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Does the use of tranexamic acid increase the risk of VTE in patients with hemoptysis?

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Abstract. – OBJECTIVE: The aim of this study was to create a predictive nomogram that can accurately identify the risk factors of venous thromboembolism (VTE) in hospitalized patients exhibiting hemoptysis.

PATIENTS AND METHODS: The present study gathered clinical and demographic data of 1,052 hospitalized patients with hemoptysis at Dongyang Hospital between January 2016 and January 2021 through the Lejiu database. The patients were categorized into two groups: the thrombotic event group (n=123) and the non-thrombotic event group (n=929), based on the presence of VTE before discharge. The study utilized univariable and multivariable logistic regression analyses to identify the independent risk factors for VTE, with the occurrence of thrombotic events serving as the dependent variable. Furthermore, a nomogram prediction model was formulated to verify the findings.

RESULTS: In hospitalized patients with hemoptysis, the risk of VTE was found to be independently associated with the administration of tranexamic acid (TXA), the presence of D-dimer, and the Charlson Comorbidity Index (CCI) score ($p<0.05$).

CONCLUSIONS: A nomogram model was constructed to evaluate the probability of VTE in patients hospitalized with hemoptysis. This model allows for the timely detection of early VTE warning signs, which may ultimately reduce its occurrence.

Key Words:
Venous thromboembolism, Hemoptysis, Tranexamic acid, Charlson Comorbidity Index.

Abbreviations

AUC=area under the ROC; CCI=Charlson Comorbidity Index; hs-CRP=high-sensitivity C-reactive protein; IBD=Inflammatory Bowel Disease; PE=pulmonary embolism; ROC=receiver-operating characteristic; TXA=tranexamic acid; VTE=venous thromboembolism.

Introduction

The symptom of hemoptysis is frequently observed in various pulmonary disorders, and its intensity is gauged based on the amount of blood expectorated. When hemoptysis reaches the level of massive bleeding, it can result in shock, respiratory failure, or, ultimately, death[1]. Life-threatening hemoptysis is estimated to occur in 5-14% of patients with hemoptysis, underscoring the criticality of promptly managing the bleeding[2].

Tranexamic acid (TXA), a synthetic analog of lysine, has emerged as a valuable tool in preventing bleeding and minimizing blood loss in the initial stages of medical treatment. Its effectiveness in achieving hemostasis among hemoptysis patients has garnered significant attention and led to its widespread use[3,4]. Additionally, a recent systematic review[2] has highlighted the potential benefits of TXA treatment, including reduced bleeding volume, decreased intervention risk, and shorter hospital stays for individuals with hemoptysis.

There are concerns regarding the potential for TXA to increase the risk of venous thromboembolism (VTE). However, no conclusive evidence suggests that TXA is an independent risk factor for thrombosis. A study conducted in 1994 by Ruiz[5] revealed that 24 patients experiencing respiratory bleeding due to pulmonary tuberculosis were given either TXA or a placebo for three days. The study demonstrated that the group treated with TXA did not demonstrate a greater likelihood of VTE than the placebo group. Similarly, a 2002 study by Tscheikuna et al[6] demonstrated that oral TXA does not increase the risk of VTE in patients with respiratory bleeding from various causes, compared to a placebo. A meta-analysis by Prutsky et al[7] in 2012 also indicated that TXA does not increase the risk of thrombosis in the

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treatment of respiratory bleeding. However, it has been reported that prolonged exposure to high concentrations of TXA may result in an increased risk of VTE events[8]. Based on these findings, further investigation into the relationship between TXA and VTE is warranted.

This research aimed to develop a prognostic nomogram model that could effectively recognize the risk factors for VTE in patients hospitalized due to hemoptysis. Upon further validation, the identification of early warning signals for VTE could be possible, leading to a decrease in VTE incidence through the appropriate administration of TXA.

Patients and Methods

Patients

Dongyang Hospital admitted patients with hemoptysis between January 1, 2016, and January 1, 2021, who met the criteria for enrollment. The inclusion criteria were as follows: (1) individuals aged between 18 and 80 years; (2) patients diagnosed with respiratory tract bleeding (ICD Code: R04.900, R04.200) upon admission; (3) patients with D-dimer negative (<500 μg/L for D-dimer in patients younger than 50 years, <age*10 μg/L in patients older than 50 years) or negative CTA scan of chest vessels upon admission; (4) patients diagnosed with lower extremity deep VTE, pulmonary embolism, lower extremity venous intermuscular thrombosis, acute pulmonary embolism, or thrombus of lower extremity veins upon discharge. Patients who had a pre-existing VTE diagnosis were not considered for inclusion.

