Prediction of Severity and Mortality in Acquired Thrombotic Thrombocytopenic Purpura (aTTP). Utility of Clinical-biological Scores

C. Pascual-Izquierdo[1,2*], A. Domingo-González[3,4]

[1]Servicio de Hematología y Hemoterapia. Hospital General Universitario Gregorio Marañón, Madrid, Spain

[2]Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain

[3]Servicio de Hematología y Hemoterapia. Hospital Universitario Virgen del Rocío, Sevilla, Spain

[4]Instituto de Investigación Sanitaria Virgen del Rocío, Sevilla, Spain

[*]Correspondence should be addressed to Cristina Pascual Izquierdo; crisizquierdo3@yahoo.es

Abstract

Acquired thrombotic thrombocytopenic purpura (aTTP), is a rare disease caused by ADAMTS13 deficiency, with an annual incidence of 1-6 million/inhabitants. Despite the effectiveness of treatment with therapeutic plasma exchange (TPE) and immunosuppressants, aTTP is still associated with a 10-20% death rate, and its clinical course is characterized by recurrent episodes in up to 50% of cases. Early recognition of patients at higher risk of mortality has become of paramount importance since new treatments such as caplacizumab could ameliorate the prognosis of this group. Over the last decade, mortality predicting models like the French TMA Reference Center Score (FTRCC) and the Mortality in TTP Score (MITS) have been developed in an attempt to personalize treatment. In a recently published study, they were applied to clinical practice to characterize first and relapsed aTTP episodes. This commentary discusses the historical evolution of aTTP prognostic scores and their current role in predicting the prognosis of first episodes and relapses of aTTP.

Keywords: Thrombotic thrombocytopenic purpura, Mortality, Scores prognostic, ADAMTS13

Abbreviations: aTTP: Acquired Thrombotic Thrombocytopenic Purpura; TPE: Therapeutic Plasma Exchange; ADAMTS13: A Disintegrin and Metalloproteinase with a Thrombospondin type 1 motif, member 13, TMA: Thrombotic Microangiopathy; VWF: von Willebrand Factor; HUS: Hemolytic Uremic Syndrome; vW: von Willebrand; FTRCC: French TMA Reference Center Score; MITS: Mortality in TTP Score (MITS); LDH: Lactate Dehydrogenase; CNS: Central Nervous System; AUC: Area Under the Curve

Introduction

Acquired thrombotic thrombocytopenic purpura (aTTP) is a life-threatening thrombotic microangiopathy (TMA) [1-3]. It has an average annual prevalence of approximately 10 cases/million people and an annual incidence between 1.5 and 6.0 cases per million according to studies conducted in France [4], the United States [5,6], the United Kingdom [7,8], and Spain [9]. The first episode of aTTP occurs mostly during adulthood (~90% of all aTTP cases), but some child and adolescent forms are also detected (~10% of cases) [5].

aTTP is caused by a severe deficiency of ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) [10]. This protein reduces the size of the ultra-large von Willebrand factor (VWF) multimers secreted by the endothelial cells. Thus, ADAMTS13 deficiency leads to a failure in VWF size regulation and the consequent dependent platelet adhesion, causing the cardinal features of TTP (thrombocytopenia, microangiopathic hemolytic anemia, and subsequent organ damage).

The ADAMTS13 deficiency can be acquired via

autoantibodies to ADAMTS13, which is the most common form of the disease, or congenitally via recessively inherited biallelic mutations of the ADAMTS13 gene. The latter is rare and represents 2% of all aTTP cases [1]. Independently of its origin, the lack of ADAMTS13 activity (less than 10%) is the only biologic marker specific for aTTP and it is a crucial factor in the diagnosis [1,3].

The presence of severe thrombocytopenia, microangiopathic hemolytic anemia, and variable organ ischemia remains the cornerstone of clinical diagnosis. However, none of these symptoms is exclusive to aTTP and they may be present in other pathologies such as hemolytic uremic syndrome (HUS), other TMA syndromes, and Evans syndrome [1,10]. For this reason, the presence of a severe deficiency of ADAMTS13 (<10% ADAMTS13 activity), although not required to start treatment, has become necessary to confirm the diagnosis [1,3].

