RESEARCH ARTICLE

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

İmmün Trombotik Trombositopenik Purpura (iTTP) Hastalarının Klinik Bulguları, Tedavi Özellikleri ve Klinik Sonuçlarının Gerçek Yaşam Değerlendirmesi: Türk iTTP Kayıt Çalışması Ara Analizi

Sema Karakuş[1], Şule Mine Bakanay[2], Sevgi Kalayoğlu Beşişik[3], Ahmet Emre Eşkazan[4], Orhan Ayyıldız[5], Emel Gürkan[6], Ozan Salim[7], Volkan Karakuş[8], Nil Güler[9], Muzaffer Keklik[10], Osman İlhami Özcebe[11], Fahir Özkalemkaş[12], Vildan Özkocaman[12], Umut Yılmaz[4], Senem Dadin[3], Mehmet Ali Uçar[6], Mehmet Sönmez[13], Abdullah Karakuş[5], Ünal Ataş[7], Lütfullah Zahit Koç[8], Eren Gündüz[14], Sibel Kabukçu Hacıoğlu[9], Başak Ünver Koluman[9], Gülsüm Özet[2], Tekin Güney[15], Kemal Fidan[10], Tülay Karaağaç Akyol[11], Cevat İlteriş Kıkılı[3], Fatih Demirkan[16], İrfan Yavaşoğlu[17], Simten Dağdaş[15], Merve Kestane[13], Havva Üsküdar Teke[14], Selami Koçak Toprak[18], Aylin Karataş[16], Münci Yağcı[19], Düzgün Özatlı[20], Zübeyde Nur Özkurt[19], Osman İlhan[21], Muhlis Cem Ar[4]

[1]*Başkent University Faculty of Medicine, Department of Hematology, Ankara, Türkiye*
[2]*Ankara Yıldırım Beyazıt University Faculty of Medicine, Bilkent City Hospital, Clinic of Hematology, Ankara, Türkiye*
[3]*İstanbul University, İstanbul Faculty of Medicine, Department of Hematology, İstanbul, Türkiye*
[4]*İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Hematology, İstanbul, Türkiye*
[5]*Dicle University Faculty of Medicine, Department of Hematology, Diyarbakır, Türkiye*
[6]*Çukurova University Faculty of Medicine, Department of Hematology, Adana, Türkiye*
[7]*Akdeniz University Faculty of Medicine, Department of Hematology, Antalya, Türkiye*
[8]*University of Health Sciences Türkiye, Antalya Training and Research Hospital, Clinic of Hematology, Antalya, Türkiye*
[9]*Pamukkale University Faculty of Medicine, Department of Hematology, Denizli, Türkiye*
[10]*Erciyes University Faculty of Medicine, Department of Hematology, Kayseri, Türkiye*
[11]*Hacettepe University Faculty of Medicine, Department of Hematology, Ankara, Türkiye*
[12]*Bursa Uludağ University Faculty of Medicine, Department of Hematology, Bursa, Türkiye*
[13]*Karadeniz Technical University Faculty of Medicine, Department of Hematology, Trabzon, Türkiye*
[14]*Eskişehir Osmangazi University Faculty of Medicine, Department of Hematology, Eskişehir, Türkiye*
[15]*University of Health Sciences, Bilkent City Hospital, Clinic of Hematology, Ankara, Türkiye*
[16]*Dokuz Eylül University Faculty of Medicine, Department of Hematology, İzmir, Türkiye*
[17]*Aydın Adnan Menderes University Faculty of Medicine, Department of Hematology, Aydın, Türkiye*
[18]*Ankara University Faculty of Medicine, Department of Hematology, Ankara, Türkiye*
[19]*Gazi University Faculty of Medicine, Department of Hematology, Ankara, Türkiye*
[20]*Ondokuz Mayıs University Faculty of Medicine, Department of Hematology, Samsun, Türkiye*
[21]*Lokman Hekim University Faculty of Medicine, Department of Hematology, Ankara, Türkiye*

Address for Correspondence/Yazışma Adresi: Prof. Sema Karakuş, M.D., Başkent University Faculty of Medicine, Department of Hematology, Ankara, Türkiye
E-mail: sema_karakus@hotmail.com **ORCID:** orcid.org/0000-0003-4766-1861

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Abstract

Objective: This study aimed to investigate the clinical manifestations, treatment patterns, and clinical outcomes of patients with immune thrombotic thrombocytopenic purpura (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 a prospective non-interventional observational multicenter iTTP registry study (ClinicalTrials.gov Identifier: NCT05950750) conducted at 19 tertiary hematology centers. Data on patient demographics, disease characteristics at initial admission, treatment characteristics and responses, exacerbations/relapses, and survival outcome were obtained from electronic case report forms.

