IJHOSCR

Original Article

International Journal of Hematology-Oncology and Stem Cell Research

Clinical Features and Risk Factors of Relapse and Mortality in Thrombotic Thrombocytopenic Purpura Patients: A Seven-Year Experience

Sahar Tavakoli Shiraji[1,2], Mohammad Reza Rostami[1], Hosein Kamranzadeh Foumani[1,4], Seied Asadollah Mousavi[1,3], Mohammad Vaezi[1,2], Soroush Rad[1,2], Davood Babakhani[1], Maryam Barkhordar[1,3], Tanaz Bahri[1,3], Ghasem Janbabaei[1,4], Ashraf Malekmohammadi[1], Saeed Mohammadi[1,3], Vahid Mansouri[5]

[1]Research Institute for Oncology, Hematology and Cell Therapy, Tehran University of Medical Sciences, Tehran, Iran
[2]Hematology, Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences, Tehran, Iran
[3]Cell Therapy and Hematopoietic Stem Cell Transplantation Research Center, Tehran University of Medical Sciences, Tehran, Iran
[4]Hematologic Malignancies Research Center, Tehran University of Medical Sciences, Tehran, Iran
[5]Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran

Corresponding Author: Vahid Mansouri, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran
E-mail: mansoury.vahid@gmail.com

Received: 15, Sep, 2022
Accepted: 22, May, 2023

ABSTRACT

Background: Thrombotic thrombocytopenic purpura (TTP) is associated with microangiopathic hemolytic anemia, thrombocytopenia, and microvascular thrombosis. No comprehensive report exists on clinical characteristics and risk factors of relapse and mortality in Iranian TTP patients. In this study, we aimed to report clinical features of Iranian TTP patients, to evaluate disease relapse and mortality rate and their associated risk factors.

Materials and Methods: This study was a cohort study of patients diagnosed with microangiopathic hemolytic anemia admitted to the Shariati Hospital, Tehran, a referral center for TTP patients, from 2010 to 2017. Demographic, clinical, and laboratory data were recorded and patients were followed for 3 years regarding disease relapse and mortality.

Results: 114 patients (80 females, 34 males) with a mean age of 39.3 ± 14.99 years were included. Hematologic and neurologic symptoms were the most common manifestations. Abnormal laboratory findings at the presentation included thrombocytopenia, anemia, and elevated LDH. All patients were treated with plasma exchange, and 75.5% of them had a response to treatment, while the 3-year relapse and mortality rate was 23.6 and 26.3%. Lower platelet count was a predictor of disease relapse. Age, hematological, or neurological initial presentation were associated with TTP mortality.

Conclusion: Based on the largest study of TTP patients ever in Iran, the demographic and clinical characteristics of Iranian TTP patients are similar to other existing reports. Knowledge of the risk factors for TTP relapse and mortality could be useful to alert hematologists for prompt therapeutic actions when necessary.

Keywords: Thrombotic thrombocytopenic purpura; Recurrence; Mortality; Risk factors

INTRODUCTION

TTP is a rare hematologic disorder with an annual prevalence of about 10 cases per million and an annual incidence of about one new case per million in the general population. TTP is two times more prevalent in women than men, and relapse is also more common in women[1-3]. The initial acute episode of the disease occurs mainly during adulthood in 90% of cases, but there have also been reports of the incidence in children and adolescents[4, 5]. In 40% of patients, patients experience one or more relapses of the disease in the long term[6].

The definition of TTP has changed over time. Early on, the acute episode of TTP was defined based on

clinical evidence (mainly visceral ischemic symptoms involving the brain) as well as standard biological markers (including microangiopathic hemolytic anemia and severe thrombocytopenia) in the absence of other causes. Later, the novel biomarker ADAMTS13, as the only specific marker for TTP, was added to help for better TTP diagnosis.

Various treatments have been proposed for TTP, including plasma replacement (TPE), Steroids, Rituximab, Other immunomodulatory drugs such as vincristine and cyclosporine. TPE is still considered the best treatment for TTP. Using Rituximab with TPE is highly recommended with faster recovery of the disease and prevention of related complications. Moreover, some newer drugs like N-acetyl cysteine[7, 8], bortezomib[9], recombinant ADAMTS13 (BAX930)[10] and caplacizumab[11] are being evaluated for the treatment of TTP. Different therapeutic approaches result in different outcomes and complications. Despite recent advances in therapeutic approaches, the disease continues to be fatal with a mortality rate of 10% to 20% [12].

The purpose of this study is to report clinical features and outcomes of TTP patients referred to Shariati hospital, a referral center for TTP patients in Iran, and to evaluate disease relapse and mortality rate and its associated risk factors in these patients in a cohort study.

