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ORIGINAL RESEARCH

Real-World Analysis of Clinical Characteristics, Treatment Outcomes, and the Novel Predictive Model for Patients with Thrombotic Thrombocytopenic Purpura (TTP) and TTP-Like Syndrome

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Purpose: It is crucial to differentiate critically ill patients exhibiting thrombocytopenia and hemolytic anemia alongside organ damage to enable rapid identification of thrombotic thrombocytopenic purpura (TTP) and TTP-like syndrome, which allows for targeted emergency interventions such as plasma exchange.

Patients and Methods: This study retrospectively analyzed clinical data from patients with TTP and TTP-like syndrome to further elucidate the potential differences between these conditions. We also established a new predictive model to facilitate early identification and differentiation between TTP and TTP-like syndrome. A new predictive model for diagnosing TTP was developed using five key indicators: reticulocyte percentage, platelet count, schistocyte percentage, LDH/ULN, and indirect bilirubin. The performance of this new model was compared with the traditional PLASMIC score by evaluating sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Results: Thirty-five patients were diagnosed with TTP and 42 were diagnosed with TTP-like syndrome. TTP is most commonly associated with autoimmune diseases (n=13, 37.14%), while TTP-like syndrome frequently arises from infections (n=23, 54.76%). The ADAMTS13 activity was significantly lower in the TTP group than in the TTP-like syndrome group (Mean 8.30% vs 46.12%). TTP-like syndrome patients had significantly higher levels of inflammatory markers. The new predictive model was developed for TTP with a predictive ability of 96.9%. Overall, 16 patients (20.77%) died, including 3 (8.57%) in the TTP group and 13 (30.95%) in the TTP-like syndrome group. Kaplan–Meier survival analysis showed significant differences in survival between TTP and TTP-like syndrome patients, with a 180-day overall survival (OS) rate of 90.6% vs 60.9% (p=0.009); and plasma exchange improved 180-day OS rate in the TTP group compared to the TTP-like syndrome group (90.6% vs 65.6%) (p=0.054).

Conclusion: This study demonstrates that TTP and TTP-like syndrome are two distinct types of diseases. The new predictive model has shown good efficacy in distinguishing TTP and TTP-like syndrome. Plasma exchange significantly improves survival in TTP patients; however, its effect on TTP-like syndrome is minimal.

Keywords: thrombotic thrombocytopenic purpura, TTP, TTP-like syndrome, systemic inflammatory response, TTP predictive model, plasma exchange

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Introduction

Thrombotic thrombocytopenic purpura (TTP) is a severe, disseminated thrombotic microangiopathy characterized by microangiopathic hemolytic anemia, consumptive thrombocytopenia, and organ damage, particularly to the kidneys and central nervous system, due to the formation of microthrombi.[1] In patients who do not receive timely recognition and plasma exchange treatment, the mortality rate can exceed 80%. A definitive diagnosis of TTP is established when ADAMTS13 activity is less than 10% and ADAMTS13 inhibitors are present. Critically ill patients often exhibit progressive thrombocytopenia, hemolytic anemia, and multiple organ dysfunctions, presenting symptoms that are similar to those of TTP.[2] However, in these cases, ADAMTS13 activity may be normal or only slightly decreased, and there are no detectable ADAMTS13 inhibitors, leading to the diagnosis of TTP-like syndrome.[3] The pathophysiological mechanisms underlying TTP-like syndrome remain poorly understood; it is thought that severe inflammatory responses may result in vascular endothelial injury or complement activation,[3,4] complicating the differential diagnosis of TTP and TTP-like syndrome. Both TTP and TTP-like syndrome frequently manifest across various medical specialties, including nephrology, neurology, hematology, and cardiology, and may present in emergency department. Thus, it is crucial to differentiate critically ill patients exhibiting thrombocytopenia and hemolytic anemia alongside organ damage to enable rapid identification of TTP and TTP-like syndrome, which allows for targeted emergency interventions such as plasma exchange.

In clinical practice, the reporting of ADAMTS13 activity and inhibitor test results is often delayed.[5,6] As such, clinical assessments currently rely on patient symptoms and relevant laboratory test results to derive the PLASMIC score,[7,8] which identifies high-risk patients who may benefit from immediate plasma exchange. Our prior study suggests that the modified PLASMIC score better predicts TTP compared to the traditional version.[9] However, it may not effectively distinguish TTP from TTP-like syndrome. To address this, we retrospectively analyzed clinical data from TTP and TTP-like syndrome patients to clarify differences in clinical features, laboratory findings, and prognosis. We also developed a new modified PLASMIC score for earlier identification and differentiation between TTP and TTP-like syndrome, enabling timely and precise treatment to improve outcomes for critically ill patients.

Materials and Methods

Data Collection

A retrospective analysis was conducted on TTP or TTP-like syndrome patients who were consecutively treated between May 2018 and April 2024. The selection criteria of TTP were as follows: (a) patients presenting with thrombocytopenia, microangiopathic hemolytic anemia (MAHA), fever, or organ dysfunction; (b) ADAMTS13 activity<10% with positive ADAMTS13 inhibitor; and (c) patients who were currently undergoing regular follow-up. The selection criteria of TTP-like syndrome were as follows: (a) patients presenting with thrombocytopenia, microangiopathic hemolytic anemia (MAHA), fever, or organ dysfunction; (b) ADAMTS13 activity >10% with negative ADAMTS13 inhibitor; and (c) patients who were currently undergoing regular follow-up.

Clinical data collection included patient gender, age, underlying disease or trigger, clinical characteristics, hematologic parameters, coagulation function, cardiac function, liver function, renal function, ADAMTS13 activity and ADAMTS13 inhibitor titers before plasma treatment, and treatment outcomes. All patients underwent ADAMTS13 activity and ADAMTS13 inhibitor testing, and the results are generally reported within 72 hours. The inflammatory markers assessment included neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), C-reactive protein-to-lymphocyte ratio (CLR), procalcitonin (PCT), and systemic immune-inflammatory index (SII), calculated as follows: SII=platelet count ($\times 10^9$/L) × neutrophil count ($\times 10^9$/L)/lymphocyte count ($\times 10^9$/L); additional markers such as albumin (ALB) and D-dimer were also collected. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of University of Science and Technology of China (approval number: 2024-RE-423) and was conducted in accordance with the Declaration of Helsinki; the written informed consent was waived due to the retrospective nature of the review, and all the data was anonymized and maintained with confidentiality.

