Comparison of clinical characteristics of first-episode Thrombotic Thrombocytopenic Purpura and TTP-like syndrome: a retrospective cohort study in a level I hematology centre in China

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Research Article

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Abstract

Aims: Comparing the characteristics of thrombotic thrombocytopenic purpura (TTP) and TTP-like syndrome patients at admission to allow early differentiation of TTP from TTP-like syndrome and help tailor initial treatment.

Methods: The medical records of 78 patients with suspected TTP in the emergency department of Peking University People's Hospital in the past five years were retrospectively analyzed retrospectively and divided into TTP and TTP-like syndrome groups based on ADAMTS13 activity and ADAMTS13 antibody titer.

Results: There were 25 and 53 patients in the TTP group and the TTP-like syndrome group, respectively. The PLASMIC score was significantly higher in the TTP group than in the TTP-like syndrome group (P=0.006). The TTP group were more susceptible to receiving plasma exchange and glucocorticoids (P<0.001), and also less vulnerable to the plasma infusion (P<0.001). The etiology induced by autoimmune disease was more prominent in the TTP group (P<0.001). The neutrophil-to-lymphocyte ratio (P=0.025) was tremendously higher, and albumin (P=0.002) was lower in the TTP-like syndrome group, indicating a more severe infection. Compared with the TTP-like syndrome group, the TTP group had an approximately two-fold to three-fold higher prevalence of central nervous system dysfunction (P<0.001). Also, hemolysis was more substantial in the TTP group as evidenced by higher schistocytes (P<0.001), reticulocyte (P<0.001), total bilirubin (P=0.002), indirect bilirubin (P<0.001), lactate dehydrogenase (P=0.007) and cell-free hemoglobin (P<0.001), simultaneously lower platelet (P<0.001), haptoglobin (P=0.044) and ADAMTS13 activity (P<0.001). The Kaplan–Meier survival analysis showed that the TTP group significantly predicted poor prognosis (log-rank test: X^2 =5.368, P=0.021).

Conclusion: TTP and TTP-like syndrome are two kinds of distinct phenotypes with different hemolysis statuses and illustrated differentiated inflammatory reactions, target organ damage (TOD), and their clinical outcome.

Background

Thrombotic thrombocytopenic purpura (TTP), a rare type of hematologic disease, is characterized by a high incidence of morbidity and mortality. Available epidemiological data showed that 2–6 individuals per million adults suffer from TTP annually [1], with the average mortality rate of currently 4–31% [2]. TTP patients commonly accompany thrombocytopenia, microangiopathic hemolytic anemia (MAHA), fever, and various organ damage [3]. The TTP-like syndrome has of late been reported as a new concept, with the features of vascular microthrombosis accompanied by thrombocytopenia and MAHA. Still, the majority of them are atypical organ dysfunction syndromes. These signs and symptoms largely overlap with TTP. In this connection, they are concurrently included in the phenotype of vascular microthrombotic disease (VMTD) [4]. Different from TTP, TTP-like syndrome occurs in major diseases and may activate two different molecular pathways (i.e., inflammatory and microthrombotic) due to complement

activation, resulting in endothelial lesions. Comparing the characteristics of TTP and TTP-like syndrome will contribute to the early diagnosis and life-saving plasma exchange (PE) and avoid expensive economic expenditure, waste of plasma, and intrusive operation and damage [5, 6].

Rapid a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) activity testing plays a vital role in the early diagnosis and optimal treatment of acute TTP. The phenomenon, namely, severe deficiency of ADAMTS13 activity(< 10%), highly suggested the possibility of suffering from TTP, and has now been incorporated into the definition of TTP [7–10]. However, response times and the insufficiency of the widely available complex tests are generally irreconcilable with the need to initiate precise treatments quickly [11, 12]. Therefore, in most instances, routine laboratory examination and clinical features can be the only straightforward approach to distinguish VMTD phenotypes.

The study aimed to retrospectively analyze the VMTD patients treated in our emergency department of level I hematology centre in China. Through the attempt to describe the characteristics and outcomes, we aimed to identify the clinical or biological features in the early stage, so as to achieve the differentiation.

Materials And Methods

Study population and study design

We inquired about the emergency department admission registration system for patients visited between January 1, 2017 to December 31, 2021 with a clinically suspected diagnosis of TTP (n = 78). The medical centre of Peking University Institute of Hematology is a national key discipline of the Ministry of education, an innovative group of the Ministry of education and a clinical key discipline of the Ministry of health.

