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Serum D-dimer as a potential new biomarker for prognosis in patients with thrombotic thrombocytopenic purpura

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Abstract

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening disease, and its mortality rate is 10% to 20%. However, there are currently only a few markers to predict the prognosis in patients with TTP. We aimed to identify several clinical indices and laboratory parameters for predicting the prognosis of TTP at admission.

A single-centre observational cohort study that included patients with TTP from the First Affiliated Hospital of Zhengzhou University in China was conducted from January 1, 2012 to November 30, 2018. The primary outcome was prognosis, including in-hospital mortality, major thromboembolic events, or failure to achieve remission at discharge. We used the random forest method to identify the best set of predictors.

Eighty-seven patients with TTP were identified, of whom 12 died during the treatment. The total number of patients within-hospital mortality, major thromboembolic events, and failure to achieve remission at discharge was 58. The machine learning method showed that the D-dimer level was the strongest predictor of the primary outcome. Receiver operating characteristic (ROC) analysis demonstrated that the sensitivity and specificity of the D-dimer level alone for identifying high-risk patients were 78% and 81%, respectively, with an optimum diagnostic cut-off value of 770 ng/mL. The area under the ROC curve (AUC) was 0.80, and the 95% confidence interval (CI) was 0.70 to 0.90.

This study found that the D-dimer level exhibited a good predictive ability for prognosis in patients with TTP. These findings may aid in the development of new and intensive treatment strategies to achieve remission among high-risk patients. However, external validation is necessary to confirm the generalizability of our approach across populations and treatment practices.

Abbreviations: ABO = ABO blood type, ALB = albumin, ALT = alanine aminotransferase, APTT = activated partial thromboplastin time, AST = aspartate aminotransferase, BUN = blood urea nitrogen, Ca = Ca^{2+} ion concentration, CHE = cholinesterase, CK = creatine kinase, CK-MB = creatine kinase-MB, CO_2CP = carbon dioxide combining power, Cr = creatinine, CRP = C-reaction protein, CTD = connective tissue disease, cTnT = cardiac troponin T, DBil = direct bilirubin, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, EOS = eosinophil count, ESR = erythrocyte sedimentation rate, FDP = fibrin degradation products, GGT = γ-glutamyltranspeptidase, GLOB = globulin, GLU = glucose, Hb = hemoglobin, HCO^{3-} = HCO^{3-} ion concentration, Hct = hematocrit, IBIL = indirect bilirubin, INR = international normalized ratio, K = K+ ion concentration, LDH = lactic dehydrogenase, LDH1 = lactic dehydrogenase-1, LDL = low density lipoprotein, MCH = mean corpuscular hemoglobin, MCV = mean corpuscular volume, MPV = mean platelet volume, Na = Na+ ion concentration, P = total phosphorus in serum, PCT = thrombocytocrit, PDW = platelet distribution width, PLT = platelet count, Pro-BNP = pro-brain natriuretic peptide, PT = prothrombin time, PTA = prothrombin time activity, RBC = red blood cell, RDW = red blood cell distribution width, SBP = systolic blood pressure, T = body temperature, TBIL = total bilirubin, TC = total cholesterol, TG = triglyceride, TP = total protein, TTP = thrombotic thrombocytopenic purpura, UA = uric acid, WBC = white blood cell.

Keywords: biomarkers, D-dimer, prognosis, thrombotic thrombocytopenic purpura

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1. Introduction

Thrombotic thrombocytopenic purpura (TTP) is a blood disorder characterized by severe thrombocytopenia and microangiopathic hemolytic anemia. The incidence of TTP was reported to be up to 10 cases per million per year.[1] The underlying mechanism of TTP typically involves a severe deficiency of the activity of a disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAMTS13), which cleaves von Willebrand factor (vWF) multimeric strings. Indeed, severe ADAMTS13 deficiency (activity <10%) causes the blood accumulation of unusually large platelet-hyper-adhesive multimers of vWF, leading to the formation of microthrombi within the systemic microcirculation.[1,2]

Current treatment consists of daily plasma exchange and immunosuppressive therapy (e.g., glucocorticoids and rituximab) to suppress anti-ADAMTS13 autoantibodies.[3] Despite appropriate therapeutic management in recent years, up to 20% of the acute episodes of TTP may be fatal.[2] TTP appears as a heterogeneous syndrome[4] with a high rate of unexplained mechanisms for ADAMTS13 deficiency. The clinical presentation, response to treatment, and outcomes vary considerably among patients with mild to severe TTP. Thus, clinical factors and biomarkers predicting clinical outcomes are necessary to identify high-risk patients.

