Utility of Different Scoring Systems for the Diagnosis of Thrombotic Microangiopathies

Seda Yilmaz[1], Ozcan Cenelİ[2] and Atakan Tekinalp[2]

[1]*Department of Hematology, Konya City Hospital, Konya, Turkey*
[2]*Department of Hematology, Faculty of Medicine, Necmettin Erbakan University, Meram, Konya, Turkey*

ABSTRACT

Objective: To investigate the appropriateness of Bentley and plasmic scores and ADAMTS-13 activity to distinguish between primary thrombotic microangiopathies (TMA) syndromes and other thrombotic microangiopathies, as well as primary thrombotic microangiopathies (TTP, complement-related TMA, *etc*).

Study Design: Descriptive study.

Place and Duration of the Study: Department of Hematology, Faculty of Medicine, from February 2013 to February 2020.

Methodology: Data of patients with non-immune hemolytic anaemia (MAHA) and thrombocytopenia who had ADAMTS-13 test, were analysed. Clinical and laboratory findings, Bentley and plasmic scores, and ADAMTS activity levels were compared.

Results: The patients were grouped as primary (n = 27) and secondary (n = 28) TMA, the age was median 38.0 (18-63) years in the primary TMA group and 49.5 (20-84) years in the secondary TMA group. Neurological findings were less in the secondary TMA group (p = 0.008). Plasmic score, lactate dehydrogenase, and total and indirect bilirubin levels were high and D-dimer levels were low in the primary TMA group. In the primary TMA group, a greater number of patients with high plasmic scores were found, whereas all patients in the secondary TMA group had low risk according to Bentley score. Calcium levels were high and platelet levels were low in those with ADAMTS activity level <10% (p = 0.006). The evaluation of primary TMAs demonstrated significant differences in platelet, urea, creatinine, and sodium values between the two groups.

Conclusion: Laboratory data and clinical scores are valuable in differentiating primary and other TMA.

Key Words: *Bentley score, Complement, Plasmic score, Thrombotic microangiopathy, Thrombotic thrombocytopenic purpura, ADAMTS-13.*

How to cite this article: Yilmaz S, Cenelİ O, Tekinalp A. Utility of Different Scoring Systems for the Diagnosis of Thrombotic Microangiopathies. *J Coll Physicians Surg Pak* 2023; **33(05)**:539-543.

INTRODUCTION

It is crucial to exclude systemic diseases in patients with microangiopathic hemolytic anaemia (MAHA) and thrombocytopenia, which may cause similar findings in order to ensure an early and appropriate treatment approach.[1] Thrombotic thrombocytopenic purpura (TTP), Shiga toxin, complement, metabolism, coagulation, and drug-related thrombotic microangiopathies constitute the primary thrombotic microangiopathies (TMA) syndromes. Disseminated intravascular coagulation, systemic infection, malignancy, pregnancy-related syndromes, severe hypertension, systemic rheumatologic diseases, and hematopoietic stem cell or solid organ transplantation are systemic conditions associated with MAHA and thrombocytopenia.

Correspondence to: Dr. Seda Yilmaz, Department of Hematology, Konya City Hospital, