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Clinical Manifestations, Treatment Characteristics and Clinical Outcome in Patients with Immune Thrombotic Thrombocytopenic Purpura (iTTP) in the Real-World Setting: An Interim Analysis of the Turkish iTTP Registry

Karakuş S. et al.: Turkish aTTP Registry Interim Analysis

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Abstract
Objective: This study aimed to investigate the clinical manifestations, treatment patterns and clinical outcomes in patients with iTTP across Türkiye via an interim analysis of the Turkish iTTP registry.
Materials and Methods: A total of 215 patients with iTTP (median age at diagnosis 41 years, 58.6% female) diagnosed between 2001 and 2023 were retrospectively analyzed in the interim analysis of the prospective non-interventional observational multicenter iTTP registry study conducted at 19 tertiary hematology centers. Data on patient demographics, disease characteristics on initial admission, treatment characteristics, and responses, exacerbations/relapses, and the survival outcome were registered via electronic case report forms.

Results: Infection (15.0%), new drug initiation (9.7%), and pregnancy/postpartum (6.3%) within 3 weeks before diagnosis were the most prevalent potential triggers. Patients presented more commonly with systemic/constitutional (fatigue 68.8%; fever 18.1%) and neurologic (headache 40.0%, vertigo 32.1%), followed by hemorrhagic, gastrointestinal, renal, and cardiovascular manifestations. Based on the PLASMIC risk scoring, 77.8% of patients were initially at high risk for TTP. The initial treatment was commenced within the first 48 hours of hospital admission in 64.1% of patients (36.2% on the day of admission). Treatment was mainly based on TPE exchange (92.1%) and steroids (63.7%), while rituximab was used in 15.8% of patients. The clinical response rate was 79.9%, and clinical remission was achieved in 68.2% of patients. As for the ADAMTS13 levels, partial and complete responses were achieved in 17.7% and 14.6%, respectively. During a median of 30 months (range, 0.1 to 262.4 months) follow-up, 35 patients experienced exacerbations/relapses. Mortality occurred in 11 (5.5%) patients and was found to be disease-related in 6 (3.0%).
Conclusion: This interim analysis of the nationwide Turkish iTTP registry study provided valuable data on the real-world clinical practice in the diagnosis and management of iTTP at different hematology clinics across the country.
Keywords: Thrombotic thrombocytopenic purpura; Acquired thrombotic disorders, Acquired platelet disorders, Autoimmune disorders, Apheresis

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a type of thrombotic microangiopathy (TMA) characterized by of microangiopathic hemolytic anemia, thrombocytopenia, and ischemic organ dysfunction. TTP results from either congenital or acquired decrease of von Willebrand factor (vWF)-cleaving protease ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13). Acquired TTP is caused by autoantibodies targeting ADAMTS13, and shows a heterogeneous clinical presentation depending on the end-organ ischemic damage (1-5).

The diagnosis of TTP is based on clinical presentation and laboratory results and is confirmed by the documentation of decreased ADAMTS13 activity, which is lower than 10% in most cases (6-8). Timely diagnosis is critical in TTP, as it is considered a medical emergency leading to multiorgan failure and death in 90% of untreated cases, while the mortality rate decreases to 10-15% with the proper treatment (1,7,9,10).

The mainstay therapeutic approach consists of therapeutic plasma exchange (TPE) to replenish functional ADAMTS13 and remove vWF autoantibodies, and immunosuppressive therapy to suppress anti-ADAMTS13 autoantibodies. However, despite the provision of appropriate treatment, the usual clinical course involves acute episodes, exacerbations (30-50%), and relapses (30%) in a considerable proportion of patients (11-14).

Caplacizumab is a humanized antibody fragment that targets the A1 domain of vWF, preventing its interaction with the platelet glycoprotein Ib-IX-V receptor and inhibiting microthrombi formation. After the phase III study showing that caplacizumab added to TPE in acute iTTP episodes resulted in faster normalization of platelet count and lower risk of TTP-associated complications, death, and relapse compared to not receiving caplacizumab, the drug was approved for use for the first step treatment as an adjunct to TPE and corticosteroids (15).

The TTP registries created worldwide are considered to enable a better understanding of the pathophysiology of TTP, allowing a significant improvement in both diagnosis and therapeutic management (6-8,16-19). To date, two studies of the national retrospective Turkish TMA registry in patients who were referred for TPE with a presumptive diagnosis of TMA and available ADAMTS13 activity/anti-ADAMTS13 antibody levels were conducted by the Turkish Hematology Research and Education Group (ThREG), including the ThREG-TMA01 study (n=154, in 2018) and ThREG-TMA02 study (n=80, in 2022). These studies revealed the presence of TTP in 67(43.5%) patients and iTTP in 29(36.2%) patients in the registry, respectively (20,21).

The present Turkish iTTP registry was established to create a nationwide resource to allow a deeper understanding of iTTP. This study aimed to investigate the clinical manifestations, treatment patterns, and clinical outcomes in patients with iTTP in the real-world setting.