Known biomarkers of TTP-related mortality include anti-ADAMTS13 antibody levels,[5] troponin I,[6] platelet recovery rate,[7] low total serum protein or albumin, and prolonged activated partial thromboplastin time.[8] A significantly increased level of D-dimer was observed in the HIV-related TTP population in a prior study.[9] In addition, plasma D-dimer levels were reported to be higher in the patients who died from TTP (2062.0 vs 7083.0 mg/L, $P = .09$) than in those in the Alabama TTP cohort who survived.[8] Therefore, we hypothesize that the D-dimer level significantly negatively correlates with prognosis in patients with acute TTP and can be applied as a prognostic biomarker for risk group stratification.

In this study, we focused on the cohort of patients with TTP presenting to our institution from January 1, 2012 to November 30, 2018. The D-dimer levels and other laboratory test results on admission were recorded, and clinical outcomes at discharge were evaluated. A non-linear machine learning algorithm was used to determine whether D-dimer was predictive of prognosis, including in-hospital mortality, major thromboembolic events, or failure to achieve remission at discharge.

2. Materials and methods

2.1. Patient cohort

All medical records requested from the record room at our medical centre were anonymous, and all information was used for research purposes only. Our study adhered to the tenets of the Declaration of Helsinki, and patient informed consent was waived by our institutional review board. Our medical centre, The First Affiliated Hospital of Zhengzhou University, which is located in central China, ranks among the largest hospitals in the world with a bed space of more than 10,000 beds. Its large size and professional hospital service allow it to attend to large numbers of patients in central China. When critically ill patients are hospitalized locally for further treatment, they are typically transferred to our centre. Therefore, our centre provides the opportunity to obtain comprehensive data on the characteristics and outcomes of patients hospitalized for TTP in Henan province.

The general process for treatment in practice was as follows: if thrombotic microangiopathy (TMA) was initially suspected by a primary care physician, local internist, or hematologist, patients were transferred to the Division of Rheumatology, Hematology or an integrated intensive care unit. Individuals with TTP were diagnosed when they presented with both microangiopathic hemolytic anemia with schistocytes seen on a blood smear and consumptive thrombocytopenia without an alternative explanation. Then, a standard treatment protocol for TTP including therapeutic plasma exchange and steroids or rituximab was urgently performed.

We reviewed electronic medical records and identified all consecutive patients with TTP from January 1, 2012 to November 30, 2018. The inclusion criteria were patients with

(1) TTP diagnosed on the basis of clinical presentations and
(2) TTP confirmed by severe ADAMTS13 deficiency (activity <10%).

Thus, this cohort included patients experiencing their first episode and/or an exacerbation or a relapse. The exclusion criteria were patients with suspected TMA that was not associated with TTP. Individuals with missing baseline data required for statistical analysis were also excluded.

Patients were divided into 2 groups according to the primary outcomes of interest. Specifically, patients who experienced in-hospital death, major thromboembolic events, or those who failed to achieve remission at discharge constituted a high-risk group of TTP, while the other patients with complete remission denoted a low-risk group. Then, demographics and laboratory parameters were compared between the 2 groups for significant differences.