Treatment Strategy Recommendations

For critically ill patients presenting with progressive thrombocytopenia, hemolytic anemia, and organ dysfunction—particularly those exhibiting central nervous system symptoms and renal impairment—there should be a high suspicion of TTP. Immediate initiation of plasma exchange therapy (with a plasma volume of 50–70 mL/kg) is essential, alongside immunosuppressive treatment using methylprednisolone at a dosage of 1 mg/kg per day. In cases where TTP is highly suspected and central nervous system symptoms are present, a high-dose pulse of methylprednisolone at 1 g daily should be administered for three consecutive days, followed by a tapering dose of 1 mg/kg per day. Concurrently, it is crucial to take blood samples for ADAMTS13 activity and inhibitor testing during the patient's first evaluation. For patients diagnosed with TTP, continue plasma exchange and corticosteroid therapy until the platelet count rises above 150×10^9/L. At this point, plasma exchange may be discontinued, and corticosteroids should be gradually tapered within 8–12 weeks. In cases where the therapeutic response is suboptimal, rituximab can be added at a dosage of 375 mg/m2, administered once weekly for four consecutive weeks. The use of caplacizumab is not recommended in China due to its current unavailability. For TTP-like syndrome patients with ADAMTS13 activity exceeding 10% and negative ADAMTS13 inhibitors, plasma exchange should be discontinued; decisions regarding the continuation of corticosteroid therapy should be tailored to the individual patient's clinical characteristics, with treatment plans developed through multidisciplinary discussions including considerations for the use of anti-C5 monoclonal antibody eculizumab (Figure 1).

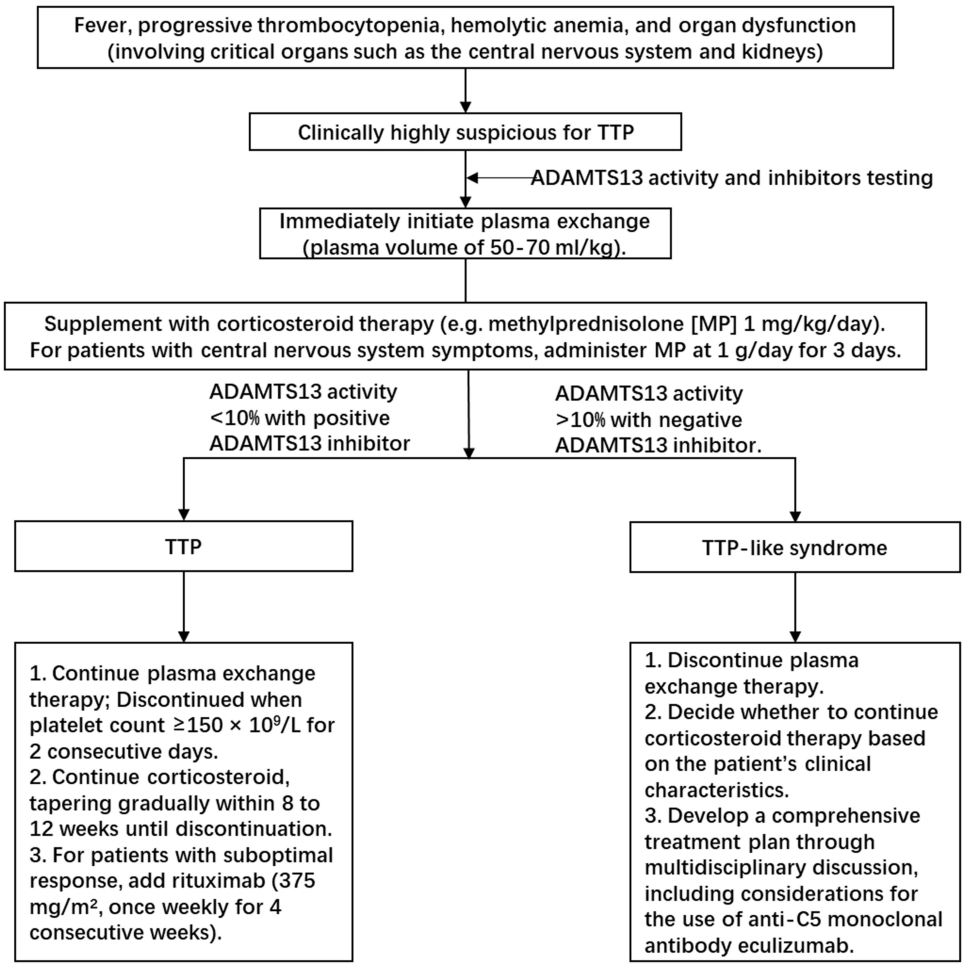

Figure 1 Treatment approaches for TTP and TTP-like syndrome.

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Statistical Analysis

Non-parametric Mann–Whitney *U*-tests were used to compare continuous variables, and Chi-square tests were applied for categorical variables. Variables with significant differences were regarded as potential diagnostic predictors for TTP and were evaluated using ROC curve analysis and binary logistic regression to compare the predictive abilities of individual variables and variable combinations. The area under the curve (AUC) was calculated to assess the predictive power of the variables, where a higher AUC value indicated a stronger overall predictive ability. Additionally, comparisons between individual predictive factors and combinations of predictors were performed to identify the most effective combination. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the new predictive combinations were calculated and compared with the traditional PLASMIC score. Furthermore, ROC curve analysis was used to determine the optimal cutoff values for the predictive factors. Risk stratification based on the traditional PLASMIC score defined low-risk patients as scoring 0–4 points, and medium- to high-risk patients as scoring 5–7 points.[8] Similarly, for the new scoring system, low-risk patients were defined as scoring 0–2 points, and medium- to high-risk patients as scoring 3–5 points. Sensitivity, specificity, PPV, and NPV of the new and traditional scoring systems were compared. Effective treatment was defined as a platelet count $\geq 150\times10^9$/L for more than two consecutive days without significant clinical symptoms. The probability of OS is estimated according to Kaplan–Meier curve. SPSS26.0 and R statistical software were used for statistical analysis and differences were considered statistically significant at $p<0.05$.