MTERIALS AND METHODS

Study population

This was a cohort study of all patients treated for the first episode of TTP at Shariati hospital from 2010 to 2017. Inclusion criteria of study include microangiopathic hemolytic anemia (MAHA) characterized by schistocytes on the peripheral blood film and thrombocytopenia, with or without fever and neurological or renal impairment. Only patients who fulfilled the criteria of TTP throughout their hospitalization were included in the study[13]. Patients with alternative causes for MAHA (e.g., disseminated intravascular coagulation, sepsis, preeclampsia, eclampsia, or HELLP syndrome) were not included. To clarify the inclusion process, first all the suspected patients who have suggestive clinical clues for TTP were evaluated. We ruled out the patients with other obvious thrombotic microangiopathies e.g., HELLP syndrome, preeclampsia, HUS and severe hypertension in this stage. Then all the patients underwent initial laboratory and physical examination tests, during which several others were excluded (e.g., patients with SLE or other diagnosed autoimmune disorders). Given the delay in reporting the result of ADAMTS13 factor test, we did not postpone the initiation of TPE for these patients considering the most critical scenario for them (TTP). Although we used the Bentley score as an initial clue for severe deficiency of ADAMTS13, all the remained patients were examined regarding ADAMTS13 and also other laboratory and clinical findings during hospitalization and possible relapses. Finally, we only keep the patients who we could not find any better diagnosis than TTP in the study (Figure 1).

Indices and outcomes

Demographic characteristics, clinical symptoms, initial laboratory tests on admission, and treatments performed were recorded. Recorded clinical manifestations include constitutional symptoms like fever and jaundice, hematologic presentations like petechiae and purpura, gastrointestinal (GI) symptoms like GI bleeding, neurological manifestations like seizures, any type of behavior changes, motor or sensory events and any loss of consciousness, and hematuria. laboratory manifestations including ADAMTS13 activity level, platelet count, hemoglobin and creatinine (Cr) were also recorded. ADAMTS13 factor was measured and reported with activity level measured by Fluorescence Resonance Energy Transfer (FRET). However, recent literature suggested repeating ADAMTS13 measurement at follow-ups, due to the low accessibility, high cost and different socioeconomic status of patients for most of them only initial ADAMTS13 factor testing was done. Hospital records, telephone calls, and face-to-face interviews were used to collect missing clinical and laboratory data. Enrolled patients were followed-up for three years on regular visits or on TTP relapse leading to hospital admission. The known or later-diagnosed underlying diseases, type of treatment performed, disease relapse, treatment response and survival of the patients were also recorded.

Definition of treatment response was based on the consensus of the International Working Group for Thrombotic Thrombocytopenic Purpura[13]. Complete clinical response was defined as sustained platelet count higher than $150\times10^3/\mu L$ and LDH lower than 1.5-fold of the upper limit of the normal range (ULN). Refractory TTP was defined as sustained thrombocytopenia, lack of permanent increase in platelet counts or platelet count lower than $50\times10^3/\mu L$ and LDH higher than 1.5-fold of ULN, despite five PEX and steroid therapy. Moreover, patients were assigned to one or more predetermined categories based on predisposing factors, previously used by Chiasakul et al. [14], including (1) autoimmune disorders (systemic lupus erythematosus, rheumatoid arthritis, etc.), (2) solid organ or hematopoietic cell transplant recipients, (3) malignancies, (4) pregnancy or postpartum state, (5) drug-related conditions (including clopidogrel, ticlopidine, mitomycin, gemcitabine, carmustine, tacrolimus, and quinine), and (6) idiopathic. These categories were not mutually exclusive.

Ethical consideration

Patients' private information was kept strictly confidential. Written informed consent was given voluntarily by all participants and any use of patient information was restricted to obtaining permission from them. The study is approved by the research ethics committee of Tehran University of Medical Sciences (TUMS). (Ethical code: IR.TUMS.MED.REC.1397.718)

Statistical analysis

The data were expressed as median and interquartile range for the quantitative variables and as count and percentages for the qualitative variables. Given the non-normal distribution of variables assessed through Shapiro-Wilk test, data was analyzed using Mann-Whitney U test or Fisher z test to assess quantitative and qualitative variables, respectively. The normality of data was assessed using the Kolmogorov-Smirnov test, and in the case of non-normal data, nonparametric tests were used. The univariate and multivariate logistic regression and univariate and multivariate cox regression models were used to determine factors related to patient relapse and survival. In addition, the long-term survival of patients was assessed using the log-rank test and Kaplan-Meier curves. The significance level was considered $p<0.05$. The SPSS software version 23 (IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp) was used for statistical analysis.

Characteristics of TTP patients in the registry

A total of 179 patients with a diagnosis of MAHA were included. After further investigations at the initial laboratory tests and during the hospitalization, 65 patients were excluded from the analysis given the diagnosis of the MAHA secondary to other underlying conditions (Figure 1). Remaining 114 cases of TTP (80 females and 34 males) were considered for analysis. Mean age of participants in the study was 39.31±14.99 years (Median = 34). Hematologic and neurologic symptoms were the most common first manifestations. The most common hematological manifestations among TTP patients were thrombocytopenia (n= 37) and anemia (n=27), while the most common neurological manifestations were cerebrovascular accidents (n= 15) and intracranial hemorrhage (n=9). Laboratory results at the time of diagnosis revealed thrombocytopenia (median platelet: $30\times10^3/\mu L$), anemia (median Hb: 8.5 g/L), elevated LDH (median LDH level: 1674.5 U/L) and normal Cr (median Cr level: 1.15). Table 1, shows demographic, clinical and laboratory characteristics of enrolled patients (Table 1).