Inclusion criteria: a) age > 16 years, b) presented with thrombocytopenia, MAHA, fever, or various degrees of organ damage, and c) ADAMTS13 activity assays. Exclusion criteria: a) received treatment from other medical institutions, b) transferred to other medical institutions or gave up treatment, and c) relapsed. The patient screening process is shown in Fig. 1.

The outcome of the present study was mainly about in-hospital mortality. The study was conducted within the framework of the Declaration of Helsinki and was approved by the local ethics committee (Ethical code: 2019-PHB-157). Due to the study design, the application for the written informed consent was chosen not to demand. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)-guideline recommendations were used as a reference guideline [13].

Data Collection And Definitions

The data from electronic healthcare record (EHR) systems was anonymized and de-identified before analysis. Demographic and clinical data were collected upon admission. The collected data included sex, age, schistocytes, white blood cell (WBC), red blood cell (RBC), platelet (Plt), neutrophil-to-lymphocyte ratio (NLR), red blood cell distribution width (RDW), mean corpuscular volume (MCV), reticulocyte (Ret), prothrombin time (PT), international normalized ratio (INR), fibrinogen (FIB), D-dimer, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine (Scr), cardiac troponin I (cTnI), total bilirubin (TBIL), indirect bilirubin (IBIL), lactate dehydrogenase (LDH), albumin (ALB), haptoglobin, cell-free hemoglobin (CFH), ADAMTS13 activity, ADAMTS13 antibody titer (if obtained), clinical presentation, intervention during the hospital, etiology, and length of stay (LOS).

Statistical analysis

SPSS 25.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism mapping software were used for data analysis. The Kolmogorov-Smirnov test was used to test for normality. Continuous variables were expressed as the median (interquartile range [IQR]), and compared using the Mann-Whitney U test. Categorical variables were presented as n (%) and compared using the chi-square test or Fisher's exact test. Kaplan–Meier survival analysis was used to assess the patients' death risk. $P < 0.05$ was considered statistically significant.

Results

Clinical and demographic characteristics of TTP and TTP-like syndrome

As demonstrated in Table 1, during the study period, 78 adults presenting with the first episode of suspected TTP were compliant with the inclusion criteria and were analyzed for the study's endpoints. The diagnostic median age was 45 years (IQR: 30–62), and females occupied the majority of the patients(53.85%). The median age of patients in the TTP group was 46 years(IQR 36-68), and that for the TTP-like syndrome group was 40 (26-64). A total of 12 patients (48.00%) in the TTP group and 30 patients (56.60%) in the TTP-like syndrome group were female. There were no differences in demographic characteristics between the two groups.

In addition, the PLASMIC score of the TTP-like syndrome group was notably lower than that of TTP group[4 (IQR 3, 4) vs. 4 (IQR 4, 5), P=0.006]. In terms of treatment, PE was used in 30 cases (38.46%), plasma infusion in 44 cases(56.41%), glucocorticoids in 57 cases(73.08%), and immunoglobulin in 38 cases (48.72%). A total of 16 (20.51%) patients received rituximab therapy, and 19 (24.36%) patients received other immunosuppressive therapies. Moreover, only two patients were treated with continuous renal replacement therapy (CRRT). In the TTP group, the proportions of patients who received PE (72.00%) and glucocorticoids (88.00%) were more than those in the TTP-like syndrome group (66.04% and 22.64%, P<0.001), respectively. In addition, the plasma infusion was significantly lower in the TTP group compared to the TTP-like syndrome group (40.00% vs. 64.15%, P<0.001).

Etiological factors

In patients with VMTD, the common etiologies included autoimmune diseases (26 cases, 33.33%), hematopoietic stem cell transplantation (HSCT, 17 cases, 21.79%), pathogen (8 cases, 10.60%), pregnancy (7 cases, 8.97%), malignant hypertension (7 cases, 8.97%), malignancy (6 cases, 7.69%), cobalamin C defect (3 cases, 3.85%), and polytrauma (1 case, 1.28%). Different from the TTP-like syndrome group, the etiologies of TTP do not appear in pregnancy, cobalamin C defect, polytrauma, and malignant hypertension. As Figure 2 illustrated, the proportion of patients in the TTP group was more remarkable in autoimmune disease than that of the TTP-like syndrome group (64.00% vs. 18.87%, P<0.001). There was no difference in the other four etiologies between the two groups.