The first-line therapy for acute aTTP is based on daily therapeutic plasma exchange (TPE) for ADAMTS13 deficiency in conjunction with steroids as an adjunct treatment due to the autoimmune nature of aTTP. The use of a humanized anti-CD20 monoclonal antibody (rituximab) as part of the frontline treatment has been proposed lately, due to the high response rates, the shorter hospitalization periods, and the fewer relapses reported in some studies [3,11].

Despite appropriate therapeutic management, aTTP still has a mortality rate of 10-20% and its clinical course is characterized by a tendency to relapse in up to 50% of cases [1]. Early recognition of patients at higher risk of mortality is of notable importance because they can benefit from emerging agents like caplacizumab, an anti-von Willebrand (vW) nanobody that blocks platelet aggregation into the small vessels [12].

Most relapses occur during the first or second year, but some of them can occur as late as 10 or 20 years after the first episode of aTTP [1]. Apart from the known short-term risk, over the last years, relapses have been associated with deficits in health-related quality of life such as chronic neurocognitive disability and arterial hypertension [2]. Relapsing TTP is related to recurrent or persistent severe ADAMTS13 deficiency, which suggests that monitoring ADAMTS13 during follow-up might enable a prompt diagnosis. However, as a severe ADAMTS13 deficiency is not always followed by the development of the clinical syndrome, the use of preemptive treatment should be individualized [1,13].

It is becoming essential to understand the factors associated with a fatal outcome to better tailor treatment. In this commentary, we will review the main TTP prognostic scores, their history and application, and the differences between first and relapsed episodes in terms of prognosis.

aTTP Prognostic Scores: A Journey through History

Since the first description of aPTT case by Eli Moschcowitz in 1924 [1], a tremendous effort has been made to deepen our knowledge of this disease and improve its dismal prognosis. The introduction of empirical treatment with plasma infusions and exchange in 1977 brought about a dramatic change in the prognosis of this disease and enabled the scientific community to describe the clinical course and outcomes of TTP survivors.

In the 1980s, the first cases of TTP relapses were described and in 1987 the first clinical severity score for TTP, later known as the Rose and Eldor score [14,15], was developed.

Rose and Eldor Score 1987

The Rose and Eldor score [14] were the result of the analysis of a retrospective series of 38 patients diagnosed and treated with TTP in 15 hospitals in Israel and the United States between 1977 and 1985. In this study, 26 patients had a first episode of TTP, while 12 patients had relapsing TTP. Ninety-five percent of patients had thrombocytopenia, 86% anemia, 37% fever, 73% renal involvement, and 94% neurologic manifestations. Treatment included plasma infusions (92% of the patients), plasma exchange (76%), steroids (95%), platelet inhibitor drugs (87%), platelet transfusions (36%), splenectomy (31%), and vincristine (8%). The mortality rate in the study was 21%.

A scoring system was developed based on 4 clinical and laboratory parameters: neurologic findings, renal function impairment, platelet count, and hemoglobin value at presentation (Table 1).

The historical importance of the Rose and Eldor score is indisputable, since it constitutes the first scoring TTP system and these authors suggested for the first time that relapsing thrombotic thrombocytopenic purpura, although not a benign disorder, was a milder form of thrombotic thrombocytopenic purpura. However, it had several limitations such as the misidentification of other primary TMA as TTP episodes, the lack of consensus on terminology regarding concepts such as relapsed or refractory TTP, and the heterogeneity of treatment.

Canadian Apheresis Model Predicting 6-month Mortality (Wyllie et al. [16])

From 1987 on, the Rose and Eldor index of TTP severity was occasionally used to predict the response of TTP to plasma exchange, however, as discussed above, it had several limitations. In fact, it did not predict outcomes when applied in another case series [17]. As a result, in 2005 a new model predicting 6-month mortality was proposed by the Canadian Apheresis Group [16]. The goal of this study

Table 1: Rose and Eldor score [14].