Results: Infection (15.0%), new drug initiation (9.7%), and pregnancy/postpartum period (6.3%) within 3 weeks before diagnosis were the most prevalent potential triggers. Patients presented most commonly with systemic/constitutional (fatigue: 68.8%; fever: 18.1%) and neurological (headache: 40.0%; vertigo: 32.1%) symptoms, followed by hemorrhagic, gastrointestinal, renal, and cardiovascular manifestations. Based on PLASMIC risk scoring, 77.8% of patients were initially at high risk for TTP. The initial treatment was begun within the first 48 hours of hospital admission for 64.1% of patients (36.2% on the day of admission). Treatment was mainly based on therapeutic plasma 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 by 68.2% of patients. Regarding a thrombospondin type 1 motif member (ADAMTS13) 13 levels, partial and complete responses were achieved by 17.7% and 14.6%, respectively. During a median of 30 months (range: 0.1-262.4 months) of follow-up, 35 patients experienced exacerbations/relapses. Mortality occurred in 11 (5.5%) patients and was found to be disease-related in 6 cases (3.0%).

Conclusion: This interim analysis of the nationwide Turkish iTTP Registry study provides valuable data on real-world clinical practices in the diagnosis and management of iTTP at different hematology clinics across the country.

Keywords: Immune thrombotic thrombocytopenic purpura, Acquired thrombotic disorders, Autoimmune disorders, Apheresis

Öz

Amaç: Bu çalışma, Türkiye genelinde immün trombotik trombositopenik purpura (iTTP) hastalarının klinik bulgularını, tedavi modellerini ve klinik sonuçlarını Türk iTTP kayıt sisteminin ara analizine dayanarak araştırmayı amaçlamıştır.

Gereç ve Yöntemler: Bu retrospektif, girişimsel olmayan, gözlemsel çok merkezli iTTP kayıt çalışmasının (ClinicalTrials.gov Identifier: NCT05950750) ara analizine 19 üçüncü basamak hematoloji merkezinden 2001-2023 yılları arasında tanı almış toplam 215 iTTP hastası (ortanca tanı yaşı 41, %58,6'sı kadın) dahil edilmiştir. Hastaların demografik özellikleri, ilk başvurudaki tanı özellikleri, aldıkları tedaviler ve tedavi yanıtları, hastalık alevlenme ve nüks oranları ve sağkalım sonuçları her merkez tarafından elektronik olgu rapor formuna kaydedilmiştir.

Bulgular: Tanıdan önceki 3 hafta içerisinde enfeksiyon (%15), yeni ilaç başlanması (%9,7) ve gebelik/postpartum durum (%6,3) en sık gözlenen potansiyel uyarıcı faktörler olarak bulunmuştur. Hastaların en sık sistemik/konstitüsyonel (bitkinlik %68,8; ateş %18,1) ve nörolojik (baş ağrısı %40, vertigo %32,1) semptomlarla geldiği, bunları kanama, gastrointestinal, renal ve kardiyovasküler semptomların takip ettiği gözlenmiştir. Başlangıç PLASMIC risk skorlamasına göre hastaların %77,8'i TTP için yüksek risk kategorisinde idi. Hastaların %64,1'ine (%36,2'sine ilk 24 saat içerisinde) başvuru sonrası ilk 48 saat içerisinde tedavi başlanmıştı. Başlangıç tedavisi plazma değişimi (%92,1) ve steroid (%63,7), yanısıra rituksimab (%15,8) da kullanılmıştı. Hastaların %79,9'unda klinik yanıt, %68,2'sinde ise klinik remisyon sağlanmıştır. ADAMTS13 yanıtı değerlendirildiğinde, sırasıyla %17,7 ve %14,6 hastada kısmi ve tam remisyon elde edilmişti. Ortanca 30 (0,1-262,4) aylık takipte 35 (%16,3) hastada alevlenme/relaps saptanırken toplam 11 (%5,5) hasta kaybedildi ve ölümlerin 6 (%3)'ünün hastalık ilişkili olduğu tespit edildi.

Sonuç: Bu ulusal iTTP kayıt çalışmasının ara analizi Türkiye'deki farklı hematoloji merkezlerinden iTTP tanı ve tedavisine ait çok değerli gerçek-yaşam verisini sağlaması açısından önemlidir.

Anahtar Sözcükler: İmmün trombotik trombositopenik purpura, Edinsel trombotik hastalıklar, Otoimmün hastalıklar, Aferez

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a type of thrombotic microangiopathy (TMA) characterized by microangiopathic hemolytic anemia, thrombocytopenia, and ischemic organ dysfunction. TTP results from either congenital or acquired decrease of von Willebrand factor (vWF)-cleaving protease a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13 (ADAMTS13). Acquired TTP is caused by autoantibodies targeting ADAMTS13 and shows a heterogeneous clinical presentation depending on end-organ ischemic damage [1,2,3,4,5].