Inflammation

Compared to patients in the TTP group, those who were among the TTP-like syndrome group were more likely to have higher NLR [9.33 μg/mL (IQR 5.24, 16.46) vs. 3.91 (IQR 2.55, 5.87), P=0.025] and more inclined to have lower ALB [32 g/L (IQR 28, 36) vs. 38 g/L (IQR 33, 42), P=0.002]. Otherwise, there were no differences in WBC count (P=0.248) or the level of FIB (P=0.645) and D-dimer (P=0.284) between the two groups. No difference in RDW (P=0.120) was observed between the two groups, either (Figure 3).

Target organ damage (TOD) caused by circulating microthrombosis

The spectrum of TOD for each group was recorded in Figure 4. Although the prevalence of acute hepatic injury (AHI), acute myocardial injury (AMI), and acute pancreatitis (AP) were higher and acute kidney injury (AKI) was lower in the TTP-like syndrome group patients, the differences were found insignificant. There was a notable difference in central nervous system dysfunction(CNSD, 33.96% vs. 76.00%, P<0.001) between the two groups.

Laboratory parameters in hematologic features

The results of laboratory tests in TTP group and TTP-like syndrome group were very different (Table 2). The higher median levels of schistocytes [3.0% (IQR 1.0, 5.0) vs. 0.8% (IQR 0.4, 2.0), P<0.001], Ret [0.167*10^6/μL (IQR 0.124, 0.234) vs. 0.074 *10^6/μL (IQR 0.032, 0.127), P<0.001], TBIL [61.6 μmol/L (IQR 29.7, 122.5) vs. 32.0 μmol/L (IQR 19.85, 69.0), P=0.002], IBIL [42.8 μmol/L (IQR 20.4, 89.3) vs. 15.1 μmol/L (IQR 9.3, 25.7), P<0.001], LDH [1150 U/mL (IQR 505, 1949) vs. 498 U/mL (IQR 317, 1135), P=0.007], and CFH [125 mg/L (IQR 88, 356) vs. 38 mg/L (IQR 23, 90), P<0.001] were evidenced among TTP group. Furthermore, TTP group showed a lower median level of Plt [8*10^9/μL (IQR 5, 20) vs. 27*10^9/μL (IQR 12, 53), P<0.001], haptoglobin [5.83 mg/dL (IQR 5.83, 19.90) vs. 5.83 mg/dL (IQR 5.83, 59.20), P=0.044], and ADAMTS13 activity [5.0% (IQR 0.0, 6.8) vs. 43.3% (IQR 31.2, 48.5), P<0.001] than TTP-like syndrome group.

Clinical outcomes

After the follow-up, the outcome of 21 (26.92%) patients was clinical death. Kaplan-Meier analysis was used to analyze the survival probability of VMTD patients in the two groups, so as to determine their

prognoses(Figure 5). Survival analysis revealed a relatively lower cumulative survival rate in the TTP group than in the TTP-like syndrome group (log-rank test: X^2 =5.368, *P*=0.021).

Discussion

TTP and TTP-like syndrome are characterized by the hematologic phenotypes of VMTD, with clinical manifestations of consumptive thrombocytopenia and MAHA. TTP can be attributed to the following two conditions: one is gene mutation-associated VMTD, and the other is antibody-associated VMTD. TTP-like syndrome is caused by endotheliopathy-associated VMTD in critical illnesses [14]. Although TTP has made progress in diagnosis and treatment in recent years, it still poses severe challenges to healthcare providers and patients [15]. In terms of the optimum diagnosis in the early stage, as well as the distinguishment from other forms of VTMD, the existing evidence remains limited and inconsistent. In this study, we compared the clinical characteristics and the outcomes of the two phenotypes of VMTD patients.

The prominent feature of VTMD is its frequent occurrence in sepsis, cancer, autoimmune disease, HSCT, and so on. However, as a phenotype of VTMD, TTP is rarely seen in malignant hypertension, drug or toxin, pregnancy, trauma, and surgery [14]. Our study acted in cooperation with it. Furthermore, the etiology-induced autoimmune disease was more prominent in the TTP group.

The most notable observation of the TTP-like syndrome patients in our study was distinctly increased SIRS. The reported release of inflammatory cytokines in the molecular pathways caused by endotheliopathy were interleukin (IL)-1, IL-6, tumor necrosis factor-α, and others [16, 17]. WBC, NLR, RDW, D-Dimer, FIB, and ALB are all classical biomarkers of SIRS reported. The experiments showed that the higher WBC, NLR, RDW, D-Dimer, FIB and the lower ALB indicated the more serious inflammatory response [18–21]. In the present study, NLR and ALB once again confirmed the existence of inflammatory reaction and supported that TTP-like syndrome had the characteristics of SIRS.