Methods

Study population

A total of 215 patients with iTTP diagnosed between 2001 and 2023 were included in the retrospective interim analysis of this real-world prospective non-interventional observational multicenter Turkish iTTP registry study (ClinicalTrials.gov Identifier: NCT05950750) conducted at 19 tertiary hematology centers across Türkiye in collaboration with the Turkish Society of Hematology. Patients with new or former iTTP diagnosis, those with available data on their initial episodes at diagnosis and confirmed ADAMTS13 activity of <10% and the autoantibody positivity demonstrated at a central laboratory were included. The study was planned as a 5-year follow up study involving the time period between February 2023 to February 2027. This paper presents a preliminary interim analysis of baseline and 1-year patient follow-up data in the registry.

This study was conducted under the ethical principles stated in the “Declaration of Helsinki” and approved by the Baskent University Ankara Hospital Clinical Research Ethics Committee (Date of Approval:22/04/2022,

Protocol No: 22/25) and the Republic of Türkiye Ministry of Health Turkish Medicines and Medical Devices Agency (Date of Approval: 21/12/2022, Protocol No: E-66175679-514.05.02-960200). Data was recruited via electronic case report forms.

Assessments

Data on patient demographics, family history, comorbid/associated conditions, potential triggers within 3 weeks before iTTP diagnosis, and the presenting symptoms and clinical manifestations, and laboratory findings on initial admission were recorded in each patient. The treatment characteristics and treatment response, the exacerbation/relapse frequency, and the survival outcome were also evaluated.

Definitions

Clinical response was defined as a sustained platelet count ≥150×10^9/L and lactate dehydrogenase (LDH) <1.5 times the upper limit of normal (ULN), with no clinical evidence of new or progressive ischemic organ injury. Clinical remission was defined as a sustained clinical response with either no TPE and no anti-vWF therapy (e.g. caplacizumab) for ≥30 days, or with the attainment of ADAMTS13 remission (partial or complete), whichever occurs first. Partial ADAMTS13 remission was considered when ADAMTS13 activity ranged from ≥20% to below the lower limit of normal (LLN), while complete ADAMTS13 remission was defined as ADAMTS13 activity at ≥LLN. Clinical exacerbation, occurring after a clinical response and before clinical remission, was characterized by a decrease in platelet count to <150× 10^9/L (with other causes of thrombocytopenia excluded), with or without clinical evidence of new or progressive ischemic organ injury, within 30 days of stopping TPE or anti-VWF therapy. Clinical relapse was defined as a decrease in platelet count to <150×10^9/L (with other causes of thrombocytopenia ruled out), with or without clinical evidence of new ischemic organ injury, and confirmed by documentation of severe ADAMTS13 deficiency (22).

Statistical analysis

Statistical analysis was made using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY). Descriptive statistics were reported for categorical data. Data were expressed as median (range), interquartile range (IQR), and percent (%) where appropriate.

Results

Demographic characteristics, medical background, and potential triggers

The median age of patients at diagnosis was 41(range 16-73) years, and females comprised 58.6% of the study population. Non-O blood groups were noted in 65.4% of patients, while comorbid autoimmune disease was noted in 7.4%. Previous history for malignancy (1.9%), and organ/stem cell transplantation were evident in less than 3% of patients. Considering potential triggers within 3 weeks before the diagnosis, infection was the leading factor (15.0%), followed by new drug initiation (9.7%) and pregnancy/postpartum (6.3%). The clopidogrel, cyclosporin, and quinine usage rates within the 3 weeks prior to diagnosis were 1.9%, 1.4%, and 0.9%, respectively (Table 1).

Presenting symptoms and clinical manifestations

Patients presented more commonly with systemic/constitutional (fatigue: 68.8%; fever: 18.1%) and neurologic (headache: 40.0%, vertigo: 32.1%), followed by the hemorrhagic (purpura: 28.8%, ecchymosis: 24.2%) and gastrointestinal (vomiting: 25.1%, abdominal pain: 19.1%), and less commonly by renal (acute kidney injury [AKI]: 15.3%) and cardiovascular (hypertension: 16.7%) manifestations (Table 2).

Laboratory findings at the time of diagnosis

Median(range) hemoglobin levels at the time of initial diagnosis were 9.2(3.9-15.7) g/dL, serum LDH was 825.5(131-6266) IU/L, and median schistocyte count per area on peripheral smear(PS) was 6.0(2-25). The PLASMIC score (median 6.0) at the time of initial diagnosis revealed that 77.8% of patients were at high risk for TTP (Table 3).

Treatment characteristics

The initial treatment was commenced within the first 48 hours of hospital admission in 64.1% of patients (on the day of admission in 36.2%), which was mainly based on TPE exchange(92.1%), steroids(63.7%), immunosuppressive therapy(20.9%, [rituximab in 15.8%]), antiplatelet/anticoagulant/thrombolytic treatment(20.9%). Supportive treatment with erythrocyte and thrombocyte transfusions was given in 31.2% and 20.0%, respectively (Table 4).