Results

Clinical Characteristics

Thirty-five patients were diagnosed with TTP and 42 were diagnosed with TTP-like syndrome (Table 1). The median age in the TTP group was 52 years (44–64), and in the TTP-like syndrome group was 57 years (35–68). Patients in the TTP group

Table 1 Clinical Characteristics of TTP and TTP-Like Syndrome Patients

Characteristics	All (n=77)	TTP Group (n=35)	TTP-Like Group (n=42)	p-value
Gender, Female, (%)	54 (70.1%)	26 (74.3%)	28 (66.7%)	0.520
Age, (years)	53 (40–68)	52 (44–64)	57 (35–68)	0.503
Infection, (%)	29 (37.7%)	6 (17.1%)	23 (54.8%)	0.001
Pregnancy, (%)	4 (5.2%)	0 (0.0%)	4 (9.5%)	0.159
Skin ecchymosis, (%)	37 (48.1%)	27 (77.1%)	10 (24.4%)	<0.001
Neuropsychiatric symptoms, (%)	49 (63.6%)	31 (88.6%)	18 (42.9%)	<0.001
Transplantation, (%)	1 (1.3%)	0 (0%)	1 (2.4%)	1.000
Antinuclear antibody profile, (%)	34 (44.2%)	22 (64.7%)	12 (33.3%)	0.015
Antiphospholipid antibodies, (%)	1 (1.3%)	1 (2.4%)	0 (0%)	1.000
SLE activity index, (%)	6 (7.8%)	2 (5.7%)	4 (9.5%)	0.009
Schistocytes, (%)	0.6 (0.10–1.80)	1.4 (0.48–3.38)	0.15 (0.10–0.50)	<0.001
WBC, ($\times10^9$/L)	8.57 (5.64–13.47)	8.88 (6.25–13.69)	8.18 (5.44–13.02)	0.509
RBC, ($\times10^{12}$/L)	2.82 (2.20–3.31)	2.40 (2.05–2.95)	2.99 (2.54–3.66)	0.001
Hb, (g/L)	86.00 (68.50–98.00)	75.00 (65.00–91.00)	91.50 (76.25–110.75)	0.003
PLT, ($\times10^9$/L)	11.00 (7.00–27.00)	7.00 (6.00–11.00)	25.00 (10.00–48.00)	<0.001

(*Continued*)

Table 1 (Continued).

Characteristics	All (n=77)	TTP Group (n=35)	TTP-Like Group (n=42)	p-value
MCV, (fL)	91.80 (87.15–97.35)	92.90 (87.30–99.80)	91.35 (86.90–96.47)	0.229
Ret, (%)	4.70 (2.43–10.33)	10.52 (6.16–15.30)	2.87 (1.46–4.63)	<0.001
ALT, (IU/L)	28.00 (18.15–43.00)	24.00 (18.30–38.60)	32.40 (18.00–65.50)	0.162
AST, (IU/L)	43.50 (26.00–78.50)	52.00 (31.90–77.00)	40.00 (21.00–100.00)	0.201
TBIL, (umol/L)	39.40 (17.55–61.20)	60.10 (39.40–80.50)	20.55 (11.18–40.83)	<0.001
DBIL, (umol/L)	10.40 (4.78–17.50)	13.95 (9.83–19.60)	6.05 (3.95–12.08)	0.001
IBIL, (umol/L)	21.00 (9.70–42.10)	41.20 (22.50–64.50)	13.00 (6.28–23.55)	<0.001
Cr, (umol/L)	70.00 (53.00–113.40)	67.00 (53.00–89.00)	82.95 (52.00–108.75)	0.192
Bun, (mmol/L)	9.39 (6.35–15.42)	9.54 (6.78–12.67)	9.29 (5.65–15.68)	0.904
ALB, (g/L)	34.70 (28.35–40.15)	38.40 (35.60–41.60)	31.55 (25.45–36.63)	<0.001
FIB, (g/L)	3.20 (2.19–3.99)	2.15 (2.20–3.54)	3.30 (2.08–4.49)	0.309
APTT, (s)	33.45 (27.58–40.50)	31.90 (25.90–38.20)	35.00 (30.15–42.15)	0.045
PT, (s)	17.30 (15.65–19.05)	17.30 (16.20–18.80)	17.15 (15.50–19.63)	0.862
TT, (s)	14.10 (13.05–15.80)	13.80 (12.30–15.80)	14.50 (13.17–16.38)	0.273
D-D, (mg/L)	3.20 (1.80–7.68)	2.80 (1.54–4.29)	4.18 (2.30–10.98)	0.036
INR	1.10 (1.04–1.26)	1.07 (1.05–1.20)	1.14 (1.03–1.37)	0.135
LDH, (IU/L)	1177.00 (472.50–2012.15)	1637.00 (795.50–2426.50)	604.20 (325.00–1671.50)	0.003
LDH/ULN	4.275 (1.86–7.02)	5.40 (3.16–8.55)	2.49 (1.46–5.46)	0.005
Myoglobin, (ng/mL)	41.80 (18.00–117.25)	29.90 (8.06–59.56)	49.00 (31.15–195.74)	0.093
Troponin, (ng/mL)	0.10 (0.04–0.57)	0.11 (0.04–0.28)	0.10 (0.04–0.74)	0.992

Notes: The values of each indicator in the table are presented as percentages, medians, and interquartile ranges (IQR). The Mann–Whitney *U*-test was utilized for comparing continuous variables, while categorical variables were analyzed using the chi-square test, with a significance level established at p<0.05. The normal reference values were added in Supplementary Table 1.