The most common TODs of TTP-like syndrome in this research were AHF and AMI, and it also had underlying TODs such as CNSD, AKI, and AP. Different from TTP, TTP-like syndrome is generally caused by complement activation in critical illness patients. Terminal C5b-9 complex causes endotheliopathy, which activates another molecular pathway: multiorgan dysfunction syndrome (MODS) [22] and presents with atypical organ phenotypic syndromes, embracing acute respiratory distress syndrome (ARDS), AMI, AP, AHF, AKI, rhabdomyolysis, non-occlusive mesenteric ischemia, to name but a few [13]. In our research, TTP was conspicuous with CNSD or other signs of organ injury. The distributions of TODs in the TTP group and the TTP-like syndrome group were basically consistent with other studies [14, 23]. We may believe that CNSD would contribute to the early diagnosis and selective and optimized treatment when presented with distinguishing features of VMTD.

In addition to inflammatory reaction and TODs, the hematologic features of the two phenotypes of VMTD patients in our study also differed, as revealed by the significantly higher schistocytes, Ret, TBIL, IBIL,

LDH, and CFH in the TTP group. Consistently, lower Plt, haptoglobin, and ADAMTS13 activity was also detected in the TTP group than in the TTP-like syndrome group, which was consistent with previous research results; namely, fewer schistocytes in TTP-like syndrome cases and intravascular hemolysis could have easily been missed [24]. Reduced ADAMTS13 activity has long been included in the diagnostic criteria of TTP [15]. Considering the remarkably different laboratory parameters between the two groups in our study, there may be significant differences in their hematologic features. Because of this, the intravascular hemolysis of TTP-like syndrome had been termed atypical MAHA (aMAHA) [4].

The proportions of the patients with treatments of CRRT, immunoglobulin, rituximab, and other immunosuppressive therapies in the study of the two groups were similar. However the proportions of PE, glucocorticoids, and fresh frozen plasma (FFP) differed. The above differences can be explained in part by the following statements. On the premise that TTP and TTP-like syndrome can not be effectively distinguished, PE and glucocorticoids are timely life-saving measures, which have a specific basis for clinical benefits in TTP-related guidelines, expert consensus, and reviews [2, 8, 10, 23, 25, 26]. Oppositely, TTP-like syndrome, as a hemostatic disease associated with endothelial lesions in critical diseases, patients should focus on the treatments of definite etiology, and FFP is an effective adjuvant treatment, but urgent intervention with PE may not always be appropriate [27].

According to prevenient literature reports, TTP has elevated the survival rate to approximately 85% [26], and our research result was close to it. However, due to the brand-new concept of VTMD, the epidemiology of TTP-like syndrome was unavailable. Our research has filled a specific gap in this regard.

The study has limitations. First of all, TTP is a rare disease, so although cases have been collected for five years, the overall sample size is still limited. Secondly, the proportion of female patients in the TTP group was lower than the officially disclosed, thereby resulting in specific random errors. Thirdly, it is the referral bias. Our institution is a level I hematology centre in China; the patients might be enriched of those with more severe diseases and more challenging to treat referred by smaller and inexperienced hospitals, and may not be generalizable to other jurisdictions in China or even the globe. Moreover, the causal conclusions can not be achieved due to the retrospective observational study. Additional observational studies are needed to evaluate further characteristics, such as ARDS, a known fatal TOD for TTP-like syndrome.

Conclusions

We compared the clinical characteristics and outcomes of TTP and TTP-like syndrome in China over five years. This study results revealed the that TTP and TTP-like syndrome are two different kinds of diseases caused by distinct pathogenesis, leading to different degrees of inflammatory reactions, TODs, and hematologic features, despite their underlying pathology of disseminated intravascular microthrombosis (DIT), as well as the diametrically opposed clinical outcome. This study and its findings may help clinicians better understand the new concepts of VTMD and TTP-like syndrome, and earlier identification of TTP, which would yield better health outcomes.