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 [6,7,8]. 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 [11,12,13,14].

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 a phase III study showing that caplacizumab

added to TPE in acute immune TTP (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 first-step treatment as an adjunct to TPE and corticosteroids [15].

The TTP registries being created worldwide are expected to enable a better understanding of the pathophysiology of TTP, allowing a significant improvement in both diagnosis and therapeutic management [6,7,8,16,17,18,19]. To date, two studies of the national retrospective Turkish TMA Registry for patients who were referred for TPE with a presumptive diagnosis of TMA and available ADAMTS13 activity/anti-ADAMTS13 antibody levels have been 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 of patients with iTTP in a real-world setting.

Materials and 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 and with available data on their initial episodes at diagnosis, confirmed ADAMTS13 activity of <10%, and autoantibody positivity demonstrated at a central laboratory were included. The study was planned as a 5-year follow-up study encompassing the time period between February 2023 and 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 in line with the ethical principles stated in the Declaration of Helsinki and approved by the Başkent University Ankara Hospital Clinical Research Ethics Committee (date of approval: 22/04/2022, decision no: 22/25) and the Republic of Türkiye Ministry of Health's Turkish Medicines and Medical Devices Agency (date of approval: 21/12/2022, protocol no: E-66175679-514.05.02-960200). Data were obtained from electronic case report forms.

Assessments

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

Definitions

Clinical response was defined as a sustained platelet count of ≥150x10^9/L and lactate dehydrogenase (LDH) <1.5 times the upper limit of normal, 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 occurred first. Partial ADAMTS13 remission was defined as ADAMTS13 activity ranging from ≥20% to below the lower limit of normal (LLN), while complete ADAMTS13 remission was defined as ADAMTS13 activity ≥LLN. Clinical exacerbation, occurring after a clinical response and before clinical remission, was characterized by a decrease in platelet count to <150x10^9/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 <150x10^9/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 performed using IBM SPSS Statistics for Windows 23.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were reported for categorical data. Data were expressed as median and range, interquartile range, or percentage as appropriate.

Results

Demographic Characteristics, Medical Background, and Potential Triggers

The median age of the patients at diagnosis was 41 (range: 16-73) years, and women 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 was present in 1.9% and history of organ/stem cell transplantation was present in less than 3% of patients. Considering potential triggers within the previous 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

The patients presented most commonly with systemic/constitutional (fatigue: 68.8%; fever: 18.1%) and neurological (headache: 40.0%; vertigo: 32.1%) symptoms, followed by 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

The median hemoglobin level at the time of the initial diagnosis was 9.2 (3.9-15.7) g/dL, median 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 scores (median: 6.0) at the time of the initial diagnosis revealed that 77.8% of patients were at high risk for TTP (Table 3).

Table 1. Demographic characteristics and potential triggers.

Demographic characteristics	
Sex, female, n (%)	126 (58.6)
Age at diagnosis, years, median (range)	41 (16-73)
Age at diagnosis of ≥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)
Antiphospholipid 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)
Neurological 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 electrocardiogram	8 (3.7)
Other	7 (3.3)

Treatment Characteristics

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

Table 3. Laboratory findings at the time of diagnosis.

Laboratory findings		Median (range)
Hemoglobin (g/dL)		9.2 (3.9-15.7)
Platelet count (x10^9/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 of 0-4)	21 (11.7)
	Intermediate risk (score of 5)	19 (10.5)
	High risk (score of 6-7)	140 (77.8)

LDH: Lactate dehydrogenase.

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 admission	32 (14.9)
2 days after admission	28 (13.0)
Delayed treatment (>48 hours after admission)	77 (35.8)
Treatments	
Plasma exchange	198 (92.1)
Plasma volume, median (range)	3 (1-6.5)
Steroids	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 of ≥20%) (n=198)	35 (17.7)
Complete remission (normalized ADAMTS13 activity) (n=198)	29 (14.6)

ADAMTS13: A thrombospondin type 1 motif member 13.