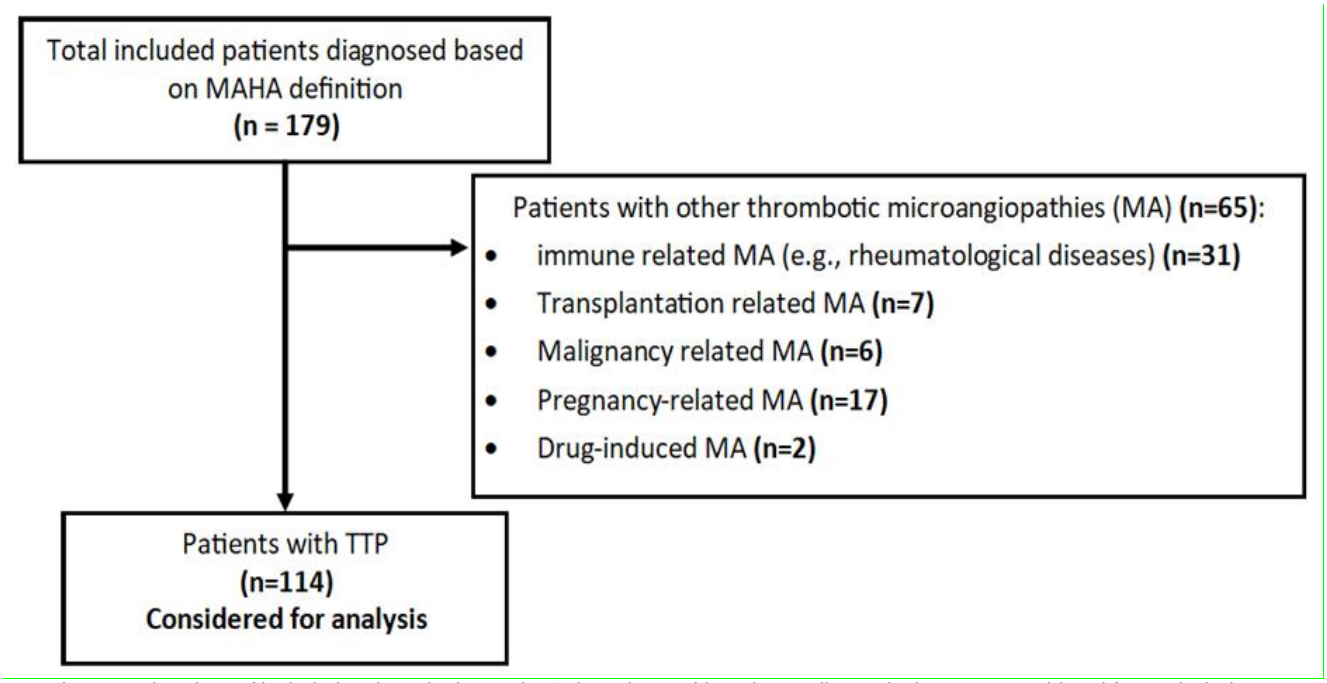

Figure 1. Flowchart of included patients in the study. Only patients with no better diagnosis than TTP considered for analysis (MAHA: microangiopathic hemolytic anemia; MA: thrombotic microangiopathy

Table 1: Demographic, clinical and laboratory characteristics of enrolled patients by disease relapse