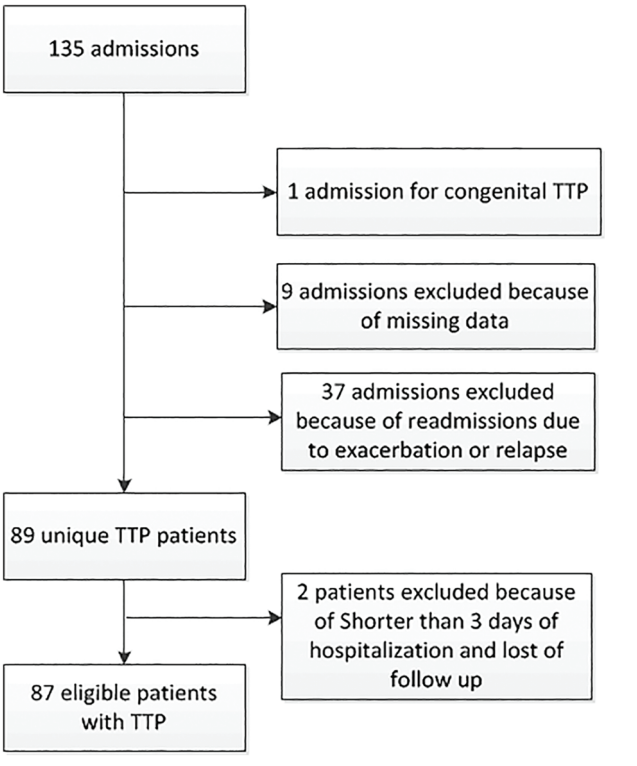

Figure 1. Flow chart of the screening process of this study. TTP, thrombotic thrombocytopenic purpura.

Table 1

Demographic, clinical, and laboratory data of this study.

Variables	Total	Low-risk	High-risk	*P* value
Number of patients (n)	87	37	50	
Demographic characteristics				
Age (yr), mean ± SD	43.6 ± 17.7	36 ± 15	49.06 ± 17.69	<.001
Male, n (%)	29 (33.3)	13 (35.1)	16 (32.0)	.759
Baseline laboratory data				
Platelet counts (10^9/L), median (IQR)	12.0 (7.0–24.0)	12.0 (7.0–25.0)	12.0 (7.2–23.2)	.904
Hemoglobin (g/dL), median (IQR)	75.0 (63.0–93.5)	5.0 (66.0–106.0)	1.0 (62.0–86.8)	.029
Hematocrit (%), median (IQR)	20 (20–30)	24 (19–29)	21 (18–27)	.155
WBC (10^9/L), median (IQR)	7.7 (5.7–11.1)	7.0 (4.9–8.6)	9.2 (6.4–14.2)	.026
PTA (%), median (IQR)	94.0 (78.0–111.0)	103.5 (84.8–118.0)	92.0 (72.0–105.0)	.012
APTT (s), median (IQR)	29.3 (27.1–32.3)	28.8 (27.0–31.0)	29.9 (27.6–34.5)	.112
D-dimer (mg/L), median (IQR)	1.05 (0.43–2.30)	0.54 (0.3–0.74)	2.11 (1.05–3.91)	<.001
Fasting blood glucose (mmol/L)	6.21 (5.08–7.90)	5.21 (4.38–6.18)	7.22 (6.04–8.87)	<.001
CRP (mg/L), median (IQR)	9.68 (2.00–45.84)	2.36 (0.83–6.66)	8.65 (9.60–68.33)	<.001
PT (s), median (IQR)	1.10 (10.10–12.20)	10.55 (9.80–11.22)	11.75 (10.47–13.00)	<.001
INR, median (IQR)	1.00 (0.91–1.09)	0.95 (0.89–1.01)	1.05 (0.97–1.14)	<.001
FDP (mg/L), median (IQR)	8.48 (3.79–18.83)	3.81 (2.80–5.49)	4.55 (7.41–24.05)	<.001
BUN (mmol/L), median (IQR)	6.94 (5.00–11.32)	5.90 (4.49–7.40)	8.90 (5.30–12.57)	.001
LDH (U/L), median (IQR)	1157.0 (569.5–1779.5)	733.0 (424.0–1473.8)	1482.0 (848.0–2027.0)	.002
CK (U/L), median (IQR)	60.0 (40.5–152.5)	47.0 (37.0–61.8)	87.0 (43.0–226.0)	.006
EOS (%), median (IQR)	1 (0–5)	3 (0–5)	0 (0–3)	.014
MCV (fL), median (IQR)	91.80 (88.05–97.10)	90.1 (86.2–95.8)	93.9 (89.2–97.5)	.023
Comorbidities				
Current smoking, n (%)	12 (13.8)	4 (10.8)	8 (16.0)	.546
Current drinking, n (%)	9 (10.3)	4 (10.8)	5 (10.0)	1.000
Hypertension, n (%)	12 (13.8)	2 (5.4)	10 (20.0)	.063
Diabetes mellitus, n (%)	3 (3.4)	0 (0.0)	3 (6.0)	.258
CHD, n (%)	5 (5.8)	1 (2.7)	4 (8.2)	.385
CTD, n (%)	25 (28.7)	14 (37.8)	11 (22.0)	.107
Clinical data				
SBP at admission (mm Hg), mean ± SD	122 ± 18	123 ± 19	121 ± 18	.576
DBP at admission (mm Hg), mean ± SD	77 ± 15	78 ± 18	76 ± 13	.505
Glasgow Coma Scale score, n (%)				.015
13– 15	61 (70.1)	31 (83.8)	30 (60.0)	
9–12	19 (21.8)	6 (16.2)	13 (26.0)	
<9	7 (8.0)	0 (0.0)	7 (14.0)	
Fever, n (%)	28 (32.2)	7 (18.9)	21 (42.0)	.023
Initial TTP, n (%)	11 (12.6)	10 (27.0)	1 (2.0)	<.001
Days of hospitalization, median (IQR)	14 (8–21)	14 (11–22)	13 (7–21)	.351