Clinical outcome

Clinical response was achieved by 79.9% of patients, including the clinical remission in 68.2%, with partial ADAMTS13 response in 17.7% of patients and complete ADAMTS13 response in 14.6% of patients (Table 4). During a median of 30(0.1-262.4) months follow-up, 35(16.3%) exacerbations/relapses were identified in 215 registry patients. Laboratory findings during acute exacerbations/relapses were consistent with a median platelet count of 23(14.8-37.5)x10^9/L, hemoglobin 10.3(9.3-11.6) g/dL, WBC count 9.1(7.1-12.2) x 10^9/L, schistocyte count 5(3.8-7.3) per area on PS and LDH 579(358-1143) IU/L, total bilirubin 1.6(0.8-1.0) mg/dL. Mortality occurred in 11(5.5%) patients and was found to be disease-related in 6 (3.0%) patients. Two and 4 patients had relapse and refractory disease, respectively at the time of death. In these patients, the main reasons for death

were sepsis, multiorgan failure, and respiratory failure. The known reasons for death in patients at clinical remission were progression of multiple myeloma, COVID-19 pneumonia, and gastric carcinoma.

Discussion

This interim analysis of the nationwide Turkish iTTP registry study provided valuable data on the real-world clinical practice in diagnosis and management of iTTP at different hematology clinics across Türkiye. The findings are consistent with results of the previous registries in iTTP patients in terms of a female preponderance (~2-fold) and a clinical course characterized by a relapsing tendency and a life-threatening potential despite appropriate treatment. On the other hand, data revealed less mortality (5.5% compared to 8-15%) and lower exacerbation/relapse (16.3% compared to 30-50%) (17-19, 23,24).

Patients in the registry appeared to present more commonly with constitutional and neurologic manifestations in addition to gastrointestinal and hemorrhagic, and less commonly with renal and cardiovascular manifestations. Likewise, the Milan TTP Registry reported a high frequency of systemic (72%), bleeding (68%), and neurological (43%) symptoms at presentation but a lower prevalence of renal (18%) and cardiovascular (10%) manifestations (18). Data from the Oklahoma Registry revealed the typical clinical presentation in acquired TTP patients to include gastrointestinal symptoms (69%), weakness (63%), bleeding or purpura (54%), major (41%), and minor (26%) neurologic findings, and fever (10%) (19). Other studies also indicated that the main presenting symptoms in patients involve fatigue, dyspnea, petechiae, or bleeding secondary to thrombocytopenia, while abdominal pain is considered amongst the most prevalent presenting symptoms, particularly in those with idiopathic acquired TTP (1,25).

Many cohort studies demonstrated the classical pentad of symptoms (fever, hemolytic anemia, thrombocytopenia, AKI, and severe neurologic findings), traditionally used to define TTP, actually coincide in less than 10% of acute TTP cases (16-18, 27-29). The neurological manifestations were particularly prevalent and highly heterogeneous in our patients, including headache and vertigo as the leading neurological manifestations, followed by dysarthria, paresthesia, motor loss, personality change, stroke, epilepsy, and coma. This supports the consideration of neurologic symptoms to dominate the clinical picture of iTTP, with at least 60% of patients having wide-spectrum neurologic symptoms at presentation (1,5, 26-28). In our cohort, renal involvement included AKI in 15.9% of patients. In contrast to the atypical hemolytic uremic syndrome, which presents predominantly with AKI, kidney impairment is considered to be mild and transient in the setting of iTTP. AKI has been reported in up to 27% of patients with iTTP, emphasizing that its absence does not exclude diagnosis of iTTP (1,5,30). Cardiac manifestations in our patients included hypertension, chest pain, ischemic heart disease, and ECG abnormality, supporting the likelihood of cardiac involvement in patients with iTTP. Indeed, an elevated serum troponin is considered a poor prognostic marker and an independent predictor of increased mortality risk (three-fold increase) and refractoriness to treatment in patients with TTP.
The clinical manifestations in our cohort emphasize the critical role of a high clinical suspicion in adequate diagnosis of iTTP, given that patients present with a myriad of signs and symptoms of varying type and severity (1, 31).

In addition to the manifestations specific to the widespread microthrombi, about 50% of TTP patients also have comorbid/associated clinical conditions or triggers of TTP (5,13,32). The most common triggers for ADAMTS13 autoantibody formation causing iTTP in previous studies include infections, autoimmune diseases, pregnancy/postpartum, surgery, trauma, a wide range of drugs, pancreatitis, cancers, and organ transplantation (1,17,33-38). The potential triggers for TTP occurrence were identified in at least 40% of our patients, such as infection, pregnancy/post-partum period, starting a new medicine, surgery, and clopidogrel, cyclosporin, or quinine, while the comorbid autoimmune disease was evident in 7.4% of patients. Besides the leading role of infections within 3 weeks before the diagnosis (15%) as a precipitating factor, almost 17% of our patients also presented with upper respiratory tract infection or flu-like syndrome at the time of initial diagnosis. Similarly, data from the Milan TTP registry revealed that infections (27%) were the most prevalent triggers among potential triggers of acute episodes occurring within three months before disease onset (18). The history of malignancy (1 hairy cell leukemia, 1 multiple myeloma, 2 basal cell carcinoma), organ (1 renal transplantation), or stem cell transplantation (1 Autologous stem cell transplantation for multiple myeloma) was evident in less than 3% of our patients. These patients were not regarded to have cancer- and organ transplantation-associated TTP because they had anti-ADAMTS13 antibodies. Cancer and transplantation-associated TTP are considered to have unique characteristics that differ from other TTP forms, such as presenting equally in men and women at an older age of onset, no relation to an immune-mediated ADAMTS13 deficiency, and a worse prognosis (8,13,39).

Considering the potential non-modifiable risk factors for iTTP (Sex, age, and blood group), ~60% of our patients were females and less than 5% of our patients were in the ≥65 years age group, while non-O blood groups (blood

type A in 42.8%) were noted in 65.4% of patients. Female sex and non-O blood groups were considered among the potential non-modifiable risk factors for iTTP (37). Approximately 2-fold increased risk of relapse has been documented in patients with non-O blood groups, while group A blood type was considered a risk factor for initial presentations (40,41). Also, the clinical outcomes and disease burden in iTTP patients are suggested to worsen with increasing age, and the higher mortality rates in older versus younger patients with iTTP have been linked to the higher prevalence of multimorbidity and polypharmacy in older patients (7,42,43).

Given the heterogeneous clinical manifestations of the disease, laboratory evaluation plays a critically important role in diagnosing TTP (1). The laboratory diagnostic work-up in the present registry seems consistent with the proposed diagnostic requirements such as microangiopathic hemolytic anemia and thrombocytopenia. Also, the PLASMIC risk scoring at the time of initial diagnosis revealed that 77.8% of patients had scores of 6-7, indicating that they were at high risk for TTP (44,45). Hence, the prevalent use of the PLASMIC score across clinics that participated in the registry seems notable in terms of its potential help in making a presumptive diagnosis of TTP in the appropriate clinical setting (44,45).

Based on the potential of TTP for rapid clinical deterioration and early mortality, commencing TPE as soon as possible after the suspected diagnosis is crucial, and thus empiric treatment with TPE is often required before confirmation of diagnosis (1-3,17,46). However, TTP care in a real-world setting is considered to be discordant with the guidelines in terms of longer treatment delays due to multiple barriers, which put patients at increased risk of mortality and thrombotic complications (17,46). In our cohort, the initial treatment was commenced within the first 48 hours of hospital admission in 64.1% of our patients (on the day of admission in 36.2%), while delayed treatment (> 48 hours of admission) was noted in 35.8% of patients. Likewise, in an Australian registry with 67 TTP patients, TPE exchange therapy was commenced on the day of stated diagnosis in 51% of patients and on the following day in 34%, while it was commenced 2 days and 3 days after the diagnosis in 10% and 4% of patients, respectively (17). In a retrospective cohort study with 163 patients with suspected TTP in the real-world setting, a significant delay (Initiation of TPE > 8 hours of admission) was noted in nearly 60% of patients (46). However, the delayed TPE between 8 and 24 hours was not associated with a significantly higher risk of death, whereas the risks of death and major thrombotic events were markedly increased with >24 hour delay (46).

The commencement of TPE (92.1%) and steroids (63.7%) within the first 48 hours of admission in most patients in our registry seems in accordance with other registries (1,11,12,29,38). Although the International Society on Thrombosis and Haemostasis (ISTH) strongly recommends the addition of corticosteroids to TPE for patients with iTTP experiencing an acute event, our data showing that steroids were not initiated at the same time as TPE in a proportion of patients underlines deficiencies in the implementation of guidelines in the real-world setting. Nonetheless, corticosteroids were the most commonly used immunosuppressant in our patients (63.7%), while rituximab was used in 18.7% of patients despite its demonstrated benefits in iTTP over the entire disease course and to prevent relapses, especially if comorbid autoimmune disorders exist (1,11,12,38). Similarly, in the Milan registry, almost all acute events were treated by TPE and steroids, and 15% by rituximab(18). Also, in the Australian registry, corticosteroids were the most commonly used immunosuppressants (71%), while rituximab use was documented in 39% of patients (17). Although the ISTH proposes a conditional recommendation for the addition of rituximab to corticosteroids and TPE at both first and subsequent episodes, there are various barriers to rituximab use. Access to rituximab for the treatment of iTTP requires regulatory authorization in Türkiye. Additionally, a minimum of 2 weeks is required for rituximab to start immunosuppression. And available evidence demonstrates a nonsignificant trend toward a reduced mortality rate with rituximab added to TPE and steroids. The use of aspirin and thromboprophylaxis was also low (20.9%) in our patients, as also reported by other registries that only 27% and 37% of patients were prescribed aspirin and thromboprophylaxis for TTP, respectively (46,47). It should be kept in mind that due to the increased risk of bleeding, antiplatelet agents are not recommended for the prevention and treatment of thrombotic events when the platelet count is less than $50x10^9$/L (38).

The treatment response (clinical response: 79.9%, clinical remission: 68.2%, partial 17.7%, complete 14.6%) and the follow-up data on exacerbation/relapse frequency of 16.3% and disease-related mortality (3.0%) in our patients support that about 80% of iTTP patients respond to initial treatment, while the post-treatment mortality occurred in 8-15%, and 30-50% of patients experienced one or more exacerbations/relapses in other cohorts. These findings justify the need for long-term follow-up of patients with TTP, particularly in terms of medical consultation and ADAMTS13 activity monitoring (13,48,49).

The laboratory findings during the first exacerbation/relapse in our registry support the likelihood of hematologic laboratory parameters being less severe in relapsing episodes compared with the first episodes. Ohio State

University registry and the Milan TTP registry also revealed that clinical characteristics and hematologic laboratory parameters were less severe in relapsing episodes compared with first episodes (2,18,50,51). The Ohio State University registry pointed to a requirement for more TPE sessions to achieve remission in patients with the first episode than those with relapses. Nonetheless, the authors also reported no significant impact of these findings on outcomes, with similar rates of clinical response, exacerbation, refractory disease, and mortality between the initial presentation and relapses (50).