Indices	Total TTP patients (n=114)	Relapse group (n=27)	No relapse group (n=87)	p[a]
Demographic				
Gender (Female) [Count (%)]	80 (70.1%)	20 (74.1%)	60 (68.9%)	0.113
Age [median (IQR)]	34 (19)	32 (17)	34 (18)	0.034
First manifestations of the disease [Count (%)]				0.078
Hematological	64 (56.1%)	19 (70.4%)	45 (51.7%)	
Neurological	24 (21%)	6 (25.0%)	18(20.0%)	
Found during check-ups	22 (19.2%)	1 (3.7%)	21 (24.1%)	
Icterus	2 (1.7%)	0	2 (2.2%)	
Fever	1 (0.8%)	1 (4.2%)	0 (0.0%)	
Creatinine rise	1 (0.9%)	0	1 (1.1%)	
Laboratory indicators [median (IQR)]				
ADAMTS13 activity (%)	2.5 (5.2)	2 (6.4)	2.7 (3.1)	0.554
Hemoglobin (g/dL)	8.5 (2.5)	8.5 (3.5)	8.5 (2.3)	0.587
Creatinine (mg/dL)	1.15 (1.7)	1.08 (0.9)	1.2 (1.7)	0.724
LDH (U/L)	1674 (1995)	1749 (2029)	1660 (1994)	0.694
Platelet count ($\times 10^3/\mu L$)	30 (30)	13 (23)	37 (47)	<0.001
AST (U/L)	41.5 (34)	39 (48)	42 (33)	0.849
ALT (U/L)	28.5 (26)	23 (20)	30 (41)	0.482
Total bilirubin (mg/dL)	2.1 (3.1)	1.9 (3.6)	2.1 (3)	0.542
Indirect bilirubin (mg/dL)	0.3 (0.1)	0.3 (0.39)	0.3 (0.2)	0.743
Count of reticulocytes	4.05 (4)	6 (8.6)	4 (3)	0.01
Treatment approach				
Rituximab added to PEX	19 (16.6%)	5 (18.5%)	14 (16.1%)	0.782
Number of PEX sessions	11.5 (13)	11 (8)	12 (14)	0.861
Treatment response				0.354
Complete response	72 (63.2%)	20 (74.1%)	52 (59.8%)	
Refractory	28 (24.6%)	4 (14.8%)	24 (27.6%)	

[a] calculated using Mann-Whitney U test, except for gender, underlying condition, first manifestation and treatment response which calculated using fisher exact test.

Treatment protocol

Treatments were done according to the local guideline for treatment of TTP patients. Accordingly, All the patients received corticosteroids at dosage of 1mg/Kg daily. For patients with initial neurological manifestations, additional corticosteroids pulse i.e., 500 mg daily for three days was also considered.

All patients were treated with plasma exchange (PEX). PEX for TTP patients was done according to local instructions using Haemonetics® PCS®2 (Haemonetics Corporation, MA, USA) via peripheral vein access or Shaldon percutaneous catheter. In each PEX session, one estimated volume of plasma (approximately 40 cc/Kg) was exchanged with fresh frozen plasma. All the patients underwent PEX daily until the criteria for tapering PEX were fulfilled. The PEX tapering criteria for TTP patients includes three consecutive days with normal platelet count (higher than $100\times10^3/\mu L$), or one day with platelet count higher than $150\times10^3/\mu L$. After the criteria have been met, PEX would continue every other day (tapering). If the platelet count following the next three PEX remained in the normal range, the patient could be discharged. The number of held sessions of PEX for each patient was recorded.

Rituximab was administered for high-risk patients with severe refractory or recurrent TTP. Rituximab was administered weekly for four weeks at the dose of 375 mg/m^2 intravenously after each PEX session.

Treatment outcome

The median treatment duration was 11.5 [inter-quartile range: 13] days. All the patients received daily PEX and Corticosteroids as previously mentioned. Twenty-four (21%) patients were treated with pulse corticosteroid given the initial neurological presentation. 19 patients (16.66%) received rituximab.

With the described treatment approach, 86 (75.5%) of patients gained clinical response and 28 (24.6%) of them developed refractory TTP. There were no differences regarding the clinical response (78.9% vs 75.5%, p=0.753), relapse rate (26.3% vs 23.33%, p = 0.782) and mortality (log rank p = 0.119) between patients with and without Rituximab in our population. The number of PEX sessions was significantly higher in patients who received Rituximab in their initial treatment (31.1 vs 13.68, p<0.001).

The adverse reactions after treatment were managed according to the local guideline for treatment of TTP patients. After PEX, 89 (78%) patients had mild reactions including mild hypotension, chill and urticaria, which were managed with intravenous Chlorpheniramine and Hydrocortisone; four (3%) patients had severe hypotension requiring a 30 minutes halt in apheresis for hydration and administering Chlorpheniramine and Hydrocortisone as needed, followed by continuance of PEX. Other patients did not develop any adverse events and no anaphylactic reactions happened.

In follow-up visits of the patients, they reported chronic stress for disease relapse -requiring long hospitalization period - after taking new drugs, pregnancy, getting infections, undergoing surgeries or other medical procedures or any other suspicious events. They were expecting disease relapse after every prominent event, which greatly reduce their quality of life. This mental state was more evident among the patient with multiple disease relapses and those who were hospitalized for long period (longer than one month) at the first course of the disease. However, no other significant complications were observed in long-term follow-ups.

Relapsed versus non-relapsed TTP patients

27 patients (23.6%) with TTP experienced one or more relapses during the next 3 years from diagnose. The median time to occurrence of relapse was 12.44 (range 4-48) months. 83.3% of patients with at least one relapse and 66.7% of patients without relapse were female (P-value = 0.113). The median (IQR) age in relapse and non-relapse groups was 32 (17) and 34 (18) years, respectively. Patients in the relapse group significantly have lower ages (P=0.034). (Table 1) In terms of clinical presentation (Hematological, Neurological, found during check-ups, Icterus, fever and 30% rise in level of creatinine), there was only a significant difference between the two groups regarding the patients diagnosed during check-ups. Assessing the laboratory characteristics of patients between the two groups, we only found a significant difference in platelet and reticulocyte counts

between the two groups (P<0.001 and 0.01, respectively). Notably, there was no significant difference in the serum level of ADAMTS13 factor between the two groups (p = 0.554). As presented in Table 1, there was no difference between two groups regarding treatment duration and number of PEX sessions (p = 0.861). There was no difference regarding response to treatment between the two groups (p 0.354) (Table 1).