APTT = activated partial thromboplastin time, BUN = blood urea nitrogen, CHD = coronary heart disease, CK = creatine kinase, CRP = C-reaction protein, CTD = connective tissue disease, DBP = diastolic blood pressure, EOS = eosinophil count, FDP = fibrin degradation products, INR = international normalized ratio, LDH = lactic dehydrogenase, MCV = mean corpuscular volume, PT = prothrombin time, PTA = prothrombin time activity, SBP = systolic blood pressure, TTP = thrombotic thrombocytopenic purpura, WBC = white blood cell.

2.2. Demographics, clinical data, and laboratory values

Fasting blood samples were collected by standard procedures on the second day of hospitalization. Routine blood indices and blood chemistry values were obtained when blood testing was completed. Additionally, demographic information, past and current medical history, and the signs and symptoms of the patient were collected by a physician and maintained in the electronic medical record system. In addition, the anticoagulated blood was recovered for blood index tests, and plasma was separated immediately. Then, the plasma samples were stored at −80 °C until analysis for ADAMTS13 activity was performed. All features collected at presentation were used as potential predictor variables for further analysis (see Supplementary Table 1, http://links.lww.com/MD/D990). The number of features reached 137 and include demographics (age, sex), comorbidities (smoking, drinking, and prevalence of hypertension, diabetes mellitus, etc), clinical data (blood pressure, temperature, Glasgow Coma Scale score, etc), and baseline laboratory values (white blood cell [WBC] count, hemoglobin, platelets, sodium [Na], potassium [K], chloride, blood urea nitrogen [BUN], creatinine [Cr], glucose [GLU], calcium, total protein, etc).

2.3. Outcome measures and definitions

The primary outcome of interest was prognosis, including in-hospital mortality, major thromboembolic events (i.e., stroke, myocardial infarction), or treatment failure at discharge. Individuals who experienced any event mentioned above were considered to be critically ill and needed intensive therapeutic management. Then, we separately analyzed the 3 endpoints of in-hospital mortality, major thromboembolic events, and treatment failure at discharge as the secondary outcomes. In addition, the failure of treatment at discharge was defined as failure of the normalization of platelet count (i.e., a platelet count of at least 100,000/mm^3) when patients were discharged from hospital.

2.4. Statistical analysis

Continuous variables with a normal distribution are expressed as the mean ± SD, while skewed variables are presented as the median (interquartile range). Categorical variables are expressed as frequencies (percentages). Student's *t* test or the Mann–Whitney *U* test was used to compare the normally distributed continuous or categorical characteristics, respectively. $P < .05$ was considered statistically significant. All analyses were performed using R version 3.4.3.