Level of abnormalities	Neurologic findings	Renal function impairment	Platelet count at presentation (x10⁹/L)	Hemoglobin level at presentation (g/dL)
0	None	None	>100	>12
1	Confusion, lethargy, behavioral changes	30 mg/dL < BUN < 70 mg/dL and/or 1.5 mg/dL < creatinine < 2.5 mg/dL and/or proteinuria > 2 g/day and/or hematuria	20-100	9-12
2	Focal neurologic deficits, convulsions, stupor, coma	BUN >70 mg/dL and/or creatinine >2.5mg/dL and/or dialysis	<20	<9

Table 2: Canadian Apheresis Model predicting 6-month mortality (Wyllie et al. 2005) [16].

Level of abnormalities	Age	Hemoglobin	Fever (Tᵃ >38.5ºC)
0	≤ 40 years	≥ 9g/dL	No
2	> 40 years	< 9g/dL	Yes

was to identify those patients who would benefit from higher treatment intensity, but no comparisons between first episodes and relapsing episodes of TTP were included.

In this registry, 171 patients with aTTP previously included in large randomized trials were chosen from 19 major medical centers across Canada over 22 years. Two cohorts with 2 different treatments (plasma exchange vs plasma infusion) were selected. Characteristics of patients from these cohorts were compared and no significant differences were found. A multivariable logistic model of 6-month survival was developed, containing age, hemoglobin, and the presence of fever at presentation (Table 2).

This model predicted 13.4% of outcome variance. Predictive scores of 0, 2, 4 and 6 correlated with 6-month mortality rates of 12.5%, 14.0%, 31.3% and 61.5% respectively. The modified Rose index (neurological abnormalities were modified as present or absent) was applied to the data set and no significant difference in scores was noted in terms of survival.

This study had several advantages in comparison to the Rose and Eldor score such as the statistical analysis performed to select the clinical and laboratory parameters and the careful data collection within large randomized

trials. Moreover, treatment was specific and homogeneous. However, some limitations of this model need to be highlighted. On one hand, a common limitation with the Rose and Eldor score was the lack of a specific diagnosis of TTP, since ADAMTS13 activity was not included as part of the initial work-up. Besides, consensus on TTP terminology was still lacking.

French TMA Reference Center Score (FTRCC) 2012

Many advances regarding diagnosis of TTP have taken place since the Canadian prognostic model was published. However, despite this significant progress, death still occurred in up to 10-20% of patients. It therefore became essential to understand the factors associated with a fatal outcome. As a result of the many efforts made in this field, in 2012 the French TMA Reference Center published a prognostic score composed of original independent risk factors associated with 30-day mortality in patients diagnosed with TTP [18].

This retrospective analysis registered 281 patients diagnosed with TTP with an acquired severe ADAMTS13 deficiency over 10 years. The features of patients who died during the 30 days starting from treatment initiation were

compared to those of patients who survived that phase. From this study group, a prognostic score was established to identify patients at risk of death during the acute phase of TTP. The results were validated on a prospective series of patients managed with the same conditions.

Increasing age, cerebral involvement and, LDH level ≥ 10 times the upper normal value was retained as risk factors in the multivariable model, and on this basis, the French TMA Reference Center Score was developed (Table 3). The sensitivity (% score = 0 > 3 among non-survivors) was 52% (95% CI: 35%, 67%) and specificity (score < 3 among survivors) was 90% (95% CI: 86%, 93%). The positive predictive value was 41% (95% CI: 28%, 57%) and negative predictive value was 93% (95% CI: 89%, 96%). The AUC was 0.77, showing that the score had discriminating ability (P<0.0001).

Table 3: The French TMA Reference Center Score and the Mortality in TTP Score [18].