Moreover, we evaluated our population for suspected triggers for TTP relapse, given the extreme anxiety of these patients for relapse due to pregnancy, prescribed new drugs, infections, surgeries and trauma. There was no generalizable pattern of history prior to disease relapses. None of these triggers was significantly associated with disease relapse. (Data not shown)

Determination of Predictors of Relapse Disease

Next, we assessed the association of patients' characteristics with the occurrence of relapse during 3-year follow up after diagnosis using univariate logistic regression. (Table 2) Age, platelet count and reticulocyte count were associated with TTP relapse. These variables were analyzed using multivariate logistic regression after entering variables with p<0.1 into multivariate model, in which the association of platelet count with the occurrence of relapse remained significant. Next, we calculated the optimal cut-off of platelet count for predicting relapse using ROC curve analysis (AUC=0.234, p<0.001). The optimal cut-off for platelet count was 30×10^3. Patients with greater than 30×10^3 platelet count experienced significantly less relapse compared to patients with less than the cut-off (Chi-square p = 0.002, Odds ratio (95%CI): 0.222 (0.081 – 0.603)) (Table 2).

Survival and its predictors

Next, we evaluated TTP patients' survival. As shown in the Kaplan-Meier curve their overall survival (after 3 years of follow-up) is 73.7 percent. Also, the one-month, one-year and 2-year overall survival rates were 82.5%, 76.3% and 74.6%. The 3-year overall survival rate was not different across both genders (log-rank P = 0.02) (Figure 2). The rates of the six-month, one-year, 2-year and 3-year relapse-free survival (RFS) were 93.8%, 89.3%, 89.3% and 85.6%. (Data not shown)

Finally, we assessed the association of patients' characteristics with mortality using the Cox Proportion Hazard Model. Univariate Cox regression showed that age, having hematological or neurological initial presentation and being pregnancy-related as a predisposing factor were associated with mortality. As shown in Table 3, age, hematological initial presentation or neurological initial presentation were associated with TTP mortality using multivariate cox regression model after entering variables with lower than p<0.1 in univariate analysis. Age and neurological presentation had a direct association and hematological presentation had a negative association with mortality. Next, we calculated the optimal cut-off of age for predicting mortality using ROC curve analysis (AUC=0.739, p<0.001). The optimal cut-off for age was 55 years. Patients greater than 55 years old significantly have more mortality compared with patients under 55 (Chi-square p<0.001, Odds ratio (95%CI): 24.923 (7.196 – 86.325)) (Table 3).

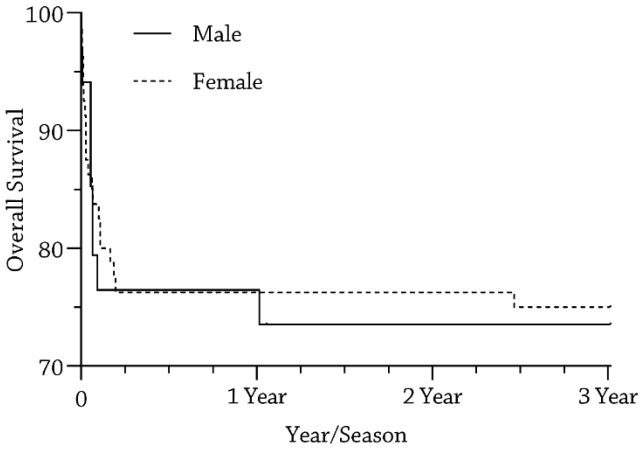

Figure 2. Kaplan Meier curve for overall survival of patients with TTP since 2010 (Males, Females)

Table 2: Association of patients' characteristics and occurrence of relapse in TTP patients using univariate and multivariate logistic regression