Abbreviations: WBC, white blood cell count; RBC, red blood cell count; Hb, hemoglobin; PLT, platelet count; MCV, mean corpuscular volume; Ret, reticulocyte count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; IBIL, indirect bilirubin; Cr, creatinine; Bun, blood urea nitrogen; ALB, albumin; FIB, fibrinogen; APTT, activated partial thromboplastin time; PT, prothrombin time; TT, thrombin time; D-D, d-dimer; INR, International normalized ratio; LDH, lactate dehydrogenase; LDH/ULN, lactate dehydrogenase/upper limit of normal.

had more skin bruising and neurological symptoms (which included confusion, agitation, delirium, seizures, and coma) than those in the TTP-like syndrome group (77.1% vs 24.4%, p<0.001; 88.6% vs 42.9, p<0.001). The ADAMTS13 activity was significantly lower in the TTP group than in the TTP-like syndrome group (mean 8.30% vs 46.12%). Compared to TTP-like syndrome patients, TTP groups had more patients with positive antinuclear antibodies (64.7% vs 33.3%, p=0.015), higher level of schistocytes (1.4% vs 0.15%, p<0.001), reticulocytes (10.52% vs 2.87, p<0.001), indirect bilirubin (41.20μmol/L vs 13.00μmol/L, p<0.001) and lactate dehydrogenase (1637.00U/mL vs 604.20U/mL, p=0.003), higher ratio of LDH/the upper limit of normal (ULN) (5.40 vs 2.49, p=0.005), and lower counts of red blood cell (p=0.001) and platelet (p<0.001), and lower levels of hemoglobin (p=0.003). On the other hand, the TTP-like syndrome group patients had more elevated APTT (35.00s vs 31.90s, p=0.045), D-dimer (4.18mg/L vs 2.80mg/L, p=0.036), and lower levels of Albumin (31.55g/L vs 38.40g/L, p<0.001).

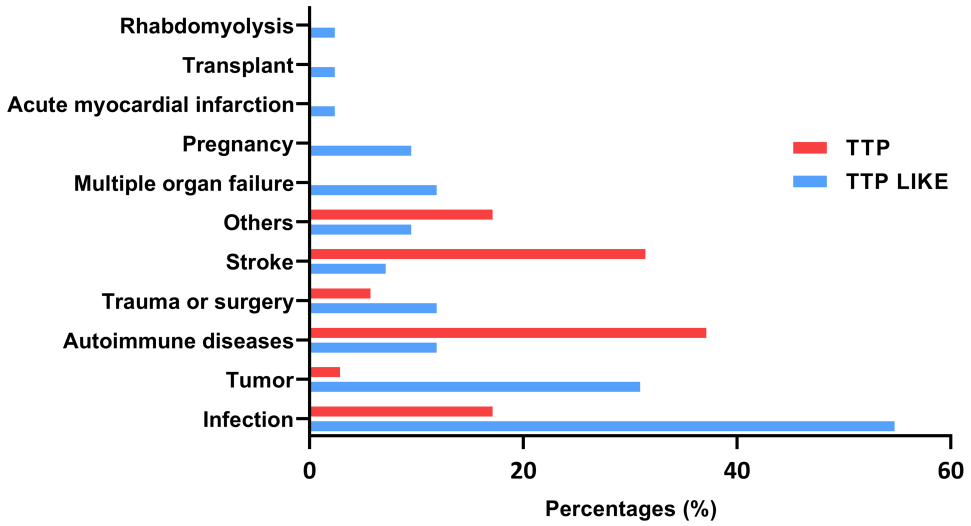

Figure 2 Underlying diseases of TTP and TTP-like syndrome.

Underlying Diseases

Underlying diseases were shown in Figure 2. In the TTP group, the main underlying diseases were autoimmune diseases (n=13, 37.14%), with 5 cases of systemic lupus erythematosus (38.46%), 6 cases of undifferentiated connective tissue disease (46%), and 2 cases of Sjogren's syndrome (15%); other underlying diseases included stroke (n=11, 31.43%), infections (n=6, 17.14%), trauma or surgery (n=2, 5.71%), malignancy (n=1, 2.86%), and unknown causes (n=6, 17.14%). The main underlying diseases in the TTP-like syndrome group were infections (n=23, 54.76%) and malignancies (n=13, 30.95%); pathogens were identified in 18 patients including fungi (n=7) (aspergillus infections, n=6; candida albicans, n=1), *Escherichia coli* (n=2), *Pseudomonas aeruginosa* (n=1), *Acinetobacter baumannii* (n=1), *Burkholderiacepacia* (n=1), *Aeromonas punctate* (n=1), cytomegalovirus (n=1) and SARS-CoV-2 (n=1), and 3 patients had multiple pathogens infections; malignancies included myelodysplastic syndrome (n=7), acute leukemia (n=2), colorectal cancer (n=1), gastric cancer (n=1), prostate cancer (n=1) and craniopharyngioma (n=1); other underlying diseases included autoimmune diseases (n=5, 11.90%), pregnancy (n=4, 9.52%), stroke (n=3, 7.14%), hematopoietic stem cell transplantation (n=1, 2.38%), acute myocardial infarction (n=1, 2.38%), rhabdomyolysis (n=1, 2.38%), and unknown causes (n=4, 9.52%).

Systemic Inflammatory Markers

TTP-like syndrome patients generally had more severe systemic inflammatory responses than TTP patients (Figure 3). In comparison, TTP-like syndrome patients had significantly higher levels of NLR (median 9.18 vs 5.25, p=0.005) (Figure 3A), PLR (median 22.81 vs 6.67, p<0.001) (Figure 3B), CLR (median 75.52 vs 8.18, p<0.001) (Figure 3C), SII (median 203.3 vs 43.67, p<0.001) (Figure 3D), CRP (median 60.10 vs 9.59, p<0.001) (Figure 3E), PCT (median 0.48 vs 0.14, p=0.002) (Figure 3F), and D-dimer (median 4.18mg/L vs 2.80mg/L, p=0.036) (Figure 3G), while albumin was significantly lower (median 31.55g/L vs 38.4g/L, p<0.001) (Figure 3H). No significant differences were found in LMR (p=0.138) (Figure 3I) and WBC (p=0.509) (Table 1).