To determine the most important factors that are predictive of the primary outcome, we established a model introducing all the baseline characteristics at presentation. Given that several characteristics of our model were highly correlated and there were some missing values in our dataset, we applied a conditional inference random forest (cforest) algorithm to screen for important predictors. As a robust statistical method, random forests are widely used for variable selection and discriminant analysis in scientific works. It is also a non-parametric method for analyzing non-linear and high-dimensional data. The cforest method is appropriate for the analysis of data with missing values and can adjust for correlations between predictor variables. We used the cforest algorithm to calculate conditional variable importance measures, which can be used to rank the importance of variables in our predictive model. In detail, the importance of each variable was computed by permutation within a grid defined by the covariates that are associated (with 1 – *P* value greater than the threshold) with the variable of interest.[10,11] To further enhance stability and obtain robust results, we calculated the conditional variable importance 100 times, each time with a different random seed. Finally, we ranked all variables from the average scores of all repetitions, and the most important predictor was selected to develop a risk stratification tool for TTP. Finally, the predictive ability of D-dimer to differentiate the primary outcome was evaluated using receiver operating characteristic (ROC) analysis and the c-statistic (area under curve, AUC).

3. Results

3.1. Patient characteristics

A total of 135 TTP admissions confirmed by ADAMTS13 activity <10% were included from January 1, 2012 to November 30, 2018. Nine admissions were excluded because of missing data. One infant who was suspected to have congenital TTP was excluded. Given that the inclusion criteria were designed to collect only unique admission events for a patient with TTP, only 89 unique patients with 125 admissions for the diagnosis and treatment of TTP were included in this study. Two patients with a duration of hospitalization shorter than 3 days and who were lost to follow-up were excluded, so 87 patients eventually formed our study cohort (Fig. 1). All of our patients were native residents from Henan Province, central China. In addition, the main ethnic group of our cohort was of Han ethnicity except for 1 of Hui Chinese ethnicity. The mean age of the study cohort was 43.6 years, with 66.7% females and 33.3% males. Of these patients, 76 (87.4%) had their first episode of TTP. The main comorbidities the patients had upon admission were hypertension (13.8%), diabetes mellitus (3.4%), coronary atherosclerotic heart disease (5.8%), and connective tissue disease (28.7%). Twelve (13.8%) were current smokers, 9 (10.3%) were current drinkers, and 12 (13.8%) died within 30 days after presentation. Eventually, 50 TTP patients experienced in-hospital death, major thromboembolic events, or failure to achieve remission at discharge and were defined as high-risk patients. The high-risk TTP patients were older and tended to have a higher proportion of initial episodes. There were no differences in the prevalence of smoking, drinking, hypertension, diabetes mellitus, coronary artery heart disease, or connective tissue disease between the 2 populations. Regarding the initial laboratory values, high-risk patients presented significantly lower hemoglobin and higher WBC counts, D-dimer, GLU, C-reaction protein (CRP), lactic dehydrogenase (LDH), creatine kinase (CK), etc. The demographics, clinical features, and several laboratory values of the high-risk, low-risk, and all populations are available in Table 1.