Patients' characteristics	Score
Cerebral involvement	+ 1
Age ≤ 40 41 − 60 > 60	 + 0 + 1 + 2
Lactate dehydrogenase (LDH) level ≥ 10 times the upper normal value.	+ 1

Mortality in TTP Score (MITS) 2016

In 2016 a comprehensive prognostic risk predictive score of all-cause mortality in hospitalized patients with TTP was published by Ruchika Goel et al, from Johns Hopkins University, Baltimore (United States) [19]. This registry included 8,203 patients diagnosed with TTP from 2007 to 2012 who received TPE treatment. Based on the results of univariate analysis, the significant variables were added in a stepwise manner in a multivariable model. This gave place to the Mortality in TTP Score (MITS), taking values from 1 to 3 for each variable (Table 4).

Table 4: The Mortality in TTP Score (MITS) [19].

Patients' characteristics	Score
Platelet transfusion	+ 1
Ischemic Stroke	+ 1
Renal failure	+ 1
Myocardial Infarction	+ 1
Age ≥ 60 years	+ 2
Central Nervous System Bleed	+ 3
Arterial Thrombosis	+ 3

This mortality score was thought to be applicable at each point of the treatment course including remission, relapse, or refractory disease.

This study provided the largest cohort of mortality in TTP patients to date with an estimated >1000 TTP-related deaths identified over 1100 hospitals nationwide. Among its limitations are the lack of information regarding ADAMTS13 data or particular treatments, and the exclusion of individuals who died before TPE initiation.

Application of the French TMA Reference Center Score and the Mortality in TTP Score in de novo and Relapsed Episodes of aTTP at a Tertiary Care Facility in Spain 2020

The above-mentioned study, conducted by the authors of this commentary (*Domingo-González A. et al.,* [20]), was aimed to give a better characterization of relapses, comparing the prognosis of TTP relapses versus first episodes according to the *French TMA Reference Center Score* [18] and the *Mortality in TTP Score* [19]. Moreover, it compared laboratory and clinical data at presentation of de novo versus relapsed episodes of TTP, along with their response to treatment [20].

A total of 29 episodes of acquired TTP (16 de novo and 13 relapses) were analyzed. All patients were diagnosed and treated in a Spanish single tertiary care center between May 2008 and May 2020. The severe deficit of ADAMTS13 activity, defined as <10%, was an indispensable requirement, so other TMAs were excluded from the registry. Disease severity at presentation was evaluated by *the French TMA Reference Center experience predictive model for death* and the *Mortality in TTP Score*. Response to treatment was described according to Scully et al. [21]. Treatment protocol consisted of daily TPE and corticosteroids as first-line treatment. Rituximab was restricted to refractory or exacerbated cases up to 2017 when it was included as front-line therapy in relapsing TTP or first episodes of TTP with severe CNS involvement. In cases of refractory/ exacerbated TTP, the attending physicians were free to use any adjuvant treatment at their discretion.

Five out of 16 (31%) first episodes scored >2 in the *French TMA Reference Center Score*, whereas every relapsed episode scored ≤ 2 (p=0.027). The median number of points according to this score was 2 (r: 1-3) for the first group and 1 (r: 0-1) for the latter (p=0.006).

On the other hand, the worse short-term prognosis of de novo TTP episodes was sustained by the *MITS*. Four out of 16 (25%) de novo episodes scored >3 in *MITS*, compared to 0% of TTP relapses (p=0.052). The median number of points scored also reflected a higher risk of short-term mortality in first TTP episodes (1 r:1-4 vs 0 r:1-2, p=0.038) (Table 5).

Table 5: Mortality predictive scores [20].

Variable	De novo n=16	Relapsed n=13	P
MITS[12]	1 (r: 1-4)	0 (r: 1-2)	**0.038**
MITS[12] >3	4 (25%)	0 (0%)	0.052
French TMA Reference Center Score[11]	2 (r: 1-3)	1 (r: 0-1)	**0.006**
French TMA Reference Center Score[11] >2	5 (31%)	0 (0%)	**0.027**
Continuous variables with normally and nor normally distributed parameters were analyzed with the unpaired t-test and Mann-Whitney U-test respectively while categorical variables were analyzed with Chi-square. Calculations were carried out using SPSS version 12.			