TTP Predictive Model

As shown in Figure 4, the AUC values for individual variables ranged from 0.6933 to 0.8515 for diagnosing TTP. When the platelet count is $<11.5x10^9$/L, the specificity is 73.81%, the sensitivity is 85.71%, and the predictive accuracy for diagnosing TTP is 82.01% (Figure 4A). The reticulocyte count >5.90% had a specificity of 85.30% and a sensitivity of 80.70%, with a predictive ability of 85.15% (Figure 4B). Indirect bilirubin >24.95 μmol/L had a specificity of 81.00% and a sensitivity of 74.30%, with a predictive ability of 72.83% (Figure 4C). LDH/ULN >2.753 had a specificity of

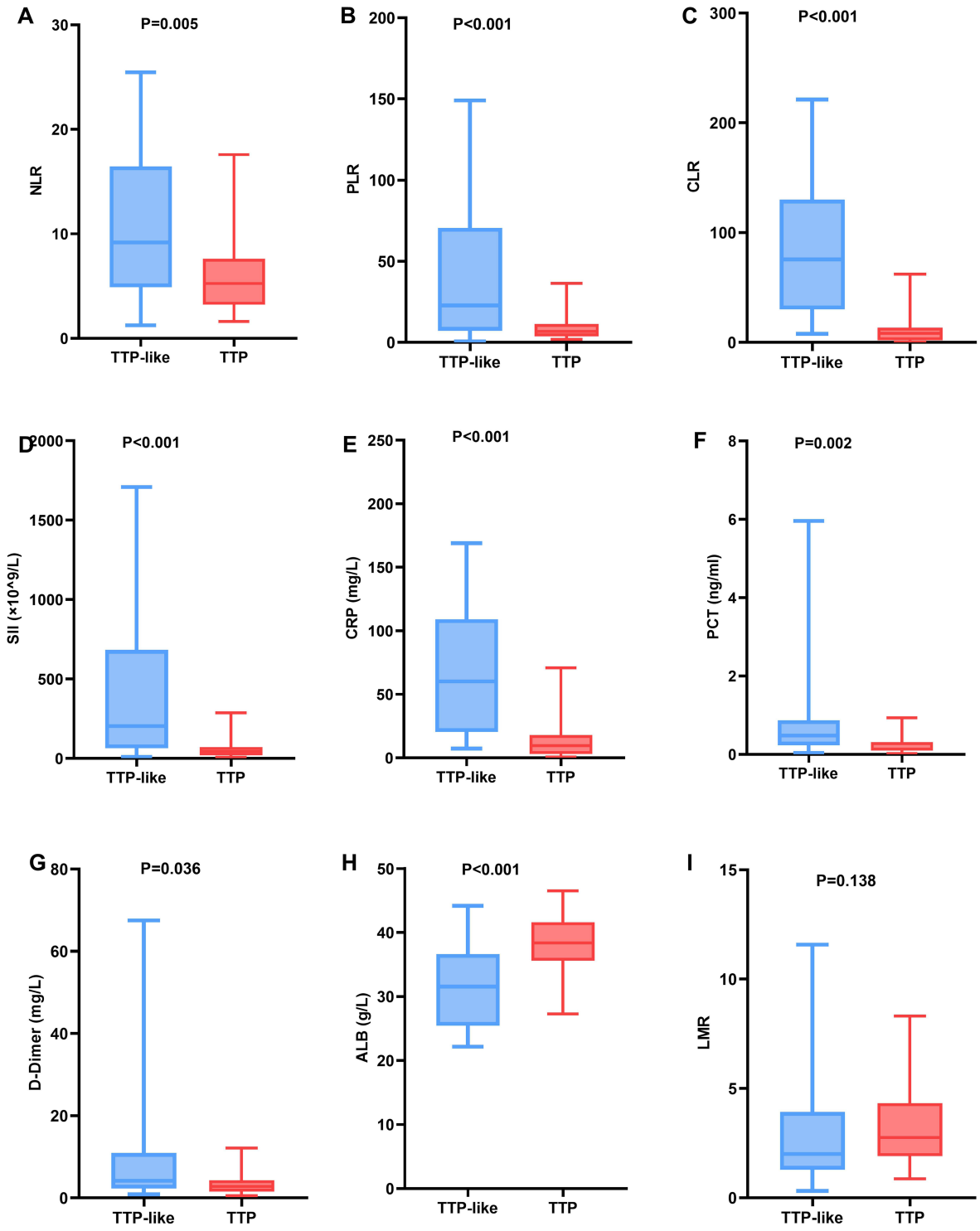

Figure 3 Systemic inflammatory markers of TTP and TTP-like syndrome. (**A**) Comparison of NLR between TTP and TTP-like syndrome patients; (**B**) Comparison of PLR between TTP and TTP-like syndrome patients; (**C**) Comparison of CLR between TTP and TTP-like syndrome patients; (**D**) Comparison of SII between TTP and TTP-like syndrome patients; (**E**) Comparison of CRP between TTP and TTP-Like syndrome patients; (**F**) Comparison of PCT between TTP and TTP-Like syndrome patients; (**G**) Comparison of D-Dimer between TTP and TTP-like syndrome patients; (**H**) Comparison of ALB between TTP and TTP-like syndrome patients; (**I**) Comparison of LMR between TTP and TTP-like syndrome patients.

Notes: The Mann–Whitney *U*-test was used to compare the TTP group with the TTP-like syndrome group, and $p<0.05$ was considered statistically significant. SII=platelet count ($\times 10^9$/L) × neutrophil count ($\times 10^9$/L)/lymphocyte count ($\times 10^9$/L).

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; CLR, C-reactive protein-to-lymphocyte ratio; SII, systemic immune-inflammatory index; CRP, C-reactive protein; PCT, procalcitonin; ALB, albumin; LMR, lymphocyte-to-monocyte ratio.

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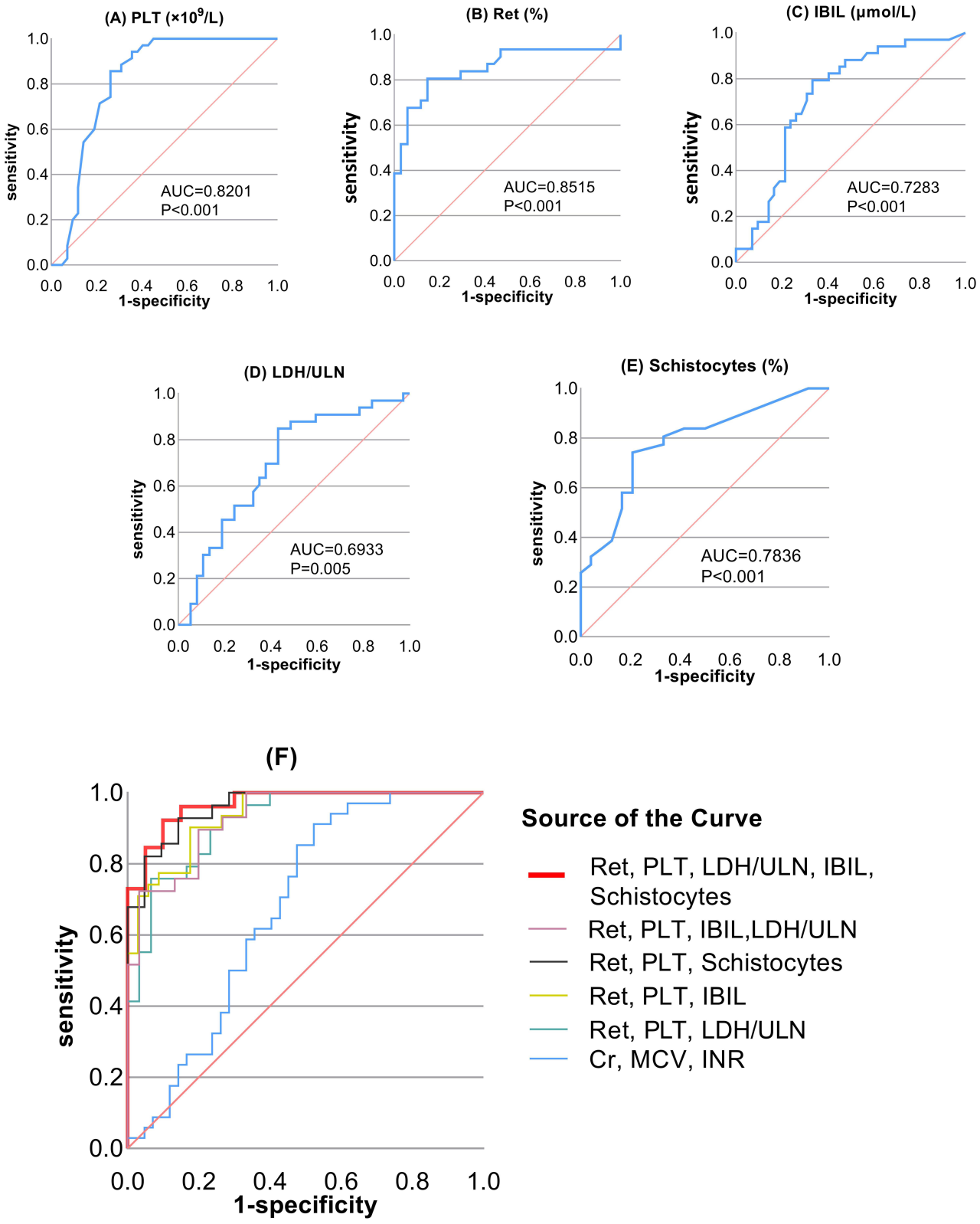

Figure 4 ROC plots to assess the diagnostic efficiency of the predictive models by distinguishing between TTP and TTP-like syndrome patients. (**A**) ROC curves of platelet count; (**B**) ROC curves of reticulocyte count; (**C**) ROC curves of indirect bilirubin; (**D**) ROC curves of lactate dehydrogenase/upper limit of normal; (**E**) ROC curves of schistocytes; (**F**) ROC curves of different indicator combinations.
Abbreviation: ROC, receiver operating characteristic curve.

56.80% and a sensitivity of 84.80%, with a predictive ability of 69.33% (Figure 4D). Schistocyte percentage >0.55% had a specificity of 79.20% and a sensitivity of 74.20%, with a predictive ability of 78.36% (Figure 4E).

The predictive ability of the combination of creatinine, mean corpuscular volume, and international normalized ratio (INR) percentage for diagnosing TTP was only 67.7%. A combination of reticulocyte percentage, platelet count, and LDH/ULN had a predictive ability of 91.8%, and the combination of reticulocyte percentage, platelet count, and indirect bilirubin had a predictive ability of 93.8%; and the combination of reticulocyte percentage, platelet count, and schistocyte percentage had a predictive ability of 96.1%; while the combination of reticulocyte percentage, platelet count, LDH/ULN and indirect bilirubin had a predictive ability of 92.9%. Furthermore, the five-variable model (reticulocyte percentage, platelet count, schistocyte percentage, LDH/ULN, and indirect bilirubin) showed the highest predictive ability of 96.9% (Figure 4F).

Subsequently, a new scoring model for diagnosing TTP was developed using these five indicators (reticulocyte percentage, platelet count, schistocyte percentage, LDH/ULN, and indirect bilirubin). When stratified into high-risk and low-risk categories, the sensitivity of the traditional PLASMIC score was 100.00%, specificity was 30.00%, PPV was 64.10%, and NPV was 100.00%; and the sensitivity of our previous modified PLASMIC score (reticulocyte percentage, platelet count, LDH/ULN and indirect bilirubin) was 88.46%, the specificity was 70.00%, the PPV was 79.31%, and the NPV was 82.35%. However, the new scoring model had a sensitivity of 100.00%, specificity of 65.00%, PPV of 78.13%, and NPV of 100.00%. Components of the new PLASMIC scoring systems between TTP and TTP-like syndrome patients were compared in Table 2.

