Predictive value of coagulation factor XIII on bleeding risk in ischemic stroke patients treated with intravenous thrombolysis

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Background: Intravenous thrombolysis (IVT) therapy with recombinant tissue plasminogen activator (rtPA) in acute ischemic stroke (AIS) has a known risk of intracerebral hemorrhage (ICH). We aimed to identify the predictive value of coagulation factor XIII (FXIII) on post-thrombolytic ICH risk in AIS patients.

Methods: The study cohort included 69 diagnosed AIS patients undergoing IVT treatment within 24 hours of symptom onset. Blood samples taken on admission were analyzed for FXIII antigen levels with an automated latex enhanced immunoassay. Conventional coagulation parameters including prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FIB), and D-dimer (DD) were also tested.

Results: Of the 69 AIS patients, 23 (33.3%) developed post-thrombolytic ICH. Plasma FXIII levels showed a significant decrease, accompanied with elevated FIB and DD levels in AIS patients with post-thrombolytic ICH. Multivariable logistic regression (LR) revealed that FXIII and FIB were independently associated with post-thrombolytic ICH progression. Area under receiver operating characteristic curve of FXIII selected by the further forward logistic regression was 0.823 [95% confidence interval (CI): 0.712–0.904], and the cutoff value of 76.6% yielded good sensitivity at 91.3% and good negative predictive value (NPV) at 93.9%.

Conclusions: Our findings indicated that plasma FXIII level may be an independent determinant for predicting post-thrombolytic bleeding risk in AIS patients.

Keywords: Acute ischemic stroke (AIS); coagulation factor XIII (FXIII); intravenous thrombolysis (IVT); post-thrombolytic intracerebral hemorrhage (post-thrombolytic ICH); predictive marker

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Introduction

Acute ischemic stroke (AIS) is a leading cause of death and disability worldwide (1). Currently, the most effective and clinically recognized therapy to improve functional outcomes is early thrombolysis guided by a time window using recombinant tissue plasminogen activator (rtPA), alteplase, urokinase, and so on (2,3). Before receiving intravenous thrombolysis (IVT), AIS patients are carefully screened to minimize bleeding risk according to the contraindications set forth in clinical guidelines (4). However, post-thrombolytic intracerebral hemorrhage (ICH) is still inevitable and fatal in approximately 7–8% of AIS patients (4-6). Many clinical and radiological variables, along with clinical laboratory indicators, have been reported to predict post-thrombolytic ICH (7-9). Among these, several biomarkers reflecting the states of coagulation and functions of fibrinolysis may be associated with hemorrhagic transformation (10-12).

Blooding coagulation factor XIII (FXIII), also called fibrin-stabilizing factor, is a tetrameric protein consisting of 2 potentially active A-subunits and 2 B-subunits (carrier proteins) that circulate in plasma (13,14). FXIII is essential for maintaining hemostasis due to its role in fibrin stabilization and in the protection of fibrin from proteolytic degradation by the fibrinolytic system (15,16). Thus, its activity is associated with A-subunits and fibrinogen concentrations (17). Growing evidence has shown that the role of FXIII as a risk factor in thrombotic disorders; however, reports on the relation of ischemic stroke and FXIII are still limited (16). Previous studies have shown that a polymorphism in the A-subunit gene (*FXIII Val34Leu*) is protective against occlusive vascular diseases, and low concentrations of FXIII A-subunit may predict poor outcome in stroke subjects (18,19). Recently, it has been reported that low levels of FXIII after IVT can predict short-term mortality in AIS patients (5), whereas the predictive value of FXIII levels before IVT on the risk of ICH is still vague. Herein, we aimed to evaluate the impact of blood FXIII levels measured before the course of thrombolysis in AIS patients on the occurrence of post-thrombolytic ICH. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-1174).

Methods

Study population

This study was retrospective in design and was conducted between October 2019 and April 2020. A total of 69 AIS patients undergoing IVT were recruited in the Department of Neurology of Tongji Hospital of Huazhong University of Science and Technology. AIS was defined as a sudden onset of nonconvulsive and focal neurological deficit. As described in our previous clinical study (20), the inclusion criteria of AIS patients were clinical presentation of first-ever stroke, age 18 years or older, and a diagnosis via brain imaging of acute cerebral infarction. Meanwhile, the exclusion criteria were the following: cerebral hemorrhage, subdural hematoma, intracranial space-occupying lesions, traumatic cerebrovascular damage, heart failure, malignant diseases, immunologic diseases, severe infection, or pregnancy. Most enrolled patients in this study suffered a large vessel thrombosis, according to the classification criteria of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) (21). The average time from symptom onset to treatment with recombinant tissue plasminogen activator (rtPA) was less than 24 hours, and the duration of thrombolysis was approximately 1 hour for each patient. According to ICH occurrence after rtPA treatment, all enrolled patients were further divided into non-bleeding and bleeding AIS subgroups. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Medicine Research Ethics Committee of Tongji Hospital of Huazhong University of Science and Technology (No. TJ-IRB20192511), and all stroke patients gave informed consent before enrollment.