The worse prognosis of first episodes compared to relapses may have been related to 2 clinical prognostic factors: older age and CNS involvement. Although, no significant difference in median age at presentation between first episodes and relapses was found, 6 out of 16 patients (37.5%) from the first group were older than 60 years whereas all recurrent TTP episodes occurred in patients below this age (p=0.013). As for CNS involvement, the prevalence was higher in first episodes compared to relapses (p=0.001) with no cases of severe neurological abnormalities identified in the last group.

Regarding clinical and laboratory findings, the results were in line with previous studies [22-25]. It is worth noting that bruising was by large the most common finding in relapses and it was found statistically significant compared to first episodes. Platelet count at presentation was found to be higher in recurrences than in the first disease episode (p=0.016) and ADAMTS13 activity <5% was more frequent in the last group (p=0.016) (Table 6). Although this could be related to a faster medical evaluation, this study was not able to prove that the time that elapsed between the disease onset and the initiation of treatment was shorter in relapsed cases. Respecting treatment outcomes, there was no significant difference in the rate of refractoriness or exacerbations or in the number of days spent in the hospital (Table 7).

Table 6: Clinical and laboratory features at presentation (n=29) [20].

	De novo n=16	Relapsed n=13	P
Female gender	9 (56%)	11 (87%)	0.10
Age at episode, years	48 (r: 40-63)	46 (r: 39-50)	0.86
>60 years old	6 (37.5%)	0 (0%)	**0.013**
>5 drugs at diagnosis	1 (6.25%)	3 (23%)	0.19
Idiopathic disease	8 (50%)	8 (62%)	0.53
CLINICAL PRESENTATION			
Anemic syndrome	5 (31%)	1 (7.7%)	0.12
Bleeding	9 (56%)	11 (85%)	0.10
- Mucocutaneous	6 (37%)	3 (23%)	
- Cutaneous	3 (19%)	8 (62%)	**0.025**
Cardiovascular symptoms	0 (0%)	1 (6,2%)	0.26
Neurological symptoms	11 (69%)	1 (7.7%)	**0.001**
- Severe	7 (44%)	0 (0%)	
- Mild	4 (25%)	1 (7.7%)	0.217
Renal involvement	7 (44%)	3 (23%)	0.24
Gastrointestinal symptoms	7 (44%)	3 (23%)	0.24
Fever	4 (25%)	0 (0%)	0.052

LABORATORY FINDINGS			
Platelet count (x10⁹/L)	11.5 (r: 7.75-18.75)	14.5 (r: 10-72)	**0.016**
Hemoglobin (mg/dL)	10 (r: 8.6-12.7)	13.6 (r: 9.2-14.7)	0.10
Lactate dehydrogenase (LDH) (U/L) Normal reference range 135-235	940 (r: 490-1500)	632 (r: 195-1020)	0.36
Creatinine (mg/dL) Normal reference range 0.7-1.2	1.15 (r: 0.9-1.35)	0.99 (r: 0.71-1.16)	0.24
Bilirubin (mg/dL) Normal reference range 0.1-1.1	2.9 (r: 1.3-3.8)	1.2 (r: 0.5-1.7)	0.15
Schistocytes %	3.5 (r: 3-4)	2.5 (r: 1.75-3.25)	0.054
ADAMTS13 activity %	0 (r: 0-1.3)	6.5 (r: 0-15)	0.051
ADAMTS13 activity <5%	13/14 (93%)	4/8 (50%)	**0.016**
PLASMIC SCORE	6 (r: 5-7)	6 (r: 5-6)	0.32

ADAMTS13 activity at presentation was not available for the first episode in n = 2 patients, for relapses in n = 5 patients. ADAMTS13 normal range was 40-130%. Continuous variables with normally and nor normally distributed parameters were analyzed with the unpaired t-test and Mann-Whitney U-test respectively while categorical variables were analyzed with Chi-square. Calculations were carried out using SPSS version 12.