The main strength of this registry study is its population-based design, providing real-world data on iTTP clinical practice at 19 centers across Türkiye, which increases the generalizability of our results with a more accurate reflection of real-world outcomes. However, this study has certain inherent limitations associated with registry analyses, such as potentially incomplete data fields, accuracy of data input at sites, and recall bias. In addition, lack of data on long-term outcomes other than TTP relapse (cognitive impairment, depression, and poor quality of life) seems to be another important limitation, given that iTTP survivors are at risk for a plethora of other adverse outcomes (51-55). Therefore, long-term outcomes and health-related quality of life should be an integral part of further TTP research.

In conclusion, this registry study demonstrated that iTTP patients are mainly younger with a slight female preponderance, with a higher prevalence of constitutional/systemic and neurological manifestations, and with precipitating factors mainly infections, medications, and pregnancy/postpartum. Early onset therapy with TPE and steroids could be initiated in two-thirds of the population with a clinical response rate of ~80%. In this interim analysis, the potential areas that deviate from current guidelines and thus are a target for improved patterns of practice appeared to be the still delayed commencement of TPE exchange and steroids in one-third of patients, and the low rates of rituximab, aspirin, and thromboprophylaxis treatments. Accordingly, further detailed analyses of the Turkish iTTP registry in a prospective setting will represent a powerful and necessary tool to systematically collect epidemiologic, clinical, and laboratory data, which may ultimately improve our understanding and management of iTTP.

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Conflict of interest
The authors declare that they have no conflict of interest

References
1. Stanley M, Killeen RB, Michalski JM. Thrombotic Thrombocytopenic Purpura. 2023 Apr 7. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: 28613472.
2. Mingot Castellano ME, Pascual Izquierdo C, González A, Viejo Llorente A, Valcarcel Ferreiras D, et al.; Grupo Español de Aféresis (GEA). Recommendations for the diagnosis and treatment of patients with thrombotic thrombocytopenic purpura. Med Clin (Barc). 2022 Jun 24;158(12):630.e1-630.e14.
3. Coppo P, Cuker A, George JN. Thrombotic thrombocytopenic purpura: Toward targeted therapy and precision medicine. Res Pract Thromb Haemost. 2019 Jan;3(1):26-37.
4. Sadler JE. Von Willebrand factor, ADAMTS13, and thrombotic thrombocytopenic purpura. Blood 2008; 112: 11-8.
5. Joly BS, Coppo P, Veyradier A. An update on pathogenesis and diagnosis of thrombotic thrombocytopenic purpura. Expert Rev Hematol. 2019;12(6):383-395.
6. Coppo P, Schwarzinger M, Buffet M, et al. Predictive features of severe acquired ADAMTS13 deficiency in idiopathic thrombotic microangiopathies: the French TMA Reference Center experience. PLoS One 2010; 5(4): e10208.
7. Adeyemi A, Razakariasa F, Chiorean A, de Passos Sousa R. Epidemiology, treatment patterns, clinical outcomes, and disease burden among patients with immune-mediated thrombotic thrombocytopenic purpura in the United States. Res Pract Thromb Haemost. 2022 Sep 16;6(6):e12802.
8. Mariotte E, Azoulay E, Galicier L, et al. Epidemiology and pathophysiology of adulthood-onset thrombotic microangiopathy with severe ADAMTS13 deficiency (thrombotic thrombocytopenic purpura): a cross-sectional analysis of the French national registry for thrombotic microangiopathy. Lancet Haematol. 2016;3(5):e237-e245.
9. Kremer Hovinga JA, Coppo P, Lammle B, Moake JL, Miyata T, Vanhoorelbeke K. Thrombotic thrombocytopenic purpura. Nat Rev Dis Primers. 2017;3:17020.
10. Goel R, King KE, Takemoto CM, Ness PM, Tobian AA. Prognostic risk-stratified score for predicting mortality in hospitalized patients with thrombotic thrombocytopenic purpura: nationally representative data from 2007 to 2012. Transfusion. 2016;56(6):1451-1458.