Clinical Outcome

Clinical response was achieved by 79.9% of patients, including clinical remission in 68.2% of cases, with partial ADAMTS13 response in 17.7% of patients and complete ADAMTS13 response in 14.6% (Table 4). During a median of 30 (0.1-262.4) months of 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 23x10^9/L (14.8x10^9/L-37.5x10^9/L), hemoglobin of 10.3 (9.3-11.6) g/dL, white blood cell count of 9.1x10^9/L (7.1x10^9/L-12.2x10^9/L), schistocyte count of 5 (3.8-7.3) per area on PS, LDH of 579 (358-1143) IU/L, and total bilirubin of 1.6 (0.8-1.0) mg/dL. Mortality occurred in 11 (5.5%) cases and was found to be disease-related in 6 (3.0%) cases. Two and 4 patients had relapse and refractory disease, respectively, at the time of death. In these cases, the main reasons for death were sepsis, multiorgan failure, and respiratory failure. The known reasons for death among the patients in 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 real-world clinical practices in the diagnosis and management of iTTP at different hematology clinics across Türkiye. The findings are consistent with the results of previous registries for iTTP patients in terms of a female preponderance (roughly twofold) and a clinical course characterized by a relapsing tendency and life-threatening potential despite appropriate treatment. On the other hand, the data revealed less mortality (5.5% compared to 8%-15%) and a lower rate of exacerbation/relapse (16.3% compared to 30%-50%) [17,18,19,23,24].

Patients in the registry appeared to present more commonly with constitutional and neurological 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 of acquired TTP patients to include gastrointestinal symptoms (69%), weakness (63%), bleeding or purpura (54%), major (41%) and minor (26%) neurological findings, and fever (10%) [19]. Other studies also indicated that the main presenting symptoms in these patients involve fatigue, dyspnea, petechiae, or bleeding secondary to thrombocytopenia, while abdominal pain is considered among the most prevalent presenting symptoms, particularly in patients with idiopathic acquired TTP [1,25,26].

Many cohort studies have demonstrated that the classical pentad of symptoms (fever, hemolytic anemia, thrombocytopenia, AKI, and severe neurological findings) traditionally used to define TTP actually coincide in less than 10% of acute TTP cases [16,17,18,27,28,29]. 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 conclusion that neurological symptoms dominate the clinical picture of iTTP, with at least 60% of patients having wide-spectrum neurological symptoms at the time of presentation [1,5,26,27,28]. In our cohort, renal involvement included AKI in 15.9% of cases. In contrast to 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 a diagnosis of iTTP [1,5,30]. The cardiac manifestations in our patients included hypertension, chest pain, ischemic heart disease, and electrocardiogram abnormality, supporting the likelihood of cardiac involvement in patients with iTTP. Elevated serum troponin is considered a poor prognostic marker and an independent predictor of increased mortality risk (threefold 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 the 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 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 have included infections, autoimmune diseases, pregnancy/postpartum, surgery, trauma, a wide range of drugs, pancreatitis, cancers, and organ transplantation [1,17,33,34,35,36,37,38]. Potential triggers for TTP occurrence were identified in at least 40% of our patients, such as infection, pregnancy/postpartum period, starting a new medicine, surgery, and clopidogrel, cyclosporin, or quinine, while a comorbid autoimmune disease was evident in 7.4% of cases. In addition to the leading role of infections within 3 weeks before the diagnosis (15%) as a precipitating factor, nearly 17% of our patients also presented with upper respiratory tract infection or a flu-like syndrome at the time of the initial diagnosis. Similarly, data from the Milan TTP Registry revealed that infections (27%) were most prevalent among potential triggers of acute episodes occurring within 3 months before disease onset [18]. A history of malignancy (1 hairy cell leukemia, 1 multiple myeloma, 2 basal cell carcinoma) or organ (1 renal transplantation) or stem cell transplantation (1 autologous stem cell transplantation for multiple myeloma) was present in less than 3% of our patients. These patients were not regarded as having cancer-associated or 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, having no relation to an immune-mediated ADAMTS13 deficiency, and entailing a worse prognosis [8,13,39].

Considering the potential non-modifiable risk factors for iTTP (sex, age, and blood group), approximately 60% of our patients were female and less than 5% of our patients were in the age group of ≥65 years, 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 are considered among the potential non-modifiable risk factors for iTTP [37]. An approximately twofold 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]. Furthermore, the clinical outcomes and disease burden in iTTP patients are suggested to worsen with increasing age, and 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 observed in the present registry seems consistent with proposed diagnostic requirements such as microangiopathic hemolytic anemia and thrombocytopenia. Furthermore, 77.8% of the patients had PLASMIC risk scores of 6 or 7, indicating that they were at high risk for TTP [44,45]. The prevalent use of the PLASMIC score across clinics that participated in the registry seems notable in terms of its potential value in making a presumptive diagnosis of TTP in appropriate clinical settings [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. Thus, empirical treatment with TPE is often required before confirmation of diagnosis [1,2,3,17,46]. However, TTP care in real-world settings 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 for 64.1% of our patients (on the day of admission for 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 therapy was commenced on the day of the stated diagnosis for 51% of patients and on the following day for 34%, while it was

commenced 2 days and 3 days after the diagnosis for 10% and 4% of patients, respectively [17]. In a retrospective cohort study of 163 patients with suspected TTP in a real-world setting, a significant delay (initiation of TPE at >8 hours after admission) was noted in nearly 60% of patients [46]. However, 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 a delay of >24 hours [46].