Treatment Outcomes

All TTP and TTP-like syndrome patients were treated according to treatment strategy recommendations. In the TTP group, all patients underwent plasma exchange (50–70 mL/kg, varying from 5 to 10 sessions). In the TTP-like syndrome group, 10 patients received plasma exchange therapy (40–60 mL/kg, varying from 3 to 8 sessions). In the TTP group, 23 patients (65.71%) responded to treatment, while in the TTP-like syndrome group, only 22 patients (52.38%) had a positive treatment response. Overall, 16 patients (20.77%) died, including 3 (8.57%) in the TTP group and 13 (30.95%) in the TTP-like syndrome group. Kaplan–Meier survival analysis showed significant differences in survival between TTP and TTP-like syndrome patients, with a 180-day overall survival (OS) rate of 90.6% (95% CI: 73.4–96.9%) vs 60.9% (95% CI: 41.7–75.5%) (p=0.009) (Figure 5A). For patients who survived, the cumulative incidence of platelet increased $\geq 150\times10^9$/L at day 60 was significantly higher in the TTP group than in the TTP-like syndrome group [80.0% (95% CI: 62.6–89.9%) vs 40.5% (95% CI: 25.8–54.7%)] (p<0.001) (Figure 5B). Plasma exchange therapy improved 180-day OS rate in the TTP group compared to the TTP-like syndrome group [90.6% (95% CI: 73.4–96.9%) vs 65.6% (95% CI: 26.0–87.6%)] (p=0.054) (Figure 5C). However, in the TTP-like syndrome group, there was no significant difference in survival rates between patients who received plasma exchange therapy and those who did not [65.6% (95% CI: 26.0–87.6%) vs 54.0% (95% CI: 34.8–69.9%)] (p=0.590) (Figure 5D).

Table 2 Laboratory Test Results Between TTP Patients and TTP-Like Syndrome Patients Based on the New Scoring Systems

Items		TTP Group (n=35)	TTP-Like Group (n=42)	p-value
Platelet count	**<11.5×10⁹/L**	30 (85.7%)	11 (26.2%)	<0.001
Indirect bilirubin	**>24.95 μmol/L**	26 (74.3)	7 (16.7)	<0.001
Reticulocyte count	**>5.9%**	25 (80.6%)	5 (14.7)	<0.001
LDH/ULN	**>2.753**	28 (84.8%)	15 (40.5%)	<0.001
Schistocyte count	**>0.55%**	23 (74.2%)	8 (25.8%)	<0.001

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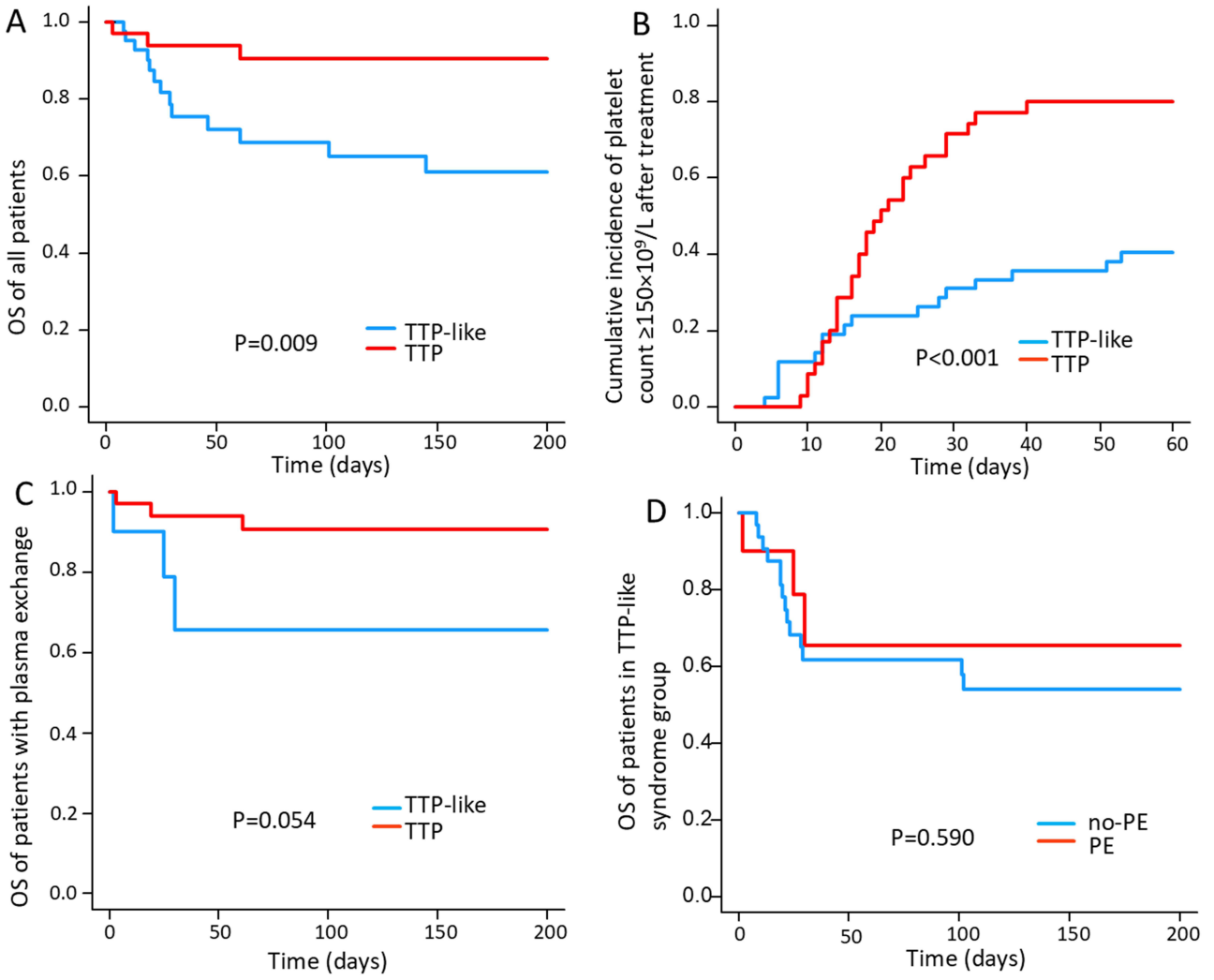

Figure 5 Treatment Outcomes. (**A**) OS of all patients; (**B**) Cumulative incidence of platelet count ≥150×10^9/L after treatment between TTP and TTP-like syndrome patients; (**C**) OS of patients with plasma exchange between TTP and TTP-like syndrome patients; (**D**) OS of patients in TTP-like syndrome group between PE and no-PE. **Abbreviations**: PE, plasma exchange group; no-PE, no-plasma exchange group; OS, overall survival.