11. Scully M, Hunt BJ, Benjamin S, et al. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br J Haematol 2012; 158: 323-35.
12. Sarode R, Bandarenko N, Brecher ME, Kiss JE, Marques MB, Szczepiorkowski ZM, Winters JL. Thrombotic thrombocytopenic purpura: 2012 American Society for Apheresis (ASFA) consensus conference on classification, diagnosis, management, and future research. J Clin Apher. 2014 Jun;29(3):148-67.
13. Joly BS, Coppo P, Veyradier A. Thrombotic thrombocytopenic purpura. Blood. 2017 May 25;129(21):2836-2846.
14. Kremer Hovinga JA, Vesely SK, Terrell DR, Lammle B, George JN. Survival and relapse in patients with thrombotic thrombocytopenic purpura. Blood. 2010;115(8):1500-1511
15. Scully M, Cataland SR, Peyvandi F, Coppo P, Knöbl P, Kremer Hovinga JA, et al. HERCULES Investigators. Caplacizumab Treatment for Acquired Thrombotic Thrombocytopenic Purpura. N Engl J Med. 2019 Jan 24;380(4):335-346.
16. Thejeel B, Garg AX, Clark WF, Liu AR, Iansavichus AV, Hildebrand AM. Longterm outcomes of thrombotic microangiopathy treated with plasma exchange: a systematic review. Am J Hematol 2016; 91: 623-30.
17. Blombery P, Kivivali L, Pepperell D, McQuilten Z, Engelbrecht S, Polizzotto MN, et al. TTP registry steering committee. Diagnosis and management of thrombotic thrombocytopenic purpura (TTP) in Australia: findings from the first 5 years of the Australian TTP/thrombotic microangiopathy registry. Intern Med J. 2016 Jan;46(1):71-9.
18. Mancini I, Pontiggia S, Palla R, Artoni A, Valsecchi C, Ferrari B, et al.; Italian Group of TTP Investigators. Clinical and Laboratory Features of Patients with Acquired Thrombotic Thrombocytopenic Purpura: Fourteen Years of the Milan TTP Registry. Thromb Haemost. 2019 May;119(5):695-704.
19. Page EE, Kremer Hovinga JA, Terrell DR, Vesely SK, George JN. Thrombotic thrombocytopenic purpura: diagnostic criteria, clinical features, and long-term outcomes from 1995 through 2015. Blood Adv. 2017 Apr 11;1(10):590-600.
20. Tekgunduz E, Yılmaz M, Erkurt MA, Kiki I, Kaya AH, Kaynar L, et al. A multicenter experience of thrombotic microangiopathies in Türkiye: the Turkish Hematology Research and Education Group (ThREG)-TMA01 study. Transfus Apher Sci 2018;57(1):27–30.
21. Akpinar S, Tekgunduz E, Esen R, Yilmaz M, Karakus V, Vural F, et al. Prospective registry of adult patients receiving TPE with a presumptive diagnosis of thrombotic microangiopathy (TMA): The Turkish hematology research and education group (ThREG)-TMA02 study. Transfus Apher Sci. 2022 Feb;61(1):103365.
22. Cuker A, Cataland SR, Coppo P, de la Rubia J, Friedman KD, George JN, et al. Redefining outcomes in immune TTP: an international working group consensus report. Blood. 2021 Apr 8;137(14):1855-1861.
23. Sadler JE. What's new in the diagnosis and pathophysiology of thrombotic thrombocytopenic purpura? Hematology Am Soc Hematol Educ Program. 2015;2015:631-636.
24. Staley EM, Cao W, Pham HP, et al. Clinical factors and biomarkers predict outcome in patients with immune-mediated thrombotic thrombocytopenic purpura. Haematologica. 2019;104(1):166-175.
25. Griffin D, Al-Nouri ZL, Muthurajah D, Ross JR, Ballard RB, Terrell DR, et al. First symptoms in patients with thrombotic thrombocytopenic purpura: what are they and when do they occur? Transfusion. 2013 Jan;53(1):235-7.
26. Ruggenenti P, Remuzzi G. Pathophysiology and management of thrombotic microangiopathies. J Nephrol. 1998 Nov-Dec;11(6):300-10.
27. Scully M, Yarranton H, Liesner R, Cavenagh J, Hunt B, Benjamin S, et al. Regional UK TTP registry: correlation with laboratory ADAMTS 13 analysis and clinical features. Br J Haematol. 2008 Sep;142(5):819-26.
28. Jang MJ, Chong SY, Kim I-H, et al. Clinical features of severe acquired ADAMTS13 deficiency in thrombotic thrombocytopenic purpura: the Korean TTP registry experience. Int J Hematol. 2011;93(2):163-169.
29. Contreras E, De La Rubia J, Del Río-Garma J, Díaz-Ricart M, García-Gala JM, LozanoM. Diagnostic and therapeutic guidelines of thrombotic microangiopathies of the Spanish Apheresis Group. Med Clin (Barc). 2015;144:331.
30. Zafrani L, Mariotte E, Darmon M, et al. Acute renal failure is prevalent in patients with thrombotic thrombocytopenic purpura associated with low plasma ADAMTS13 activity. J Thromb Haemost. 2015;13(3):380-389.
31. Benhamou Y, Boelle PY, Baudin B, Ederhy S, Gras J, Galicier L, et al., Reference Center for Thrombotic Microangiopathies. Cardiac troponin-I on diagnosis predicts early death and refractoriness in acquired thrombotic thrombocytopenic purpura. Experience of the French Thrombotic Microangiopathies Reference Center. J Thromb Haemost. 2015 Feb;13(2):293-302.
32. Lotta LA, Mariani M, Consonni D, et al. Different clinical severity of first episodes and recurrences of thrombotic thrombocytopenic purpura. Br J Haematol. 2010;151(5):488-494.
33. Booth KK, Terrell DR, Vesely SK, George JN. Systemic infections mimicking thrombotic thrombocytopenic purpura. Am J Hematol. 2011 Sep;86(9):743-51.