Factor		**Univariate regression odds ratio (95% CI)**	**P**	**Multivariate regression odds ratio (95% CI)**	**P**
Demographic					
	Gender (ref: Female)	1.286 (0.486 – 3.403)	0.613		
	Age	0.959 (0.923 – 0.998)	0.037	0.969 (0.929 – 1.011)	0.148
First manifestations of the disease					
	Neurological	1.095 (0.385 – 3.115)	0.865		
	Hematological	2.217 (0.877 – 5.601)	0.092	2.163 (0.746 – 6.269)	0.155
Laboratory indicators					
	ADAMTS13	1.006 (0.991 – 1.021)	0.438		
	Hemoglobin	0.947 (0.801 – 1.119)	0.521		
	Creatinine	0.981 (0.738 – 1.304)	0.894		
	LDH	1 (0.999 – 1)	0.409		
	Platelet count ($\times 10^3$)	1 (1-1)	0.001	1 (1-1)	0.002
	AST	0.999 (0.995 – 1.003)	0.536		
	ALT	0.998 (0.992 – 1.003)	0.394		
	Total bilirubin	0.935 (0.756 – 1.156)	0.534		
	Indirect bilirubin	0.852 (0.425 – 1.709)	0.653		
	Count of reticulocytes	1.203 (1.073 – 1.349)	0.002	1.044 (0.906 – 1.204)	0.552
Treatment approach					
	Rituximab added to PEX	1.173 (0.378 – 3.640)	0.782		
	Number of PEX sessions	0.999 (0.972 – 1.027)	0.940		

Table 3: Association of patients' characteristics and mortality in TTP patients using univariate and multivariate cox regression

Factor	Univariate cox regression hazard ratio (95% CI)	P	Multivariate cox regression hazard ratio (95% CI)	P
Demographic				
Gender (ref: Female)	0.845 (0.395 – 1.806)	0.664		
Age	1.053 (1.033 – 1.074)	<0.001	1.051 (1.028 – 1.076)	<0.001
First manifestations of the disease				
Neurological	3.689 (1.771 – 7.683)	<0.001	2.859 (0.999 – 8.187)	0.050
Hematological	0.262 (0.120 – 0.573)	0.001	0.286 (0.109 – 0.753)	0.011
Laboratory indicators				
ADAMTS13	0.976 (0.946 – 1.007)	0.135		
Hemoglobin	0.868 (0.697 – 1.082)	0.208		
Creatinine	1.140 (0.950 – 1.368)	0.158		
LDH	1 (1 – 1)	0.438		
Platelet count ($\times 10^3$)	1 (1-1)	0.436		
AST	0.997 (0.989 – 1.004)	0.424		
ALT	1 (0.998 – 1.002)	0.878		
Total bilirubin	1.007 (0.861 – 1.179)	0.927		
Indirect bilirubin	1.085 (0.821 – 1.434)	0.567		
Count of reticulocytes	0.887 (0.781 – 1.007)	0.065	0.985 (0.855 – 1.135)	0.834
Treatment approach				
Rituximab added to PEX	0.777 (0.234 – 2.580)	0.680		
Number of PEX sessions	1.007 (0.983 – 1.032)	0.563		

DISCUSSION

In this study, we assess the demographic, clinical and laboratory characteristics of Iranian TTP patients along with their prognosis. Hence, 104 patients with a clinical diagnosis of thrombotic thrombocytopenic purpura who were treated at the Shariati hospital in 2010 were included. It is revealed that the incidence of TTP is higher in females compared to males. Autoimmune-related conditions were the most common underlying condition in patients with MAHA. Neurological and hematological manifestations are the common first symptoms that TTP patients are admitted for. The overall response rate, 3-year relapse rate and 3-year mortality rate in the described population are 75.5%, 23.6% and 26.3%, respectively. Having a lower platelet count is associated with TTP relapse. The optimal cut-off of platelet count for predicting TTP relapse was 30×10^3. Moreover, age and neurological first presentation had a direct association and hematological presentation had a negative association with mortality. The optimal cut-off of age for predicting mortality in our population was 55 years.

In this study, 70.1% of patients were female and the mean age of TTP patients in this study was 39.3 ± 14.99. In terms of sexual distribution as well as the median age of onset of the disease, our findings were almost similar to other reports from other populations around the world [12, 15-17].

The main accompanied predisposing factor with MAHA was autoimmune-related conditions; however, most MAHA patients did not have a specific predisposing factor (idiopathic). In the study by El-Husseiny et al., 76.66% of patients were diagnosed as idiopathic primary[17]. In addition, 50% of MAHA patients in another study were idiopathic, while others had predisposing factors such as pregnancy, infection, hematopoietic stem cell transplantation, and autoimmune diseases [18].