Clinical assessment

The medical information of all patients was collected, including age, sex, risk factors, common comorbidities, standard laboratory tests, and previous medical history. Physical and neurological examinations, and cerebral computed tomography (CT) or magnetic resonance imaging (MRI) were also performed. Neurological severity was assessed on admission according to the National Institutes of Health Stroke Scale (NIHSS) score and Glasgow Coma Scale (GCS) score (22,23). Risk factors like hypertension, diabetes mellitus, and related heart diseases were determined by the corresponding diagnostic criteria combined with medical history. Occurrence of post-thrombolytic ICH was routinely assessed by cerebral CT or MRI, after which the AIS patients were divided into the bleeding group and non-bleeding group.

Sample collection and laboratory test

Blood samples of sodium citrate anticoagulant were collected from each of the 69 AIS patients within 24 hours before thrombolytic therapy. Following this, the platelet-poor plasma was separated, and the coagulation factors in plasma samples were tested immediately within 2 hours. Quantitative determination of FXIII antigen in human citrated plasma was tested by latex enhanced immunoassay on an ACL TOP automated coagulation analyzer using a commercially available reagent kit (Factor XIII Antigen, Hemosil, Instrumentation Laboratory Company, Bedford, MA, USA; reference range 75.2–154.8%, CV 3.5%). Conventional coagulation parameters including prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FIB), and D-dimer (DD) were also detected by routine methods from the same sample.

Statistical analysis

SPSS 19.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 7.0 (GraphPad Software, San Diego, CA, USA) were used for statistical analysis. Descriptive data are presented as mean ± standard deviation (SD), median (interquartile range, IQR), or proportions. Between-group and across-group differences were compared by Student's t-test, Mann-Whitney U test, one-way analysis of variance (ANOVA), and Kruskal-Wallis test or χ^2 test, where appropriate. Multivariable logistic regression (LR) using the Wald test was performed to study which variables were independently associated with ICH developed after IVT in stroke. Additionally, forward LR was employed to select determinants of ICH to build a predictive model. A 2-sided P value <0.05 was considered statistically significant.

Results

Clinical characteristics of enrolled AIS patients with and without post-thrombolytic bleeding

The clinical background of the AIS patients with and without post-thrombolytic ICH is shown in *Table 1*. After IVT with rtPA, ICH developed in 23 of 69 (33.3%) AIS patients. The gender and age distribution did not differ significantly between the bleeding and non-bleeding AIS group. No obvious difference was found in the incident of risk factors, such as hypertension, diabetes, related heart diseases, and other common complications. Compared to the AIS patients without post-thrombolytic bleeding, AIS patients with post-thrombolytic bleeding had significantly higher NIHSS and GCS scores, suggesting more severe neurological function deficits.

AIS patients with post-thrombolytic ICH had lower FXIII levels detected before thrombolysis

We first analyzed the baseline changes of coagulation parameters before thrombolysis, including PT, APTT, FIB, DD, and FXIII. The results found that the FXIII antigen levels on admission (before thrombolysis) showed a significant decrease (59.9%; IQR 55.0–78.5%) in AIS patients with post-thrombolytic ICH, compared with the non-bleeding AIS patients (85.5%; IQR 73.8–94.5%). Conversely, the levels of plasma FIB and DD in the patients with post-thrombolytic ICH were obviously higher than those in the non-bleeding AIS patients (*Table 1*).

Plasma FXIII antigen level may be an independent determinant for predicting post-thrombolytic bleeding in AIS patients

Multivariable LR using the Wald test was performed to calculate the likelihood ratio (LR) of the variables that changed between the non-bleeding and bleeding AIS groups. Considering that (I) age in stroke patients has been associated with a higher risk of development of ICH after IVT (24,25), that (II) male sex has been reported to be independently associated with ICH (26), and (III) biological plausibility, we also included age and sex in the multivariable model. The results showed that the FIB and FXIII levels were significantly associated with post-thrombolytic ICH progression, independent of other coagulation and biological covariates (*Table 2*).

The further forward LR method suggested that the FXIII level (P<0.001) but not FIB (P=0.062) was an independent determinant for predicting ICH after thrombolysis. The receiver operating characteristic (ROC) curve showed that the area under curve (AUC) of FXIII on predicting bleeding risk of AIS patients treated with IVT was 0.823 (*Figure 1*); furthermore, the optimal cutoff value of 76.6% yielded good sensitivity at 91.3%, with specificity at 67.4%, positive predictive value (PPV) at 58.3%, and negative predictive value (NPV) at 93.9% (*Table 3*).