Abbreviations

A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13); acute hepatic injury: AHI; acute kidney injury: AKI; alanine aminotransferase: ALT; albumin: ALB; acute myocardial injury: AMI; acute pancreatitis: AP; acute respiratory distress syndrome: ARDS; aspartate aminotransferase :AST; cell-free hemoglobin: CFH; central nervous system injury: CNSD; continuous renal replacement therapy: CRRT; cardiac troponin I: cTnI; disseminated intravascular microthrombosis: DIT; electronic health-care record: EHR; fresh frozen plasma: FFP; fibrinogen: FIB; hematopoietic stem cell transplantation: HSCT; indirect bilirubin: IBIL; interleukin: IL; international normalized ratio: INR; lactate dehydrogenase: LDH; length of stay: LOS; microangiopathic hemolytic anemia: MAHA; mean corpuscular volume: MCV; multiorgan dysfunction syndrome: MODS; neutrophil-to-lymphocyte ratio: NLR; plasma exchange: PE; platelet: Plt; prothrombin time: PT; red blood cell: RBC; red blood cell distribution width: RDW; reticulocyte: Ret; serum creatinine: Scr; systemic inflammatory response syndrome: SIRS; strengthening the reporting of observational studies in epidemiology: STROBE; total bilirubin: TBIL; target organ damage: TOD; thrombocytopenic purpura: TTP; vascular microthrombotic disease: VMTD; white blood cell: WBC.

Declarations

Acknowledgements

Not applicable.

Author' contributions

Analysing and interpreting the data and writing: G Dong; resources: W Gao and F Shi; review and editing: X Zhang and J Zhu. All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials

For materials, correspondence and requests should be addressed to J Zhu.

Declarations Ethics approval and consent to participate

It was authorised by the ethics committee of the Peking University People's Hospital (2019-PHB-157).

Consent for publication

Not applicable.

Competing interests

The authors report no conflict of interest.

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Tables

Table 1.Baseline demographics and clinical characteristics.

	All (n=78)	TTP (n=25)	TTP-like syndrome (n=53)	*P* value
Demographics				
Female	42 (53.85%)	12 (48.00%)	30 (56.60%)	0.477
Age (years)	45 (30, 62)	46 (36, 68)	40 (26, 64)	0.107
PLASMIC Score	4 (3, 5)	4 (4, 5)	4 (3, 4)	0.006*
Intervention during Hospital				
PE	30 (38.46%)	18 (72.00%)	12 (22.64%)	0.001*
Plasma infusion	44 (56.41%)	10 (40.00%)	34 (64.15%)	0.045*
Glucocorticoids	57 (73.08%)	22 (88.00%)	35 (66.04%)	0.041*
Immunoglobulin	38 (48.72%)	16 (64.00%)	22 (41.51%)	0.064
Rituximab	16 (20.51%)	8 (32.00%)	8 (15.09%)	0.084
Other immunosuppressive therapies	19 (24.36%)	3 (12.00%)	16 (30.19%)	0.143[c]
CRRT	2 (2.56%)	1 (4.00%)	1 (1.89%)	1.000[c]

Data are presented as the median (IQR) or n (%). P was the comparison between TTP and TTP-like syndrome. *$P < 0.05$ was considered statistically significant.

PE:plasma exchange; CRRT: continuous renal replacement therapy. LOS: length of stay.

Table 2. Laboratory findings about MAHA for TTP and TTP-like syndrome.

.	All (n=78)	TTP (n=25)	TTP-like syndrome (n=53)	*P* value
Schistocytes (0%)	1.6 (0.5, 2.0)	3.0 (1.0, 5.0)	0.8 (0.4, 2.0)	0.001*
RBC (4.30~5.80*10^9/L)	2.54 (2.00, 3.00)	2.55 (1.87, 2.94)	2.41 (2.00, 2.97)	0.860
MCV (82.0~100.0fL)	92.7 (86.8, 96.8)	91.5 (84.4, 96.5)	90.6 (86.5, 96.5)	0.797
Plt (125~350*10^9/L)	39 (8, 45)	8 (5, 20)	27 (12, 53)	0.001*
Ret (0.024~0.084*10^6/μL)	0.129 (0.054, 0.170)	0.167 (0.124, 0.234)	0.074 (0.032, 0.127)	0.001*
TBIL (3.4~17.1μmol/L)	63.2 (20.3, 78.6)	61.6 (29.7, 122.5)	32.0 (19.85, 69.0)	0.002*
IBIL (1.7~10.2μmol/L)	30.1 (10.3, 41.0)	42.8 (20.4, 89.3)	15.1 (9.3, 25.7)	0.001*
LDH (109~245U/mL)	965 (321, 1305)	1150 (505, 1949)	498 (317, 1135)	0.007*
Haptoglobin (36.00~195.00mg/dL)	25.87 (5.83, 44.13)	5.83 (5.83, 19.90)	5.83 (5.83, 59.20)	0.044*
CFH (0~40mg/L)	127 (28, 135)	125 (88, 356)	38 (23, 90)	0.001*
ADAMTS13 activity (70~120%)	36.2 (6.4, 46.7)	5.0 (0.0, 6.8)	43.3 (31.2, 48.5)	0.001*

