoring indicators (including D-dimer and Fib) frequently fail to reflect the coagulation balance *in vivo* and only partially record the process of blood coagulation (51). The

results are easily influenced by low molecular weight heparin, which may exhibit a strong antithrombotic effect by controlling the activity of coagulation factors, patriculaly Xa, and thus promoting the release of tissue plasminogen activator (T-PA) and the dissolution of fibrin (52). However, this may also be influenced by other substances, including low molecular dextran and urokinase (53). A study by Ridker *et al* (54) found that the presence of D-dimers was closely associated with ischemic cardiomyopathy. The elevated levels of D-dimers indicate an increased risk of MI, however, D-dimer was not an independent predictor (49). Previous studies have suggested that the activation of blood coagulation was an independent risk factor of cerebral infarction, where the D-dimer level and the degree of cerebral infarction were linearly correlated, and could be used to infer the prognosis of patients with cerebral infarction (55,56). pAgt primarily reflects the aggregation function of PLTs. The results of the present study suggested that pAgt was elevated in patients with AT, which is consistent with the results of previous research (54). pAgt function is positively associated with Fib levels in plasma (54). In the present study, the plasma Fib concentration in the AT group was significantly increased compared with the non-AT group, which also confirmed previous results (56). Although D-dimer levels and pAgt can provide reference data for clinical thrombosis, the information provided by TEG detection is more comprehensive and can reflect the coagulation function state more accurately. Furthermore, TEG is a simpler, faster and more sensitive detection method and can be implemented by the bedside (37).

The present study has limitations which should be considered when interpreting the results. The retrospective design of the present study does not allow for subject recruitment and outcome design, which could be adapted in a prospective study. The results after matching cannot completely reflect the results of the original data. To determine whether TEG parameters, D-dimer levels and pAgt results are independent predictors of AT in patients with GIB, a large prospective cohort study should be performed. Another limitation is that patients with NSAID-associated GIB had additional comorbidities at baseline that could have contributed to the development of AT events during the follow-up period. Although the present study attempted to match certain variables, the multivariate model did not account for all potential adjusted confounding factors associated with GIB. Finally, the number of thromboembolic events was relatively small, which may have resulted in insufficient statistical power for multivariate analysis of certain variables.

In conclusion, TEG-derived parameters including the R value, solidification angle, MA, and CI, as well as D-dimer levels and pAgt results may be significant predictors of AT in patients with NSAID-induced GIB. These parameters may aid early identification of patients with NSAID-induced GIB who are at a higher risk of developing AT events.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

T-YC wrote the manuscript. T-YC, H-MZ and YL performed the experiments. T-YC analyzed the data. MZ and TC interpreted the data and revised the manuscript. MZ conceived and managed the study design and approved the manuscript for publication.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Xuanwu Hospital. The patients signed informed consent was also obtained.

Patient consent for publication

The patients agreed to the publication of any associated data in the present study.

Competing interests

The authors declare that they have no competing interests.

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