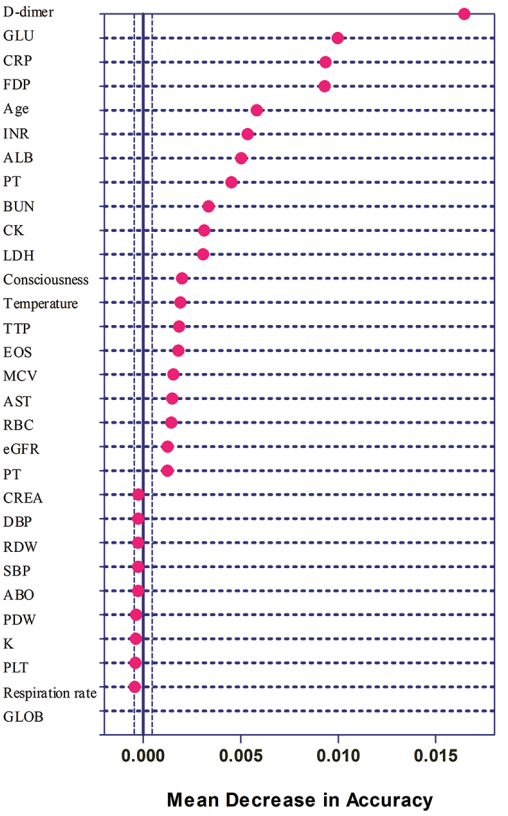

Figure 2. The importance of the variables included in the predictive model for the prognosis of the primary outcome in TTP patients. The primary outcomes were in-hospital mortality, major thromboembolic events, and failure to achieve remission at discharge. ABO = ABO blood type; ALB = albumin; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatine kinase; Cr = creatinine; CRP = C-reactive protein; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; EOS = eosinophil count; FDP = fibrin degradation products; GLOB = globulin; GLU = glucose; INR = international normalized ratio; K = K+ ion concentration; LDH = lactic dehydrogenase; MCV = mean corpuscular volume; PDW = platelet distribution width; PT = prothrombin time; PTA = prothrombin time activity; PLT = platelet count; RBC = red blood cell; RDW = red blood cell distribution width; SBP = systolic blood pressure; T = body temperature; TTP = thrombotic thrombocytopenic purpura.

3.2. Biomarker for the prognosis of TTP patients

In the primary outcome analysis, D-dimer was the best predictor of prognosis. Other characteristics that may be predictive included GLU, CRP, fibrin degradation products (FDP), age, international normalized ratio (INR), albumin (ALB), and prothrombin time (PT) (Fig. 2).