Data Collection

The demographic and clinical particulars of the registered patients were gathered from the Lejiu database. These particulars encompassed the age of the patients, the employment of TXA, the total quantity of TXA consumed, the average levels of high-sensitivity C-reactive protein (hs-CRP), the average D-dimer, the average platelet count, and the Charlson Comorbidity Index (CCI) score (which includes all comorbidities such as cardiac, pulmonary, renal, cerebrovascular, diabetic, gastrointestinal, and oncological diseases of several systems essentially). The selection of these parameters was based on prior research and discussions with the research team, which consisted of a respiratory physician with extensive clinical experience.

Statistical Analysis

Data analysis was conducted using SPSS 26.0 software (IBM Corp., Armonk, NY, USA). The mean ± SD was used to express measurement data, while frequency (percentage) was used for count data. The Mann-Whitney U test was employed to compare differences, while the Chi-square test was used for disordered categorical data. Statistical significance was set at $p<0.05$. The logistic regression model was used to incorporate the selected variables, and a variable was considered an independent risk factor for VTE when $p<0.05$. The RMS package (R Foundation for Statistical Computing, version 4.1.3; available at: https://www.r-project.org/) was utilized to generate nomogram and receiver-operating characteristic (ROC) curves based on the independent variables. The area under the ROC (AUC) represented the differentiation degree of the model. The fit of the model was assessed using the Hosmer-Lemeshow test.

Results

Demographic and Clinical Data

This study involved a total of 1,052 patients, out of which 123 experienced thrombotic events upon discharge. Based on the discharge status, the patients were classified into two groups - those who experienced thrombotic events and those who did not. In Table I, the demographic and clinical characteristics of both groups were summarized, including factors such as age, utilization of TXA, the quantity of TXA, average levels of hs-CRP, D-dimer, and platelet count, as well as the CCI score. The results indicated significant differences in age, TXA dosage, mean hs-CRP levels, mean D-dimer levels, and the CCI score between the two groups ($p<0.01$).

Logistic Regression Analysis

According to the results of the univariate logistic regression analysis, all variables, except for age, exhibited statistical significance. The occurrence of VTE was significantly associated with the dosage of TXA, mean D-dimer, and the CCI score (Table II).

Multivariate logistic regression was employed to scrutinize the three variables, which led to the discovery that they all posed an independent risk for VTE, with a level of significance of $p<0.001$ for each variable (Table III).

Table I. Demographic and clinical characteristics of patients with or without thrombotic events.

Items	Thrombotic events group (n = 123)		Non-thrombotic events group (n = 929)		p
	N	% or SD	N	% or SD	
Age	68	13	66	20	0.001
Use of TXA					
Yes	67	54.5%	514	55.3%	
No	56	45.5%	415	44.7%	0.86
Dosage of TXA (g)	1.5	5	1	3	0.012
Mean hs-CRP (mg/L)	10.6	27	5.35	26	0.001
Mean D-dimer (μg/mL)	6.11	8	0.94	1	< 0.001
CCI score	6	4	4	3	< 0.001
Mean platelet count ($\times 10^9$/L)	60.78	19	59.82	23	0.30

Tranexamic acid (TXA), Charlson Comorbidity Index (CCI), high-sensitivity C-reactive protein (hs-CRP).

Table II. Univariate logistic regression analysis of thrombotic events.

Variable	OR (95% CI)	p
Use of TXA	0.97	0.857
Dosage of TXA (g)	1.11	< 0.001
Mean hs-CRP (mg/L)	1.00	0.489
Mean D-dimer (μg/mL)	1.33	0.026
CCI score	1.44	< 0.001
Mean platelet count ($\times 10^9$/L)	1.00	0.525

Tranexamic acid (TXA), Charlson Comorbidity Index (CCI), high-sensitivity C-reactive protein (hs-CRP).

Prediction Model

Multivariate logistic regression analysis revealed that three independent risk factors for thrombotic events exist: the dosage of TXA, mean D-dimer, and the CCI score. To create a nomogram prediction model, the R software was employed (Figure 1). This model utilized scores for CCI, the dosage of TXA, and mean D-dimer, which were determined to be 12 (82.5 points), 26 (55 points), and 20 (100 points), respectively. By summing the scores of each risk factor, the total score of the nomogram was calculated to be 180 points.