**P* < 0.05 was considered statistically significant.

RBC: Red blood cell; Plt: platelet; MCV: mean corpuscular volume; Ret: Reticulocyte; TBIL: total bilirubin; IBIL: indirect bilirubin; LDH: lactate dehydrogenase; CFH: cell-free hemoglobin.

Figures

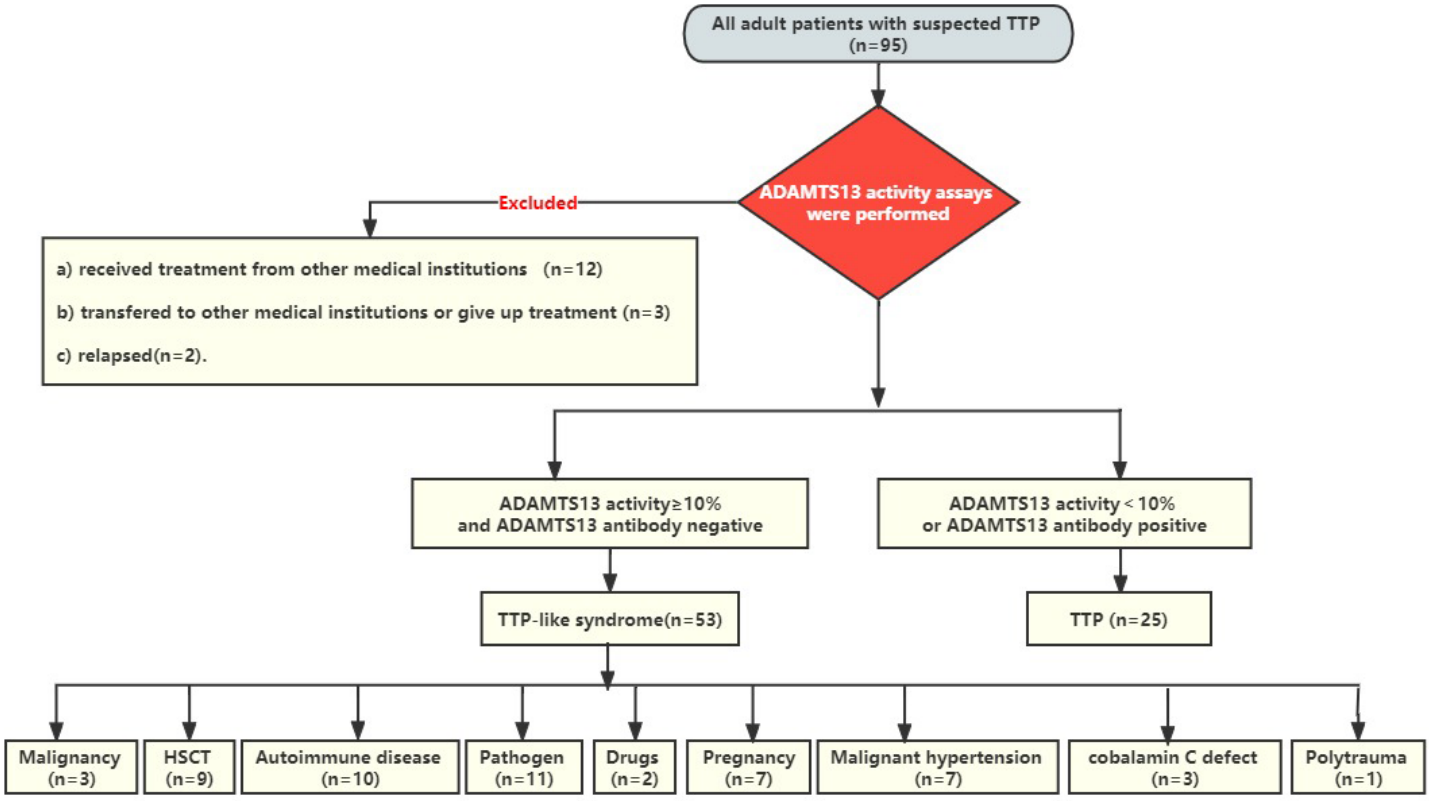

Figure 1

Patient flow chart illustrating enrollment of the study population.