34. Khodor S, Castro M, McNamara C, Chaulagain CP. Clopidogrel-induced refractory thrombotic thrombocytopenic purpura successfully treated with rituximab. Hematol Oncol Stem Cell Ther. 2016 Jun;9(2):76-9.
35. Béranger N, Coppo P, Tsatsaris V, Boisseau P, Provôt F, Delmas Y, et al. Management and follow-up of pregnancy-onset thrombotic thrombocytopenic purpura: the French experience. Blood Adv. 2024 Jan 9;8(1):183-193.
36. Fakhouri F, Scully M, Provo F, et al. Management of thrombotic microangiopathy in pregnancy and postpartum: Report from an International Working Group. Blood. 2020;136(19):2103-2117.
37. Oliver M, Patriquin CJ, Pavenski K. Predictors of relapse and prophylactic management of immune thrombotic thrombocytopenic purpura. Transfus Apher Sci. 2023 Aug;62(4):103749.
38. Zheng XL, Al-Housni Z, Cataland SR, Coppo P, Geldziler B, Germini F, et al. International Society on Thrombosis and Haemostasis. 2025 focused update of the 2020 ISTH guidelines for management of thrombotic thrombocytopenic purpura. J Thromb Haemost. 2025 Jun 17:S1538-7836(25)00360-5.
39. Morton JM, George JN. Microangiopathic hemolytic anemia and thrombocytopenia in patients with cancer. J Oncol Pract. 2016;12(6):523-530.
40. Sun L, Mack J, Li A, Ryu J, Upadhyay VA, Uhl L, et al. Predictors of relapse and efficacy of rituximab in immune thrombotic thrombocytopenic purpura. Blood Adv 2019;3:1512–8.
41. Yıldırım M, Sayın S, Güneş AK, Reis Aras M, Safak Yılmaz E, Albayrak M, et al. Effect of Blood Groups on Clinical Presentations and Treatment Outcomes in Immune Thrombotic Thrombocytopenic Purpura Patients with Severe ADAMTS13 Deficiency: A Multi-Center Experience. Transfus Med Hemother. 2022 Jun 10;50(1):18-25.
42. Agosti P, Mancini I, Gianniello F, Bucciarelli P, Artoni A, Ferrari B, et al.; Italian Group of TTP Investigators. Prevalence of the age-related diseases in older patients with acquired thrombotic thrombocytopenic purpura. Eur J Intern Med. 2020 May;75:79-83.
43. Prevel R, Roubaud-Baudron C, Gourlain S, Jamme M, Peres K, Benhamou Y, et al. Immune thrombotic thrombocytopenic purpura in older patients: prognosis and long-term survival. Blood. 2019 Dec 12;134(24):2209-2217.
44. Jamme M, Rondeau E. The PLASMIC score for thrombotic thrombocytopenic purpura. Lancet Haematol. 2017 Apr;4(4):e148-e149.
45. Paydary K, Banwell E, Tong J, Chen Y, Cuker A. Diagnostic accuracy of the PLASMIC score in patients with suspected thrombotic thrombocytopenic purpura: A systematic review and meta-analysis. Transfusion. 2020 Sep;60(9):2047-2057.
46. Sawler D, Parker A, Britto J, Goodyear MD, Sun HL. Time from suspected thrombotic thrombocytopenic purpura to initiation of plasma exchange and impact on survival: A 10-year provincial retrospective cohort study. Thromb Res. 2020 Sep;193:53-59.
47. Patriquin CJ, Clark WF, Pavenski K, Arnold DM, Rock G, Foley SR; Canadian Apheresis Group. How we treat thrombotic thrombocytopenic purpura: Results of a Canadian TTP practice survey. J Clin Apher. 2017 Aug;32(4):246-256.
48. Ferrari S, Scheiflinger F, Rieger M, Mudde G, Wolf M, Coppo P, et al.; French Clinical and Biological Network on Adult Thrombotic Microangiopathies. Prognostic value of anti-ADAMTS 13 antibody features (Ig isotype, titer, and inhibitory effect) in a cohort of 35 adult French patients undergoing a first episode of thrombotic microangiopathy with undetectable ADAMTS 13 activity. Blood. 2007 Apr 1;109(7):2815-22.
49. Hie M, Gay J, Galicier L, Provôt F, Presne C, Poullin P, et al; French Thrombotic Microangiopathies Reference Centre. Preemptive rituximab infusions after remission efficiently prevent relapses in acquired thrombotic thrombocytopenic purpura. Blood. 2014 Jul 10;124(2):204-10.
50. Masias C, Wu H, McGookey M, Jay L, Cataland S, Yang S. No major differences in outcomes between the initial and relapse episodes in patients with thrombotic thrombocytopenic purpura: The experience from the Ohio State University Registry. Am J Hematol. 2018 Mar;93(3):E73-E75.
51. George JN. TTP: long-term outcomes following recovery. Hematology Am Soc Hematol Educ Program. 2018 Nov 30;2018(1):548-552.
52. Lewis QF, Lanneau MS, Mathias SD, Terrell DR, Vesely SK, George JN. Long-term deficits in health-related quality of life after recovery from thrombotic thrombocytopenic purpura. Transfusion. 2009;49(1):118-124.
53. Bayer G, von Tokarski F, Thoreau B, Bauvois A, Barbet C, Cloarec S, et al; Etiology and Outcomes of Thrombotic Microangiopathies. Clin J Am Soc Nephrol. 2019 Apr 05;14(4):557-566.
54. Sukumar S, Gavriilaki E, Chaturvedi S. Updates on thrombotic thrombocytopenic purpura: Recent developments in pathogenesis, treatment and survivorship Thrombosis Update 5 (2021) 100062.
55. Vesely SK. Life after acquired thrombotic thrombocytopenic purpura: morbidity, mortality, and risks during pregnancy. J Thromb Haemost. 2015 Jun;13 Suppl 1:S216-22.