Table 7: Treatment outcomes [20].

Variable	De novo n=16	Relapsed n=13	P
Days from symptom onset to treatment	4.5 (r: 1-7)	2 (r: 0-5)	0.12
≥ 5 days from symptom onset to treatment	8 (50%)	4 (31%)	0.23
Hospitalization, days	21.5 (r: 14-30)	9 (r: 1-18)	0.064
ICU, days	0 (0-2.75)	0 (r: 0-0)	0.62
Red blood transfusion	9 (56%)	4 (31%)	0.17
Platelet transfusion	6 (37.5%)	4 (31%)	0.70
Number of TPE	15 (r: 11-26)	14 (r: 5-19)	0.059
Adjuvant therapy	8 (50%)	6 (46%)	0.29
Refractoriness	2 (12.5%)	2 (15%)	0.82
Exacerbation	7 (44%)	3 (23%)	0.24
Mortality due to TTP	1 (6.2%)	0 (0%)	0.26

Continuous variables with normally and nor normally distributed parameters were analyzed with the unpaired t-test and Mann-Whitney U-test respectively while categorical variables were analyzed with Chi-square. Calculations were carried out using SPSS version 12.

Conclusions

Despite the undeniable improvement in the prognosis of aTTP over the last few decades, aTTP is still related to significant mortality and relapsing tendency, with deficits in health-related quality in the long term. As a result, many prognostic scores have been developed to assist physicians in treating this life-threatening disease. The characterization of the pathophysiology of the disease and the great effort made by the scientific community to achieve consensus in terminology has enabled a continuous amelioration of these scores. In this commentary, we reviewed the main TTP prognosis scores and highlighted their contribution to the field. We also set out the results of the clinical application of the *French TMA Reference Center Score* and the *Mortality in TTP Score* in a tertiary hospital in Spain, to offer an up-dated characterization in terms of prognosis of first and relapsed episodes of TTP in our population.

In summary, the results presented are in line with previous studies and show that relapsed TTP episodes have a lower probability of short-term mortality compared to first TTP episodes. Nationwide studies are needed for prospective validation and to reevaluate these results considering new therapeutic strategies such as the addition of caplacizumab to standard treatment.

Funding

Conflict of Interest

None.

References

1. Joly BS, Coppo P, Veyradier A. Thrombotic thrombocytopenic purpura. Blood. 2017 May 25;129(21):2836-46.

2. Sadler JE. Pathophysiology of thrombotic thrombocytopenic purpura. Blood. 2017 Sep 7;130(10):1181-8.

3. Sukumar S, Lämmle B, Cataland SR. Thrombotic thrombocytopenic purpura: Pathophysiology, diagnosis, and management. Journal of Clinical Medicine. 2021 Jan;10(3):536.

4. Veyradier A. editor PTT. épidémiologie de la cohorte du CNR-MAT sur 16 ans 2015.

5. Reese JA, Muthurajah DS, Hovinga JA, Vesely SK, Terrell DR, George JN. Children and adults with thrombotic thrombocytopenic purpura associated with severe, acquired Adamts13 deficiency: comparison of incidence, demographic and clinical features. Pediatric Blood & Cancer. 2013 Oct;60(10):1676-82.

6. 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 Advances. 2017 Apr 11;1(10):590-600.

7. 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. British Journal of Haematology. 2008 Sep;142(5):819-26.

8. Hassan S, Westwood JP, Ellis D, Laing C, Mc Guckin S, Benjamin S, et al. The utility of ADAMTS 13 in differentiating TTP from other acute thrombotic microangiopathies: results from the UK TTP Registry. British Journal of Haematology. 2015 Dec;171(5):830-5.