The ROC curves were utilized to verify the statistical efficacy of the prediction model. As depicted in Figure 2, the results indicated that the AUC was 0.883, which was greater than 0.7, and has a 95% CI of 0.738-0.919. These data suggest that the prediction model was capable of identifying thrombotic events. The SE was 0.016, with a 95% CI of 0.738-0.919 and a *p*-value lower than 0.001. By selecting an appropriate cut-off point, it was discovered that the highest Youden index was achieved at t=0.087. The sensitivity and specificity of this model at the aforementioned cut-off point were 90.24% and 76.32%, respectively. Moreover, the nomogram's calibration curve demonstrated that the model had an average predictive ability. The c-index was 0.883.

Discussion

The present study demonstrated that the quantity of TXA given, the mean D-dimer value, and the CCI score were all factors that independently increased the risk of VTE in patients who were hospitalized because of hemoptysis.

Table III. Multivariate logistic regression analysis of thrombotic events.

Variable	β	OR	95% CI	p
Dosage of TXA (g)	0.12	1.12	1.06-1.19	< 0.001
Mean D-dimer (μg/mL)	0.28	1.32	1.25-1.40	< 0.001
CCI score	0.38	1.46	1.33-1.60	< 0.001

β is the regression coefficient. Tranexamic acid (TXA), Charlson Comorbidity Index (CCI), high-sensitivity C-reactive protein (hs-CRP).

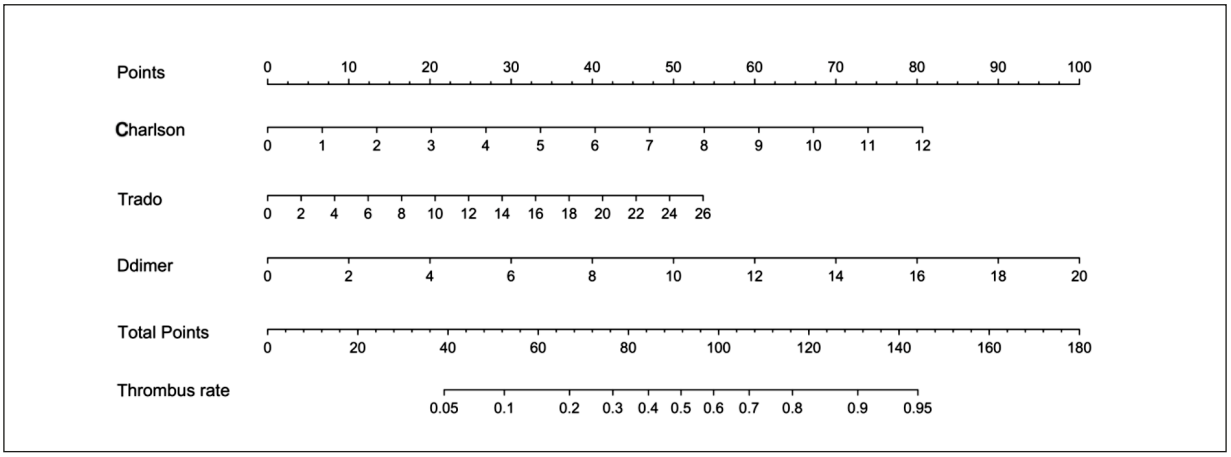

Figure 1. The nomogram model used for assessing thrombotic events in patients with respiratory bleeding.

D-dimer is a crucial marker in assessing the activation of coagulation and fibrinolysis and is widely utilized in the diagnosis and prediction of VTE. A D-dimer level exceeding 500 ng/mL indicates a high probability of pulmonary embolism (PE)[9,10]. Conversely, patients with a normal D-dimer level can be excluded from further imaging testing for PE. Furthermore, multiple studies[11] have established a significant association between D-dimer levels and an increased risk of incident VTE, recurrent VTE, higher mortality, and subsequent VTE in various diseases. Our study also found that patients with thrombotic events had significantly higher D-dimer levels compared to those without such events [6.11 (8) *vs.* 1 (3)].

The CCI score is a valid predictor of mortality in patients with VTE. Recent studies[12] indicate a significant increase in the risk of VTE or mortality with a higher CCI score. Zöller et al[13] also reported that a lower CCI score in patients with a family history of VTE is associated with better survival and lower mortality. The CCI score is an effective predictor of mortality in patients with comorbid diseases. Kim et al[14] reported that it is a significant risk factor for thrombosis in patients with Inflammatory Bowel Disease (IBD). Our findings are consistent with these studies[12-14], revealing that a higher CCI score is associated with a greater number of chronic comorbidities and severe acute medical diseases. In cases where hemoptysis is accompanied by other conditions that are known risk factors for VTE, such as malignant lung tumors[15], the use of TXA may result in an elevated risk of thrombosis. Of the three independent risk factors identified in this study, VTE had the highest OR value, further highlighting the significance of the CCI score as a risk factor for VTE.