The commencement of TPE (92.1%) and steroids (63.7%) within the first 48 hours after admission for most patients in our registry seems to be in accordance with the findings of 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 significant proportion of patients underlines deficiencies in the implementation of guidelines in real-world settings. Nonetheless, corticosteroids were the most commonly used immunosuppressant in our patients (63.7%), while rituximab was used by only 18.7% of patients despite its demonstrated benefits in iTTP over the entire disease course and in preventing relapses, especially if comorbid autoimmune disorders exist [1,11,12,38]. Similarly, in the Milan Registry, nearly all acute events were treated by TPE and steroids, and 15% by rituximab [8]. In an Australian registry, corticosteroids were the most commonly used immunosuppressants (71%), while rituximab use was documented in 39% of patients [17]. Although the ISTH has proposed a conditional recommendation for the addition of rituximab to corticosteroids and TPE for 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 non-significant 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, in line with the findings of other registries that demonstrated 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 rate (clinical response: 79.9%; clinical remission: 68.2%; partial: 17.7%; complete: 14.6%) and follow-up data revealing an exacerbation/relapse frequency of 16.3% and disease-related mortality of 3.0% in our patients support previous observations that about 80% of iTTP patients respond to initial treatment, while post-treatment mortality occurs in 8%-15% and 30%-50% of patients experience one or more exacerbations/relapses [13,48,49]. These findings indicate the need for long-term follow-up of patients with TTP, particularly in terms of medical consultation and ADAMTS13 activity monitoring.

The laboratory findings obtained during the first exacerbation/relapse in our registry support the likelihood of hematological laboratory parameters being less severe in relapse episodes compared to first episodes. The Ohio State University Registry and the Milan TTP Registry also revealed that clinical characteristics and hematological laboratory parameters were less severe in relapse episodes compared to first episodes [2,18,50,51]. The Ohio State University Registry emphasized a requirement for more TPE sessions to achieve remission in patients experiencing a first episode compared to those with relapses. Nonetheless, no significant impact of these findings on outcomes was observed, with similar rates of clinical response, exacerbation, refractory disease, and mortality between the initial presentation and relapses [50].

Study Limitations

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, the accuracy of data input at sites, and recall bias. In addition, lack of data on long-term outcomes other than TTP relapse (e.g., cognitive impairment, depression, or poor quality of life) is another important limitation, given that iTTP survivors are at risk of a plethora of other adverse outcomes [51,52,53,54,55]. Therefore, long-term outcomes and health-related quality of life should be integral parts of further TTP research.

Conclusion

This registry study has 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 including mainly infections, medications, and pregnancy/postpartum. Early onset of therapy with TPE and steroids could be initiated in two-thirds of the population with a clinical response rate of approximately 80%. In this interim analysis, the potential areas that deviate from current guidelines and are thus a target for improved patterns of practice appeared to be the still delayed commencement of TPE 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 would constitute powerful

and necessary tools for systematically collecting epidemiological, clinical, and laboratory data, which may ultimately improve our understanding and management of iTTP.

Ethics

Ethics Committee Approval: This study was conducted in line with the ethical principles stated in the Declaration of Helsinki and approved by the Başkent University Ankara Hospital Clinical Research Ethics Committee (date of approval: 22/04/2022, decision no: 22/25) and the Republic of Türkiye Ministry of Health's Turkish Medicines and Medical Devices Agency (date of approval: 21/12/2022, protocol no: E-66175679-514.05.02-960200).

Informed Consent: The requirement for informed consent was waived due to the retrospective nature of the study.

Footnotes

Authorship Contributions

Concept: S.K., Ş.M.B., M.C.A.; Design: S.K., Ş.M.B., S.K.B., A.E.E., E.G., M.C.A.; Data Collection or Processing: S.K., Ş.M.B., S.K.B., A.E.E., O.A., E.G., O.S., V.K., N.G., M.K., O.İ.Ö., F.Ö., V.Ö., U.Y., S.D., M.A.U., M.S., A.K., Ü.A., L.Z.K., E.G., S.K.H., B.Ü.K., G.Ö., T.G., K.F., T.K.S, C.I.K., F.D., İ.Y., S.D., M.K., H.Ü.T., S.K.T., A.K., M.Y., D.Ö., Z.N.Ö., O.İ., M.C.A.; Analysis or Interpretation: S.K., Ş.M.B., S.K.B., A.E.E., M.C.A.; Literature Search: Ş.M.B., V.K., Ü.A., E.G., M.K.; Writing: S.K., Ş.M.B.