In our population, the most common first manifestation of disease was hematological and neurological manifestations. Moreover, the laboratory abnormalities observed at admission in TTP patients include anemia, thrombocytopenia and elevated LDH. In the study by Iqbal et al., the most common first manifestations included neurological symptoms, renal impairment, and thrombocytopenia as one of the components of TTP diagnostic triad [16]. In the study by Wang et al., all of the patients had neurological symptoms, hemolytic anemia, and decreased platelet count. Eight of fourteen patients also had fever and eight patients had renal impairment[18]. In the study of Sun et al., the common symptoms were thrombocytopenia in 100%, hemolytic anemia in 92.1%, neurological symptoms in 88.2%, fever in 72.5% and renal impairment in 70.5% of patients[19]. In the study by Chaturuedi et al., diagnostic symptoms included microangiopathic hemolytic anemia, thrombocytopenia with or without fever, neurological problems, or renal impairment [20]. Therefore, in TTP patients, the occurrence of neurological complications as well as renal disorders are prominent findings other than the classical triad. Various treatments have been proposed for TTP, including (1) Plasma exchange or PEX, still considered as the best treatment for TTP, improves the overall survival rate to approximately 80%[21], (2) Steroids with well-known therapeutic response when used in combination with PEX[22], (3) Rituximab; Using rituximab with PEX is highly recommended, given the associated faster recovery of the disease and prevention of related complications[23, 24]. We treated the patients according to our local guideline for treating TTP patients. All the patients received PEX and corticosteroids, while rituximab is prescribed for high-risk patients. The overall response rate in this study was 75.5 percent, while the 3-year relapse and mortality rates were 23.6 and 26.3 percent. In our study, 10.5% of patients received rituximab. We did not observe a significant difference regarding response, relapse rate or survival comparing the patients with and without rituximab. In the study by Swart et al., primary treatment of the disease majorly included PEX in 87.8%, antiviral therapy in 78.3% and steroids in 61%. Recurrence and mortality rates were 9.8% and 29.3%, respectively [15], which was very close to the results of our study. In the study by Iqbal et al., all patients received PEX, 95.8% received steroids, and 54% received rituximab. Complete response was reported in 87.5% and 83.3% of patients who survived after 22-month from the treatment, which

was slightly higher compared to our study [16]. In the study by Wang et al., complete remission was achieved in 85.7% of patients after treatment with PEX, steroids and rituximab. However, they reported a 2-year mortality rate of 14.3%, the relapse rate was surprisingly as high as 66.7%[18]. In a study by Sun et al., PEX treatment was associated with a response in 72.3% of patients. Among 36 surviving patients (out of 51), 22.2% had recurrences[19], which was very close to our results. Also, in the study by El-Husseiny et al., the 2-year overall response rate was 85.6%, but a similar recurrence rate was reported compared to this study[17]. Hence, the outcomes of our study are in line with studies in other communities with an acceptable response and relapse rates.

At last, we evaluated the risk factors for the occurrence of relapse or mortality. A lower platelet count is associated with TTP relapse. Age, neurological and hematological presentation at first presentation had significant association with mortality. In other studies, different risk factors have been reported to predict mortality and recurrence. Higher age, decreased platelet count, high LDH (above 10 times higher than normal), disease-associated organ damage, decreased albumin levels, elevated cardiac troponin levels and severe neurological symptoms have been associated with poor prognosis and failure to respond to treatment [17, 20, 25-28]. Therefore, a set of these factors can be used to predict the relapse and mortality rates in TTP patients. Development of a new scoring system for the prediction of the outcomes and prognosis of TTP patients could be helpful in this regard.

Limitations and strengths

The major limitation of the study was about the ADAMS13 factor measurement. However, recent literature suggested repeating ADAMTS13 measurement at follow-ups, due to low accessibility, high cost, lack of insurance coverage and socioeconomic status of patients, for most of them only a single initial ADAMTS13 factor measurement was done. In the past two years, this test has become more accessible and current local protocol suggests follow-up ADAMTS13 test each 3-6 months during disease remission. The major strength of the study was its sample size that is the biggest report of Iranian TTP patients ever. Results of this study helped us in determining high-risk patients in our local TTP management guideline, thus we more accurately could consider administration of rituximab in initial management of these patients, closer monitoring during treatment, and ADAMTS13 follow-up measurements for them.

CONCLUSION

Based on the largest study of TTP patients ever in Iran, the demographic and clinical characteristics of Iranian TTP patients are similar to other existing reports. 3-year relapse and mortality rates in TTP patients were 21.1% and 26.3%, respectively. A lower platelet count was predictor of long-term relapse. Age and neurological presentation had a direct association, while the hematological presentation had a negative association with mortality.

ACKNOWLEDGMENT

We should thank all the personnel working in the hematology ward of Shariati hospital for their amazing contribution to TTP patients.

Declarations

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.MED.REC.1397.718).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Funding and resources

This project is supported by the Tehran University of Medical Sciences and was originally obtained from MR Rostami thesis.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

State the availability of data

All data collected, without personally identifiable information, is available as electronic

supplementary material or available from the corresponding author.