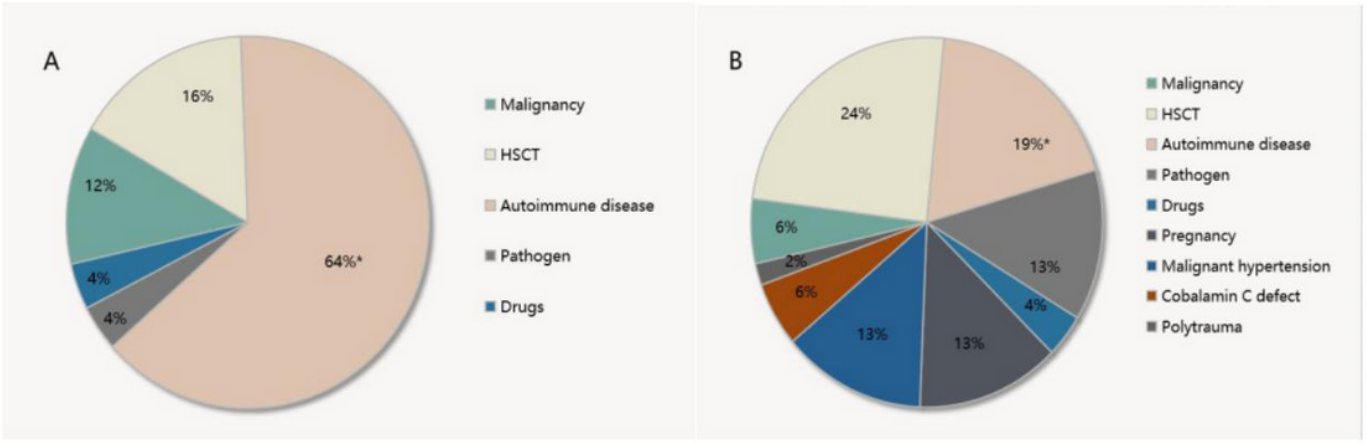

Figure 2

Etiologies in the two groups. A: TTP group. B: TTP-like syndrome group.

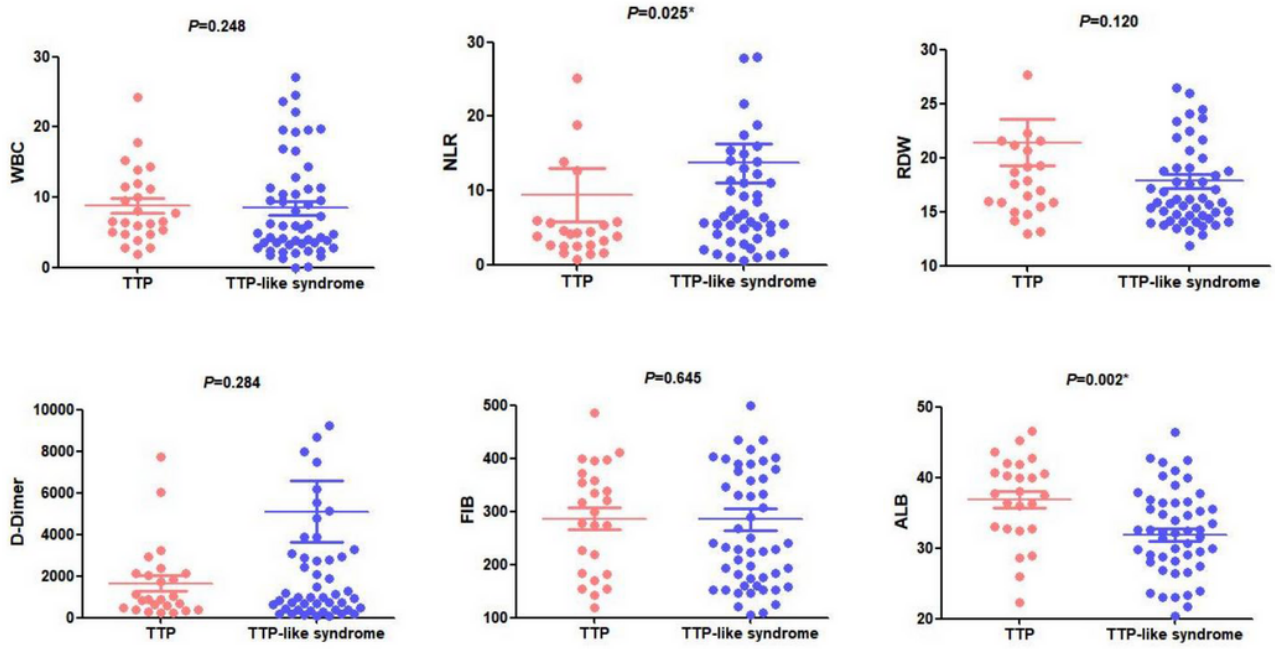

Figure 3

Spectrum of target organ damage.