9. Pascual-Izquierdo C, del Rio-Garma J, de la Rubia J, Viejo A, Mingot E, Cid J, et al. Incidence, diagnosis, and outcome of immune-mediated thrombotic thrombocytopenic purpura: A nationwide survey by the Spanish registry of thrombotic thrombocytopenic purpura. Journal of Clinical Apheresis. 2021 Mar 29.

10. Sadler JE. What's new in the diagnosis and pathophysiology of thrombotic thrombocytopenic purpura. Hematology. 2015 Dec 5;2015(1):631-6.

11. Scully M, McDonald V, Cavenagh J, Hunt BJ, Longair I, Cohen H, et al. A phase 2 study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura. Blood, The Journal of the American Society of Hematology. 2011 Aug 18;118(7):1746-53.

12. Scully M, Cataland SR, Peyvandi F, Coppo P, Knöbl P, Kremer Hovinga JA, et al. Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura. New England Journal of Medicine. 2019 Jan 24;380(4):335-46.

13. Hie M, Gay J, Galicier L, Provôt F, Presne C, Poullin P, et al. Preemptive rituximab infusions after remission efficiently prevent relapses in acquired thrombotic thrombocytopenic purpura. Blood, The Journal of the American Society of Hematology. 2014 Jul 10;124(2):204-10.

14. Rose M, Eldor A. High incidence of relapses in thrombotic thrombocytopenic purpura: clinical study of 38 patients. The American Journal of Medicine. 1987 Sep 1;83(3):437-44.

15. Rose M, Rowe JM, Eldor A. The changing course of thrombotic thrombocytopenic purpura and modern therapy. Blood Reviews. 1993 Jun 1;7(2):94-103.

16. Wyllie BF, Garg AX, Macnab J, Rock GA, Clark WF, Canadian Apheresis Group. Thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome: a new index predicting response to plasma exchange. British Journal of Haematology. 2006 Jan;132(2):204-9.

17. Bobbio-Pallavicini E, Gugliotta L, Centurioni R, Porta C, Vianelli N, Billio A, et al. Antiplatelet agents in thrombotic thrombocytopenic purpura (TTP). Results of a randomized multicenter trial by the Italian Cooperative Group for TTP. Haematologica. 1997 Jul-Aug;82(4):429-35.

18. Benhamou Y, Assié C, Boelle PY, Buffet M, Grillberger R, Malot S, 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 Aug;97(8):1181-6.

19. 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 Jun;56(6):1451-8.

20. Domingo-González A, Regalado-Artamendi I, Martín-Rojas RM, Pérez-Rus G, Pérez-Corral A, Díez-Martín JL, Pascual C. Application of the French TMA Reference Center Score and the mortality in TTP Score in de novo and relapsed episodes of acquired thrombotic thrombocytopenic purpura at a tertiary care facility in Spain. Journal of Clinical Apheresis. 2021 Feb 3.

21. Scully M, Cataland S, Coppo P, De La Rubia J, Friedman KD, Kremer Hovinga J, et al. Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and related thrombotic microangiopathies. Journal of Thrombosis and Haemostasis. 2017 Feb;15(2):312-22.

22. Alvarez-Larrán A, del Río-Garma J, Pujol M, de la Rubia J, Hernández-Jodra M, Borrell M, et al. Newly diagnosed versus relapsed idiopathic thrombotic thrombocytopenic purpura: a comparison of presenting clinical characteristics and response to treatment. Annals of Hematology. 2009 Oct;88(10):973-8.

23. Lotta LA, Mariani M, Consonni D, Mancini I, Palla R, Maino A, et al. Different clinical severity of first episodes and recurrences of thrombotic thrombocytopenic purpura. British Journal of Haematology. 2010 Dec;151(5):488-94.

24. 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 Advances. 2017 Apr 11;1(10):590-600.

25. Mancini I, Pontiggia S, Palla R, Artoni A, Valsecchi C, Ferrari B, et al. Clinical and laboratory features of patients with acquired thrombotic thrombocytopenic purpura: fourteen years of the Milan TTP registry. Thrombosis and Haemostasis. 2019 May;119(05):695-704.