Discussion

This study demonstrates that TTP and TTP-like syndrome are two distinct types of diseases based on a real-world clinical study, though their clinical features exhibit significant similarities such as microangiopathic hemolytic anemia, consumptive thrombocytopenia, and organ damage. Acquired TTP is mainly an autoimmune disorder characterized by the formation of inhibitory antibodies against ADAMTS13, leading to a marked decrease in its activity; this reduction results in the accumulation of ultra-large von Willebrand factor (VWF) multimers that cannot be effectively degraded, causing extensive platelet aggregation and microthrombus formation.[10] The pathophysiological mechanism of TTP-like syndrome remains unclear; however, previous studies suggest that it often occurs in the context of critical illnesses, such as sepsis, trauma, or surgical complications, potentially related to endothelial cell injury or complement activation.[3,4,11] Dong et al reported that TTP and TTP-like syndrome are two kinds of distinct phenotypes with different clinical outcomes.[12] This study indicates that TTP and TTP-like syndrome have different disease spectrums, for instance, TTP is most commonly associated with autoimmune diseases, while TTP-like syndrome frequently arises from infections caused by various pathogens. Moreover, inflammatory markers such as NLR, PLR, CRP, PCT, and D-dimer levels are

significantly elevated in patients with TTP-like syndrome; these findings strongly suggest the presence of severe systemic inflammatory responses in these patients.

It is crucial for clinicians to rapidly differentiate between TTP and TTP-like syndrome in emergency situations to enable timely treatment such as plasma exchange. Currently, the diagnosis of TTP primarily relies on the assessment of ADAMTS13 activity and the presence of inhibitors against ADAMTS13; however, these tests are often delayed. The traditional PLASMIC score is a commonly used criterion for identifying high-risk TTP patients, but it has limitations in differentiating between TTP and TTP-like syndrome;[13,14] in this study, the sensitivity and NPV of the traditional PLASMIC score for diagnosis of TTP are all 100.00%; however, the specificity was only 30.00%, and PPV was 64.10%. In our previous clinical study, we proposed an improved PLASMIC scoring system that incorporates platelet count, reticulocyte percentage, indirect bilirubin and the LDH/ULN ratio, achieving a sensitivity of 100% and a specificity of 95.2%, with a misdiagnosis rate of only 4.8%;[9] nonetheless, this modified PLASMIC score still has shortcomings in distinguishing TTP from TTP-like syndrome (sensitivity of 88.46%, specificity of 70.00%, PPV of 79.31% and NPV of 82.35%). In this study, we enhanced the modified PLASMIC score by adding the percentage of schistocytes to the existing parameters (platelet count, reticulocyte percentage, IBIL, and LDH/ULN ratio); thereby creating a novel scoring system that better meets clinical needs for diagnosing TTP; this new scoring model had a sensitivity of 100.00%, specificity of 65.00%, PPV of 78.13%, and NPV of 100.00% and with a higher predictive ability of 96.9%.

Plasma exchange is the cornerstone of treatment for TTP.[1,15] Early initiation of plasma exchange can significantly improve the prognosis for TTP patients, with overall survival rates exceeding 80%. However, due to the challenges in differentiating between TTP and TTP-like syndrome in the early clinical stages, clinicians should consider starting urgent plasma exchange for patients with a high suspicion of TTP.[2,16] This study indicates that plasma exchange treatment achieves a 180-day survival rate of 90.6% for TTP patients; however, its efficacy for TTP-like syndrome is notably lower, with a 180-day survival rate of only 65.6%. Furthermore, when comparing patients with TTP-like syndrome who received plasma exchange to those who did not, there was no significant difference in overall survival rates. These findings suggest that plasma exchange is not the preferred treatment for TTP-like syndrome, and a multidisciplinary consultation should be considered to establish a comprehensive treatment approach. The diagnostic and therapeutic protocols developed by our team for TTP and TTP-like syndrome demonstrate good clinical applicability (Figure 1).

Conclusion

In conclusion, this study demonstrates that TTP and TTP-like syndrome are two distinct types of diseases with different clinical characteristics. Acquired TTP is often associated with autoimmune disorders, while TTP-like syndrome is frequently linked to systemic inflammatory response by infection. The new modified PLASMIC score has shown good efficacy in distinguishing TTP and TTP-like syndrome, highlighting its clinical significance for early and differential diagnosis. Our findings indicate that plasma exchange significantly improves survival in TTP patients; however, its effect on TTP-like syndrome is minimal, necessitating a multidisciplinary consultation for comprehensive treatment. There are several limitations in this study. First, we did not explore the pathophysiological mechanisms of TTP-like syndrome, including the roles of endothelial injury and complement activation. Second, due to the low incidence of TTP, clinical data were derived from retrospective study in a real-world setting; thus, the results might exhibit some discrepancies with actual conditions. Third, although patients with TTP-like syndrome received a multidisciplinary team-developed comprehensive treatment approach, the variability in individual treatment protocols might impact the survival of these patients.

Data Sharing Statement

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of University of Science and Technology of China (approval number: 2024-RE-423) and was conducted in accordance with the Declaration of Helsinki; the written informed consent was waived due to the retrospective nature of the review.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Mengya Lv reports a patent A scoring table for predicting the diagnosis of thrombotic thrombocytopenic purpura (TTP) pending to Changcheng Zheng Mengya Lv. The author(s) report no other conflicts of interest in this work.

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