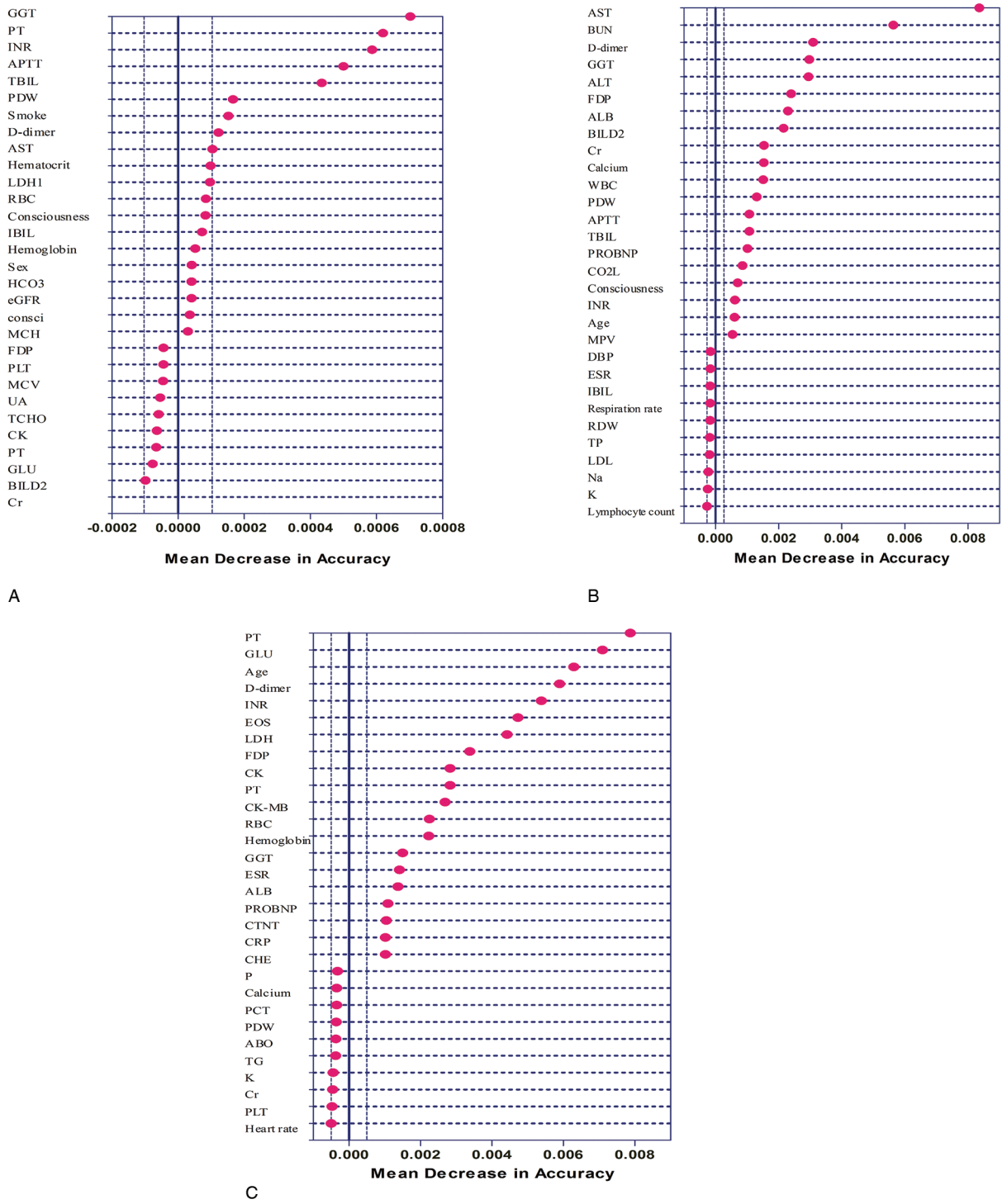

Figure 3. The importance of the variables included in the predictive model for the prognosis of secondary outcomes in TTP patients. The secondary outcomes were in-hospital mortality (A), major thromboembolic events (B), and failure to achieve remission at discharge (C). ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; Ca = Ca2+ ion concentration; CHE = cholinesterase; CK = creatine kinase; CK-MB = creatine kinase-MB; CO2CP = carbon dioxide combining power; CRP = C-reactive protein; cTnT = cardiac troponin T; DBil = direct bilirubin; EOS = eosinophil count; ESR = erythrocyte sedimentation rate; GGT = g-glutamyltranspeptidase; Hb = hemoglobin; HCO3- = HCO3- ion concentration; Hct = hematocrit; IBIL = indirect bilirubin; LDL = low density lipoprotein; MCH = mean corpuscular hemoglobin; MPV = mean platelet volume; Na = Na+ ion concentration; P = total phosphorus in serum; PCT = thrombocytocrit; Pro-BNP = pro-brain natriuretic peptide; RDW = red blood cell distribution width; TBIL = total bilirubin; TC = total cholesterol; TG = triglyceride; TP = total protein; UA = uric acid; WBC = white blood cell.

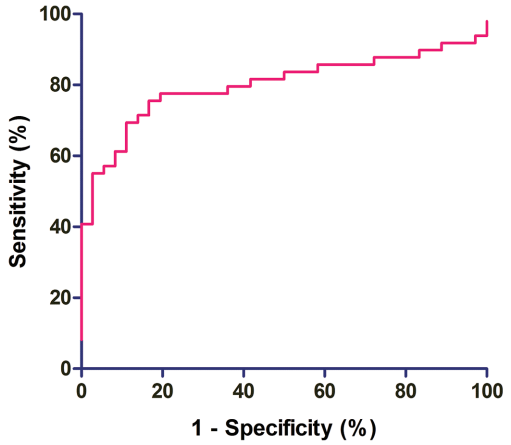

Figure 4. ROC curve for predicting the prognosis of the primary outcome in TTP patients using the predictive model.

In the secondary outcome analysis of in-hospital mortality, γ-glutamyltranspeptidase (GGT), PT, INR, activated partial thromboplastin time (APTT), and total bilirubin (TBIL) were the best predictors. Other characteristics, including D-dimer, were close to the significant threshold and may also be predictive for TTP in-hospital mortality (Fig. 3A). The most important predictors of major thromboembolic events were aspartate amino transferase (AST) and BUN followed by D-dimer (Fig. 3B). For the treatment failure at discharge, PT was the most predictive characteristic. GLU, age, D-dimer, and INR were also predictive but to a lesser degree (Fig. 3C).