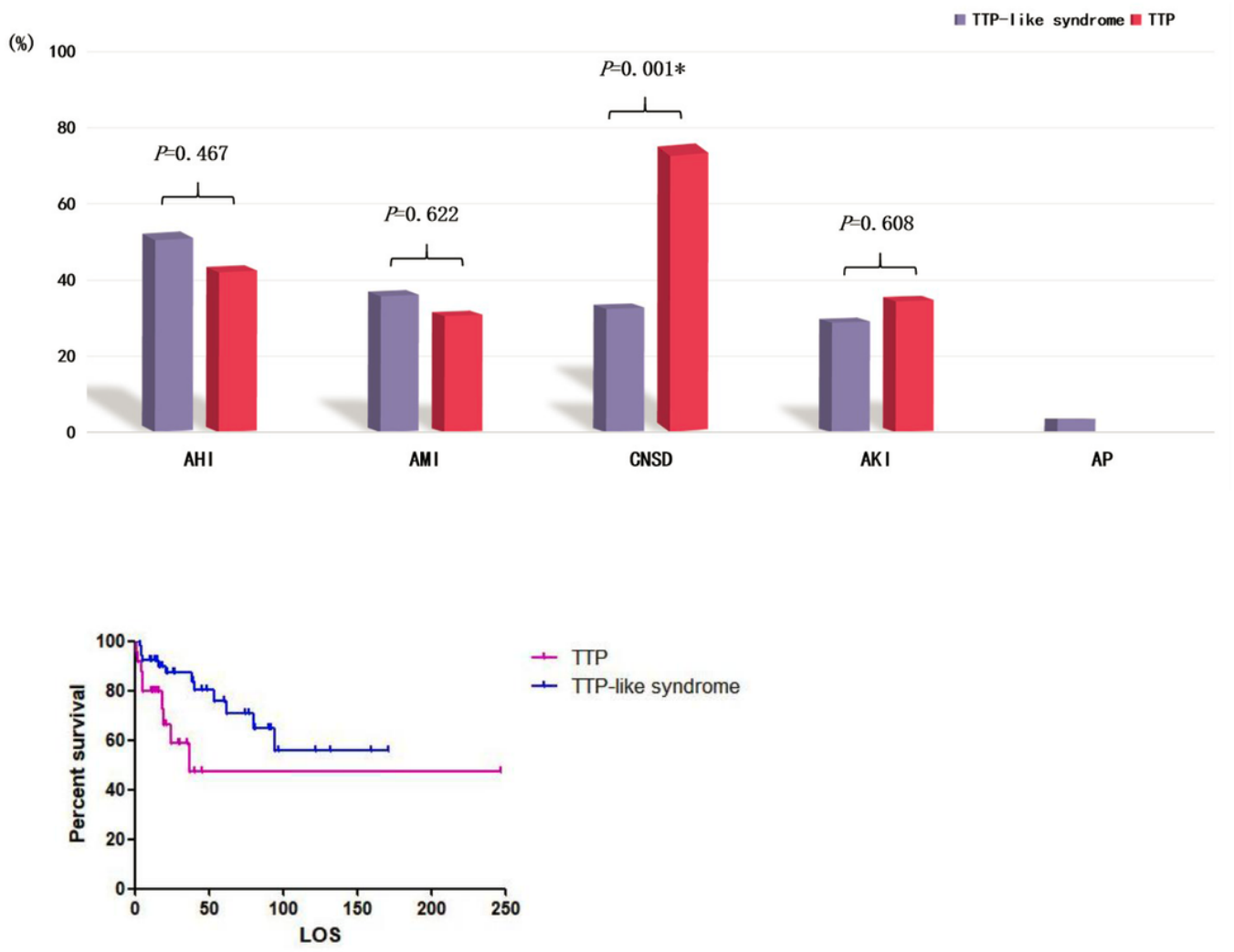

Figure 4

Kaplan-Meier analysis for prognosis of TTP group and TTP-like syndrome group.