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References

1. Stanley M, Killeen RB, Michalski JM. Thrombotic thrombocytopenic purpura. In: StatPearls [Internet]. Treasure Island, StatPearls Publishing, 2023. Available online at https://www.ncbi.nlm.nih.gov/books/NBK430721/.
2. Mingot Castellano ME, Pascual Izquierdo C, González A, Viejo Llorente A, Valcarcel Ferreiras D, Sebastián E, García Candel F, Sarmiento Palao H, Gómez Seguí I, de la Rubia J, Cid J, Martínez Nieto J, Hernández Mateo L, Goterris Viciedo R, Fidalgo T, Salinas R, Del Rio-Garma J; Grupo Español de Aféresis (GEA). Recommendations for the diagnosis and treatment of patients with thrombotic thrombocytopenic purpura. Med Clin (Barc). 2022;158:630.e1-630.e14.
3. Coppo P, Cuker A, George JN. Thrombotic thrombocytopenic purpura: toward targeted therapy and precision medicine. Res Pract Thromb Haemost. 2019;3:26-37.
4. Sadler JE. Von Willebrand factor, ADAMTS13, and thrombotic thrombocytopenic purpura. Blood. 2008;112:11-18.
5. Joly BS, Coppo P, Veyradier A. An update on pathogenesis and diagnosis of thrombotic thrombocytopenic purpura. Expert Rev Hematol. 2019;12:383-395.
6. Coppo P, Schwarzinger M, Buffet M, Wynckel A, Clabault K, Presne C, Poullin P, Malot S, Vanhille P, Azoulay E, Galicier L, Lemiale V, Mira JP, Ridel C, Rondeau E, Pourrat J, Girault S, Bordessoule D, Saheb S, Ramakers M, Hamidou M, Vernant JP, Guidet B, Wolf M, Veyradier A; French Reference Center for Thrombotic Microangiopathies. Predictive features of severe acquired ADAMTS13 deficiency in idiopathic thrombotic microangiopathies: the French TMA Reference Center experience. PLoS One. 2010;5: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;6:e12802.
8. Mariotte E, Azoulay E, Galicier L, Rondeau E, Zouiti F, Boisseau P, Poullin P, de Maistre E, Provôt F, Delmas Y, Perez P, Benhamou Y, Stepanian A, Coppo P, Veyradier A; French Reference Center for Thrombotic Microangiopathies. 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:e237-e245.
9. Kremer Hovinga JA, Coppo P, Lämmle 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;56:1451-1458.
11. Scully M, Hunt BJ, Benjamin S, Liesner R, Rose P, Peyvandi F, Cheung B, Machin SJ; British Committee for Standards in Haematology. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br J Haematol. 2012;158:323-335.
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;29:148-167.
13. Joly BS, Coppo P, Veyradier A. Thrombotic thrombocytopenic purpura. Blood. 2017;129:2836-2846.
14. Kremer Hovinga JA, Vesely SK, Terrell DR, Lämmle B, George JN. Survival and relapse in patients with thrombotic thrombocytopenic purpura. Blood. 2010;115:1500-1511.
15. Scully M, Cataland SR, Peyvandi F, Coppo P, Knöbl P, Kremer Hovinga JA, Metjian A, de la Rubia J, Pavenski K, Callewaert F, Biswas D, De Winter H, Zeldin RK; HERCULES Investigators. Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura. N Engl J Med. 2019;380:335-346.
16. Thejeel B, Garg AX, Clark WF, Liu AR, Iansavichus AV, Hildebrand AM. Long-term outcomes of thrombotic microangiopathy treated with plasma exchange: a systematic review. Am J Hematol 2016;91:623-630.
17. Blombery P, Kivivali L, Pepperell D, McQuilten Z, Engelbrecht S, Polizzotto MN, Phillips LE, Wood E, Cohney S; 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;46:71-79.
18. Mancini I, Pontiggia S, Palla R, Artoni A, Valsecchi C, Ferrari B, Mikovic D, Peyvandi F; 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;119:695-704.
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;1:590-600.
20. Tekgündüz E, Yılmaz M, Erkurt MA, Kiki I, Kaya AH, Kaynar L, Alacacioglu I, Cetin G, Ozarslan I, Kuku I, Sincan G, Salim O, Namdaroglu S, Karakus A, Karakus V, Altuntas F, Sari I, Ozet G, Aydogdu I, Okan V, Kaya E, Yildirim R, Yildizhan E, Ozgur G, Ozcebe OI, Payzin B, Akpinar S, Demirkan F. A multicenter experience of thrombotic microangiopathies in Turkey: the Turkish Hematology Research and Education Group (ThREG)-TMA01 study. Transfus Apher Sci. 2018;57:27-30.