The AUC from ROC analysis demonstrated that the predictive value of the admission D-dimer level alone for the primary outcome is 0.80 (95% confidence interval (CI), 0.70–0.90) (Fig. 4). The best predictive cut-off value of the D-dimer level for the primary outcome was 0.77, with a sensitivity of 78% (95% CI, 63–88%) and a specificity of 81% (95% CI, 64–92%). TTP patients with a D-dimer level >0.77 mg/L at admission could be classified as high-risk and need more intensive therapeutic management.

4. Discussion

This study included 87 TTP patients and demonstrated that the D-dimer level at admission may be a valuable predictor of prognosis, including in-hospital mortality, major thromboembolic events, or failure to achieve remission at discharge. The predictive power of D-dimer assessed by ROC analysis yielded an AUC of 0.80 in differentiating high-risk individuals from all TTP patients. The cut-off value of the D-dimer level was 770 ng/mL, and the optimal sensitivity and specificity were 78% and 81%, respectively.

In this study, the plasma D-dimer level moderately increased in patients with TTP, which was consistent with the findings of previous studies. For instance, in Hideo's study that consisted of 15 TTP patients, the D-dimer level (mean ± SD) was 451.0 ± 436.0 ng/mL.[12] Similarly, in Rika's cohort study involving 15 TTP patients, the D-dimer level (mean ± SD) at TTP onset was 1754.0 ± 786.0 ng/mL,[13] which was moderately increased compared with that in the healthy participants.

Furthermore, Hideo et al showed that a higher mean D-dimer level was associated with poor prognosis, although this trend had no statistical significance.[12] In a cohort of 73 unique patients with TTP, the D-dimer level significantly increased in the participants with fatal outcome (survived vs died: 2062.0 vs 7083.0 mg/L, $P = .09$) with a marginal P value.[8] The results of these studies were in line with our study, which reported a median D-dimer level of 1050.0 mg/L in the whole cohort, and the low-risk TTP patients had a significantly lower D-dimer level than the high-risk patients (low-risk vs high-risk: 540.0 vs 2110.0 mg/L, $P < .001$).

Previous studies also identified clinical and laboratory parameters, such as serum troponin I levels,[6] total serum protein,[8] albumin,[8] and ADAMTS13 antibody and antigen levels,[5] as predictors of poor prognosis in TTP. However, in our study, using a statistically robust method, the plasma D-dimer level was proved to be the most important predictor. These differences may be derived from the different populations, the limited sample size, and regional treatment bias.

The pathophysiological mechanisms behind the role of D-dimer in TTP remain incompletely understood. Recently, it was suggested that a severe deficiency of ADAMTS13 activity (<10%) by congenital defect or inhibition by autoantibodies is specific for TTP.[14] At the beginning of acute TTP episodes, ADAMTS13 deficiency and concomitant triggering factors such as pregnancy and inflammation cause the accumulation of ultra-large vWF multimers in the blood.[14] Subsequently, the multimers bind spontaneously to platelets, leading to the formation of platelet-rich microthrombi within small arterioles and capillary.[15,16] Simultaneously, the fibrinolysis pathways are activated, and this process would give rise to the raised D-dimer levels noted.[17] We propose that the D-dimer level in plasma correlates with the cumulative burden of microvascular thrombosis. When TTP patients are critically ill or in advanced stages, the large burden of microthrombi may contribute to the markedly elevated D-dimer levels in plasma. Therefore, high D-dimer levels may indicate a worse prognosis for TTP, and more intensive therapies, including twice-daily plasma exchange, are considered for these high-risk patients.

5. Conclusion

In general, the present study found that the D-dimer level exhibited a good predictive ability for prognosis in patients with TTP. These findings may aid in the development of new and intensive treatment strategies for remission among high-risk patients. However, external validation is necessary to confirm the generalizability of our approach across populations and treatment practices.

Author contributions

Conceptualization: Hai-Xu Wang, Lai-Jun song.
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Writing – review & editing: Tong-Wen Sun.

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