Discussion

The present study aimed to determine whether a lower

Table 1 Baseline characteristics of the study population (n=69)

Characteristics	Normal range	AIS patients		P value
		Non-bleeding	Bleeding	
Number of patients (%)		46 (66.7)	23 (33.3)	
Male, n (%)		39 (84.8)	15 (65.2)	0.063
Age, y ± SD		61.6±13.2	56.3±12.8	0.116
Comorbidities, n (%)				
Hypertension		37 (80.4)	15 (65.2)	0.167
Diabetes		7 (15.2)	3 (13.0)	0.809
Heart diseases		11 (23.9)	3 (13.0)	0.290
Others		9 (19.6)	4 (17.4)	0.828
NIHSS score		3 [1–6.5]	8 [4–14]	<0.001
GCS score		14 [11.75–15]	10 [7–14]	<0.001
Laboratory tests, median (interquartile range)				
PLT, ×10^9/L	125–350	190 [166–246]	220 [190–256]	0.281
PT, s	9.4–12.5	13.3 [12.8–14.0]	13.5 [12.9–14.2]	0.412
APTT, s	25.1–36.5	39.0 [35.5–42.0]	38.6 [37.0–40.8]	0.930
FIB, g/L	2.38–4.98	3.17 [2.88–4.01]	4.63 [3.37–6.52]	0.004
DD, µg/mL	0–0.5	0.30 [0.22–0.62]	0.91 [0.44–1.50]	< 0.001
FXIII, %		85.5 [73.8–94.5]	59.9 [55.0–78.5]	< 0.001

Data reported as number (%), mean ± standard deviation (SD) or median [interquartile range, IQR]. $P<0.05$, considered statistically significant. AIS, acute ischemic stroke; NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale; PLT, platelets; PT, prothrombin time; APTT, activated partial thromboplastin time; FIB, fibrinogen; DD, D-dimer; FXIII, coagulation factor XIII.

plasma FXIII level in AIS patients before thrombolysis is an independent determinant for predicting post-thrombolytic ICH. To our knowledge, this may be the first study on clinical determinants of predicting ICH progression in stroke patients treated with IVT. Considering the high overall mortality and morbidity of bleeding in AIS patients, it is essential at an early stage to identify patients at a higher risk of developing ICH after IVT-rtPA. Several prognostic scores have been used to identify AIS patients with a high risk of post-thrombolysis ICH, such as NIHSS and GCS score (27,28). Nevertheless, the value of these scores for individualized outcome predictions is limited due to the dichotomization or categorization of continuous variables, and results have varied across different studies (29,30). The recent multiple prognostic scoring systems were investigated and mainly used to predict the clinical outcome, such as SPAN-100 index, the GPASPS score, in which no coagulation markers were included (27,28,31). Thus, the

possible coagulation defects cannot be reflected when using these systems. Maybe the effective coagulation indicators combined with scoring system can improve the accuracy of predicting hemorrage risk. Among conventional coagulation markers, high D-dimer concentrations have been reported to be associated with both cardiovascular events and major bleeding during anticoagulant therapy (32). Thus, the cardiovascular risk factors must be taken into consideration when investigating the relationship between D-dimer and ICH (33). Previously, a high level of fibrinogen degradation factors (FDPs) and decreased fibrinogen at 2 hours after thrombolysis was found, called "early fibrinogen degradation coagulopathy", which was predictive of early ICH (34). However, potential predictive factors for assessing the bleeding risk before thrombolysis in the earlier stage of AIS patients have not been definitively clarified.

It has been suggested that one of the mechanisms

Table 2 Coagulation and biological variables associated with post-thrombolytic ICH in multivariable analysis

Variable	OR (95% CI)	P value
Age at AIS diagnosis (years)	0.957 (0.895–1.023)	0.196
Male sex	4.299 (0.767–24.095)	0.097
GCS score	1.041(0.634–1.710)	0.874
NIHSS score	1.111(0.829–1.488)	0.482
FIB	2.177 (1.021–4.639)	0.044
DD	1.434 (0.673–3.057)	0.351
FXIII	0.919 (0.870–0.971)	0.003

P<0.05, considered statistically significant. ICH, intracerebral hemorrhage; AIS, acute ischemic stroke; LR, likelihood ratio; CI, confident interval; NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale; FIB, fibrinogen; DD, D-dimer; FXIII, coagulation factor XIII.