21. Akpinar S, Tekgunduz E, Esen R, Yilmaz M, Karakus V, Vural F, Gediz F, Aydogdu I, Kaynar L, Goker H, Kelkitli E, Ayyildiz O, Demirkan F. 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;61:103365.
22. Cuker A, Cataland SR, Coppo P, de la Rubia J, Friedman KD, George JN, Knoebl PN, Kremer Hovinga JA, Lämmle B, Matsumoto M, Pavenski K, Peyvandi F, Sakai K, Sarode R, Thomas MR, Tomiyama Y, Veyradier A, Westwood JP, Scully M. Redefining outcomes in immune TTP: an international working group consensus report. Blood. 2021;137:1855-1861.
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, Kim CH, Kocher NK, Zheng L, Gangaraju R, Lorenz RG, Williams LA, Marques MB, Zheng XL. Clinical factors and biomarkers predict outcome in patients with immune-mediated thrombotic thrombocytopenic purpura. Haematologica. 2019;104:166-175.
25. Griffin D, Al-Nouri ZL, Muthurajah D, Ross JR, Ballard RB, Terrell DR, Vesely SK, George JN, Marques MB. First symptoms in patients with thrombotic thrombocytopenic purpura: what are they and when do they occur? Transfusion. 2013;53:235-237.
26. Ruggenenti P, Remuzzi G. Pathophysiology and management of thrombotic microangiopathies. J Nephrol. 1998;11:300-310.
27. Scully M, Yarranton H, Liesner R, Cavenagh J, Hunt B, Benjamin S, Bevan D, Mackie I, Machin S. Regional UK TTP registry: correlation with laboratory ADAMTS 13 analysis and clinical features. Br J Haematol. 2008;142:819-826.
28. Jang MJ, Chong SY, Kim IH, Kim JH, Jung CW, Kim JY, Park JC, Lee SM, Kim YK, Lee JE, Jang SS, Kim JS, Jo DY, Zang DY, Lee YY, Yhim HY, Oh D. Clinical features of severe acquired ADAMTS13 deficiency in thrombotic thrombocytopenic purpura: the Korean TTP registry experience. Int J Hematol. 2011;93:163-169.
29. Contreras E, de la Rubia J, Del Río-Garma J, Díaz-Ricart M, García-Gala JM, Lozano M; Grupo Español de Aféresis. Diagnostic and therapeutic guidelines of thrombotic microangiopathies of the Spanish Apheresis Group. Med Clin (Barc). 2015;144:331.e1-331.e13.
30. Zafrani L, Mariotte E, Darmon M, Canet E, Merceron S, Boutboul D, Veyradier A, Galicier L, Azoulay E. Acute renal failure is prevalent in patients with thrombotic thrombocytopenic purpura associated with low plasma ADAMTS13 activity. J Thromb Haemost. 2015;13:380-389.
31. Benhamou Y, Boelle PY, Baudin B, Ederhy S, Gras J, Galicier L, Azoulay E, Provôt F, Maury E, Pène F, Mira JP, Wynckel A, Presne C, Poullin P, Halimi JM, Delmas Y, Kanouni T, Seguin A, Mousson C, Servais A, Bordessoule D, Perez P, Hamidou M, Cohen A, Veyradier A, Coppo P; 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;13:293-302.
32. Lotta LA, Mariani M, Consonni D, Mancini I, Palla R, Maino A, Vucelic D, Pizzuti M, Mannucci PM, Peyvandi F. Different clinical severity of first episodes and recurrences of thrombotic thrombocytopenic purpura. Br J Haematol. 2010;151:488-494.
33. Booth KK, Terrell DR, Vesely SK, George JN. Systemic infections mimicking thrombotic thrombocytopenic purpura. Am J Hematol. 2011;86:743-751.
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;9:76-79.
35. Béranger N, Coppo P, Tsatsaris V, Boisseau P, Provôt F, Delmas Y, Poullin P, Vanhoorelbeke K, Veyradier A, Joly BS. Management and follow-up of pregnancy-onset thrombotic thrombocytopenic purpura: the French experience. Blood Adv. 2024;8:183-193.
36. Fakhouri F, Scully M, Provôt F, Blasco M, Coppo P, Noris M, Paizis K, Kavanagh D, Pène F, Quezada S, Hertig A, Kissling S, O'Brien P, Delmas Y, Alberio L, Winer N, Veyradier A, Cataland S, Frémeaux-Bacchi V, Loirat C, Remuzzi G, Tsatsaris V. Management of thrombotic microangiopathy in pregnancy and postpartum: report from an international working group. Blood. 2020;136:2103-2117.
37. Oliver M, Patriquin CJ, Pavenski K. Predictors of relapse and prophylactic management of immune thrombotic thrombocytopenic purpura. Transfus Apher Sci. 2023;62:103749.
38. Zheng XL, Al-Housni Z, Cataland SR, Coppo P, Geldziler B, Germini F, Iorio A, Keepanasseri A, Masias C, Matsumoto M, McCrae KR, McIntyre J, Mustafa RA, Peyvandi F, Russell L, Tarawneh R, Vesely SK; International Society on Thrombosis and Haemostasis. 2025 focused update of the 2020 ISTH guidelines for management of thrombotic thrombocytopenic purpura. J Thromb Haemost. (in press). doi: 10.1016/j.jtha.2025.06.002.
39. Morton JM, George JN. Microangiopathic hemolytic anemia and thrombocytopenia in patients with cancer. J Oncol Pract. 2016;12:523-530.
40. Sun L, Mack J, Li A, Ryu J, Upadhyay VA, Uhl L, Kaufman RM, Stowell CP, Dzik WS, Makar RS, Bendapudi PK. Predictors of relapse and efficacy of rituximab in immune thrombotic thrombocytopenic purpura. Blood Adv. 2019;3:1512-1518.
41. Yıldırım M, Sayın S, Güneş AK, Reis Aras M, Safak Yılmaz E, Albayrak M, Özet G, Aylı M. 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;50:18-25.
42. Agosti P, Mancini I, Gianniello F, Bucciarelli P, Artoni A, Ferrari B, Pontiggia S, Trisolini SM, Facchini L, Carbone C, Peyvandi F; Italian Group of TTP Investigators. Prevalence of the age-related diseases in older patients with acquired thrombotic thrombocytopenic purpura. Eur J Intern Med. 2020;75:79-83.
43. Prevel R, Roubaud-Baudron C, Gourlain S, Jamme M, Peres K, Benhamou Y, Galicier L, Azoulay E, Poullin P, Provôt F, Maury E, Presne C, Hamidou M, Saheb S, Wynckel A, Servais A, Girault S, Delmas Y, Chatelet V, Augusto JF, Mousson C, Perez P, Halimi JM, Kanouni T, Lautrette A, Charvet-Rumpler A, Deligny C, Chauveau D, Veyradier A, Coppo P. Immune thrombotic thrombocytopenic purpura in older patients: prognosis and long-term survival. Blood. 2019;134:2209-2217.
44. Jamme M, Rondeau E. The PLASMIC score for thrombotic thrombocytopenic purpura. Lancet Haematol. 2017;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;60:2047-2057.
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;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;32:246-256.
48. Ferrari S, Scheiflinger F, Rieger M, Mudde G, Wolf M, Coppo P, Girma JP, Azoulay E, Brun-Buisson C, Fakhouri F, Mira JP, Oksenhendler E, Poullin P, Rondeau E, Schleinitz N, Schlemmer B, Teboul JL, Vanhille P, Vernant JP, Meyer D, Veyradier A; 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;109:2815-2822.
49. Hie M, Gay J, Galicier L, Provôt F, Presne C, Poullin P, Bonmarchand G, Wynckel A, Benhamou Y, Vanhille P, Servais A, Bordessoule D, Coindre JP, Hamidou