REFERENCES

1. Blombery P, Kivivali L, Pepperell D, 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;46(1):71-9.
2. Sukumar S, Lammle B, Cataland SR. Thrombotic Thrombocytopenic Purpura: Pathophysiology, Diagnosis, and Management. J Clin Med. 2021;10(3):536.
3. Hovinga JAK, Vesely SK, Terrell DR, et al. Survival and relapse in patients with thrombotic thrombocytopenic purpura. Blood. 2010;115(8):1500-11.
4. Joly BS, Stepanian A, Leblanc T, et al. Child-onset and adolescent-onset acquired thrombotic thrombocytopenic purpura with severe ADAMTS13 deficiency: a cohort study of the French national registry for thrombotic microangiopathy. Lancet Haematol. 2016;3(11):e537-e546.
5. Joly BS, Coppo P, Veyradier A. Pediatric thrombotic thrombocytopenic purpura. Eur J Haematol. 2018;101(4):425-34.
6. Pavenski K, Huang SS, Patriquin CJ. Predictors of relapse and preventative strategies in immune thrombotic thrombocytopenic purpura. Expert Rev Hematol. 2021;14(11):1027-40.
7. Masias C, Cataland SR. Novel therapies in thrombotic thrombocytopenic purpura. Res Pract Thromb Haemost. 2017;2(1):19-26.
8. Pan T, Qi J, Tang Y, et al. N-Acetylcysteine as Prophylactic Therapy for Transplantation-Associated Thrombotic Microangiopathy: A Randomized, Placebo-Controlled Trial. Transplant Cell Ther. 2022;28(11):764 e1-e7.
9. Ssali FN, Aturinde J, Muyanja D, et al. Bortezomib As Frontline Therapy in the Management of TTP. Blood. 2021;138(Supplement 1):4226.
10. Jain N, Marquez C, Martell L. Recombinant ADAMTS13 for Patients with Severe Congenital Thrombotic Thrombocytopenic Purpura: Design of a Phase 3b Open-Label Continuation Study of Prophylactic and on-Demand Treatment. Blood. 2021;138(Supplement 1):4252.
11. Peyvandi F, Scully M, Kremer Hovinga JA, et al. Caplacizumab for acquired thrombotic thrombocytopenic purpura. N Engl J Med. 2016;374(6):511-22.
12. Alwan F, Vendramin C, Vanhoorelbeke K, et al. Presenting ADAMTS13 antibody and antigen levels predict prognosis in immune-mediated thrombotic thrombocytopenic purpura. Blood. 2017;130(4):466-71.
13. Scully M, Cataland S, Coppo P, et al. Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and related thrombotic microangiopathies. J Thromb Haemost. 2017;15(2):312-22.
14. Chiasakul T, Cuker A. Clinical and laboratory diagnosis of TTP: an integrated approach. Hematology Am Soc Hematol Educ Program. 2018; 2018(1):530-8.
15. Swart L, Schapkaitz E, Mahlangu JN. Thrombotic thrombocytopenic purpura: A 5-year tertiary care centre experience. J Clin Apher.2019;34(1):44-50.
16. Iqbal S, Zaidi SZ, Motabi IH, et al. Thrombotic thrombocytopenic purpura-analysis of clinical features, laboratory characteristics and therapeutic outcome of 24 patients treated at a Tertiary Care Center in Saudi Arabia. Pak J Med Sci. 2016;32(6):1494-1499.
17. El-Husseiny NM, Goubran H, Fahmy HM, et al. Outcome and relapse risks of thrombotic thrombocytopaenic purpura: an Egyptian experience. Postgrad Med J. 2012; 88(1042):433-6.
18. Wang Y, Zhang JY, Niu ZY, et al. [Clinical analysis of 14 patients with thrombotic thrombocytopenic purpura]. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2014; 22(2):407-11.
19. Sun L, Yu Z, Bu Y, et al. [The clinical studies of 51 patients with thrombotic thrombocytopenic purpura]. Zhonghua Xue Ye Xue Za Zhi. 2014;35(2):147-51.
20. Chaturvedi S, Carcioppolo D, Zhang L, et al. Management and outcomes for patients with TTP: analysis of 100 cases at a single institution. Am J Hematol. 2013;88(7):560-5.
21. Bae SH, Kim SH, Bang SM. Recent advances in the management of immune-mediated thrombotic thrombocytopenic purpura. Blood Res. 2022;57(S1):37-43.
22. George JN. Corticosteroids and rituximab as adjunctive treatments for thrombotic thrombocytopenic purpura. Am J Hematol. 2012;87 Suppl 1:S88-91.
23. Lim W, Vesely SK, George JN. The role of rituximab in the management of patients with acquired thrombotic thrombocytopenic purpura. Blood. 2015;125(10):1526-31.
24. Page EE, Kremer Hovinga JA, Terrell DR, et al. Rituximab reduces risk for relapse in patients with thrombotic thrombocytopenic purpura. Blood. 2016;127(24):3092-4.
25. Benhamou Y, Assie C, Boelle PY, et al. Development and validation of a predictive model for death in acquired severe ADAMTS13 deficiency-associated idiopathic thrombotic thrombocytopenic purpura: the French TMA Reference Center experience. Haematologica. 2012;97(8):1181-6.

26. Hughes C, McEwan JR, Longair I, et al. Cardiac involvement in acute thrombotic thrombocytopenic purpura: association with troponin T and IgG antibodies to ADAMTS 13. J Thromb Haemost. 2009;7(4):529-36.
27. 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):166-75.
28. Frawley N, Ng A, Nicholls K, et al. Thrombotic thrombocytopenic purpura is associated with a high relapse rate after plasma exchange: a single-centre experience. Intern Med J. 2009;39(1):19-24.