Table 3 Predictive value of FXIII activity <76.6% on bleeding risk in AIS patients treated with IVT

Variable	Plasma FXIII activity
Sensitivity	91.3%
Specificity	67.4%
PPV	58.3%
NPV	93.9%
AUC	0.823
95% CI	0.712–0.904
P	<0.001

P<0.05, considered statistically significant. FXIII, coagulation factor XIII; AIS, acute ischemic stroke; IVT, intravenous thrombolysis; PPV, positive predictive value; NPV, negative predictive value; AUC, area under curve; 95% CI, 95% confidence interval.
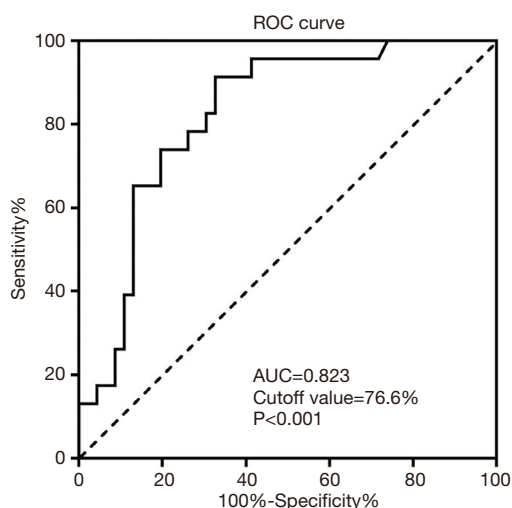

Figure 1 Receiver operating characteristic (ROC) curve in AIS patients with post-thrombolytic ICH. The area under ROC curve was 0.823 for plasma FXIII level. AIS, acute ischemic stroke; ICH, intracerebral hemorrhage; FXIII, coagulation factor XIII.

of ICH may be a defect in anti-fibrinolysis through an excessive consumption of anti-fibrinolytic components (34). One hypothesis speculates that a decrease in the level of fibrinolytic inhibitors, such as the FXIII, or factors participating in clot stability could be useful predictors of ICH (35). However, the levels of FXIII before thrombolysis as evaluated by sandwich enzyme-linked immunosorbent assay (ELISA) have been reported to be within a normal or not-significantly-lower range (5,35). In our study, highly

specific antigen latex enhanced immunoassay was used to capture the A-subunit of FXIII, which indicated a lower FXIII level before thrombolysis present in AIS patients who developed ICH after IVT-rtPA, accompanied by high D-dimer and FIB levels. The mechanism involved in the reduction of FXIII level and activity is still unclear. One hypothesis posits that a considerable amount of FXIII being incorporated into the growing thrombus leads to consumption and/or degradation of FXIII and inactivation by plasmin due to ongoing activity of the coagulation system after stroke (36). One study found that FXIII activity measured before and after thrombolysis was not significantly changed (5), suggesting a potential earlier predictive value. Considering these findings in combination with our data, we speculate that low FXIII antigen activity in AIS patients is associated with high bleeding risk, and should be monitored closely to prevent the development of post-thrombolytic ICH.

The independent association of low FXIII level with a higher risk of post-thrombolytic ICH is novel. According to the multivariable LR, low FXIII and high FIB levels, but not high D-dimer before thrombolytic treatment, were independent factors for predicting ICH, suggesting the high D-dimer may be present at least partly because of concurrent cardiovascular diseases. The NIHSS and GCS scores on admission, commonly used to access the severity of stroke, were higher in the AIS patients with post-thrombolytic ICH. However, these 2 scores were not identified as the independent factors for predicting ICH in

our study. Data from further forward LR analysis revealed that a low FXIII level may be used as a clinical determinant to predict the ICH risk, whereas a high FIB level before thrombolysis may be not an independent determinant. Moreover, the AUC in ROC curve analysis of FXIII level was 0.823, which is close to 1, indicating a superior predictive value in AIS patients with post-thrombolytic ICH. A cutoff value of 76.6% yielded good sensitivity at 91.3% and good NPV at 93.9%.

Taken together, plasma FXIII level may be valuable for predicting post-thrombolytic bleeding risk in AIS patients, and low FXIII level should be included in the consideration of thrombolysis contraindications. For AIS patient with low FXIII level, the alternative treatments should be given. Two recent studies have shown a survival increase for FXIII substitution in trauma patients, suggesting the potential effectiveness of FXIII for the treatment of hemorrhage (37,38). Moreover, increased FXIII levels may result in elevated incorporation of α2-plasmin inhibitor (α2-PI), showing an association with the outcome of IVT therapy (39). Therapeutic plasma exchange or albumin solutions enriched FXIII, and purified plasma-derived FXIII may restore coagulation potential, which may be a promising treatment strategy and merits further verification (40,41,42). However, some limitations to our study should be addressed. Given the nature of the study design, we were unable to elucidate the mechanism linking low FXIII levels before thrombolysis with post-thrombolytic ICH progression, and additional multicenter studies using larger samples of AIS patients are needed to validate our findings.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-1174

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-1174). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Medicine Research Ethics Committee of Tongji Hospital of Huazhong University of Science and Technology (No. TJ-IRB20192511), and all stroke patients gave informed consent before enrollment.

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