M, Vernant JP, Veyradier A, Coppo P; French Thrombotic Microangiopathies Reference Centre. Preemptive rituximab infusions after remission efficiently prevent relapses in acquired thrombotic thrombocytopenic purpura. Blood. 2014;124:204-210.

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;93:E73-E75.
51. George JN. TTP: long-term outcomes following recovery. Hematology Am Soc Hematol Educ Program. 2018;2018:548-552.
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;49:118-124.
53. Bayer G, von Tokarski F, Thoreau B, Bauvois A, Barbet C, Cloarec S, Mérieau E, Lachot S, Garot D, Bernard L, Gyan E, Perrotin F, Pouplard C, Maillot F, Gatault P, Sautenet B, Rusch E, Buchler M, Vigneau C, Fakhouri F, Halimi JM. Etiology and outcomes of thrombotic microangiopathies. Clin J Am Soc Nephrol. 2019;14:557-566.
54. Sukumar S, Gavriilaki E, Chaturvedi S. Updates on thrombotic thrombocytopenic purpura: recent developments in pathogenesis, treatment and survivorship. Thromb Update. 2021;5:100062.
55. Vesely SK. Life after acquired thrombotic thrombocytopenic purpura: morbidity, mortality, and risks during pregnancy. J Thromb Haemost. 2015;13(Suppl 1):S216-S222.