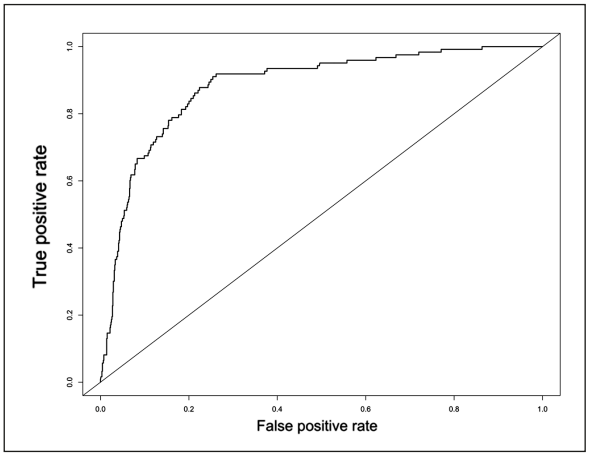

Figure 2. The ROC curve analysis was used to test the resolution of the nomogram model.

TXA is a synthetic antifibrinolytic acid that is commonly administered during the early stages of medical treatment to prevent bleeding and reduce blood loss[14,16-20]. VTE is a frequent adverse reaction of TXA treatment. Myers et al[17] found that patients with trauma who received TXA treatment had a significantly higher prevalence of VTE compared to those who did not receive such treatment (11.4% *vs.* 7.4%), suggesting that TXA may be an independent risk factor for VTE. Additionally, prolonged exposure to high concentrations of TXA has been shown[21] to elevate the risk of VTE. A propensity-matched multivariate analysis[17] of a large database found

that cardiac trauma patients treated with TXA had nearly three times the risk of VTE. In the HALT-IT clinical trial[22], the use of high dosages of TXA (4 g, >24 hours of treatment) led to an increased occurrence of venous thrombosis within 24 hours in patients with acute gastrointestinal bleeding.

It is noteworthy that the studies mentioned above utilized high doses of TXA, while other studies[8] have reported the use of relatively low doses. For example, Nilsson[8] suggested that TXA can be administered intravenously at a dosage of 10 mg/kg, 3 to 4 times per day, to manage local fibrinolytic bleeding, and at 10 mg/kg every 3 to 4 hours to prevent systemic fibrinolysis and massive bleeding. In the CRASH-2 trial[23], patients with severe post-traumatic hemorrhage were treated with a dose of 1 g of TXA, followed by an infusion of 1 g within 8 hours. While other studies in the literature did not identify TXA as a risk factor for thrombosis, the higher incidence of VTE observed in this trial may be attributed to the use of high doses of TXA. Our findings also indicate that the dosage of TXA is a significant risk factor for VTE in hospitalized patients with hemoptysis. Recently, a new therapy called atomization inhalation therapy, which uses TXA, has been proposed[10,24-26] for the treatment of hemoptysis. This therapy has been shown to be effective with minimal adverse reactions. Further studies with larger sample sizes are required to investigate the efficacy of this therapy.

Limitations

One limitation of our study was the absence of patient categorization based on the underlying causes of hemoptysis. It is plausible that the probability and mechanism of thromboembolism may differ among patients with hemoptysis caused by different etiologies. Additionally, we did not incorporate factors related to bronchial artery embolization, which was observed to improve the condition of some patients. This outcome may be attributed to the limited number of oncology patients in our cohort. Future studies should consider these variables to enhance the comprehensiveness of the model.

Conclusions

A nomogram model was developed in this investigation to anticipate the probability of VTE in individuals experiencing hemoptysis. This model facilitates the timely identification of VTE warning signals, which could decrease its incidence through the judicious administration of TXA. Additional research is necessary to investigate the underlying mechanisms.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

The study was approved by the Medical Ethics Committee of the Dongyang Hospital (China) (protocol code: 2021-YX-126, date of approval: 19 August, 2021) and was conducted in accordance with the Declaration of Helsinki.

Informed Consent

Written informed consent was obtained from all the patients for the study.

Availability of Data and Materials

All data generated for this study are included in the article.

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The research did not receive funding.

Authors' Contribution

JZ designed the study. JZ, YD and SF acquired, analyzed and interpreted the data. JZ wrote the first draft. All authors contributed to reviewing, revising and approving the manuscript.

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