Table 1. Demographic Characteristics and Potential Triggers

Demographic characteristics	
Gender (female), n(%)	126 (58.6)
Age at diagnosis (year), median(min-max)	41 (16-73)
Age at diagnosis ≥65 years, n(%)	9 (4.2)
Time of diagnosis, n(%)	
2020-2023	89 (41.4)
2010-2019	112 (52.1)
2001-2009	14 (6.5)
Comorbidities/associated conditions, n(%)	
Autoimmune diseases	16 (7.4)
Malignancy	4 (1.9)
Chronic inflammatory disorder	3 (1.4)
Trauma	2 (0.9)
Anti phospholipid syndrome	1 (0.4)
Organ transplantation	1 (0.4)
Stem cell transplantation	1 (0.4)
Family history, n(%)	
Thrombotic thrombocytopenic purpura	2 (1.0)
Autoimmune diseases	2 (1.0)
Blood group (n=208), n(%)	
0	72 (34.6)
A	89 (42.8)
B	36 (17.3)
AB	11 (5.3)
Potential triggers within 3 weeks prior to diagnosis (n=206), n(%)	
Infection	31 (15.0)
New medicine initiation	20 (9.7)
Pregnancy /postpartum	13 (6.3)
Surgery	10 (4.8)
Ticlopidine/clopidogrel usage	4 (1.9)
Cyclosporin usage	3 (1.4)
Quinine usage	2 (0.9)
Trauma	1 (0.4)

Table 2. Presenting Symptoms and Clinical Manifestations

Systemic /constitutional manifestations, n(%)	
Fatigue	148 (68.8)
Fever	39 (18.1)
Upper respiratory tract infection	18 (8.4)
Flu-like syndrome	18 (8.4)
Other	54 (25.1)
Neurologic manifestations, n(%)	
Headache	86 (40.0)
Vertigo	69 (32.1)
Dysarthria	32 (14.9)
Paresthesia	25 (11.6)
Motor loss	23 (10.7)
Personality change	13 (6.0)
Stroke	12 (5.6)
Epilepsy	12 (5.6)
Coma	9 (4.2)
Other	50 (23.3)
Hemorrhagic manifestations, n(%)	
Purpura	62 (28.8)
Ecchymosis	52 (24.2)
Hematuria	33 (15.3)
Melena	15(7.3)
Menometrorrhagia	9 (4.2)
Epistaxis	6 (2.8)
Other	18 (8.4)
Gastrointestinal manifestations, n(%)	
Vomiting	54 (25.1)
Abdominal pain	41 (19.1)
Jaundice	27 (12.6)
Bloody diarrhea	5 (2.4)
Renal manifestations, n (%)	
Acute kidney injury	33 (15.3)
Dialysis requirement	7 (3.3)
Other	11 (5.1)
Cardiovascular manifestations, n(%)	
Hypertension	36 (16.7)
Chest pain	21 (9.8)
Ischemic heart disease	13 (6.0)
Abnormal ECG	8 (3.7)
Other	7 (3.3)

Table 3. Laboratory Findings at the Time of Diagnosis

Laboratory findings		**Median(min-max)**
Hemoglobin (g/dL)		9.2 (3.9-15.7)
Platelet count (10^9/L)		13.0 (9.0-23.0)
Schistocyte count per area on peripheral smear		6.0 (2-25)
Total bilirubin (mg/dL)		2.2 (1.2-3.5)
Serum LDH (IU/L)		825.5 (131-6266)
Creatinine (mg/dL)		0.9 (0.7-1.2)
PLASMIC score (n=180)		6 (1-7)
PLASMIC score category, n(%)	Low risk (score 0-4)	21 (11.7)
	Intermediate risk (score 5)	19 (10.5)
	High risk (score 6-7)	140 (77.8)

Table 4. Treatment and Response Characteristics

Initial treatment characteristics	N (%)
Treatment onset within 48 hours of admission	138(64.1)
On the day of admission	78(36.2)
1 day after the admission	32(14.9)
2 days after admission	28(13.0)
Delayed treatment (> 48 hours of admission)	77(35.8)
Treatments	
Plasma exchange	198 (92.1)
Plasma volume, median (min-max)	3 (1-6.5)
Steroid	137 (63.7)
Erythrocyte transfusion	67 (31.2)
Immunosuppressive	45 (20.9)
Rituximab	34 (15.8)
Antiplatelet/anticoagulant /thrombolytic	45 (20.9)
Thrombocyte transfusion	43 (20.0)
Immunoglobulin	5 (2.3)
Cryo-supernatant plasma	2 (0.9)
Treatment response	
Clinical response (n=204)	163 (79.9)
Clinical remission (n=198)	135 (68.2)
Partial remission (ADAMTS13 activity ≥ 20%) (n=198)	35 (17.7)
Complete remission (normalized ADAMTS13 activity) (n=198)	29 (14.6)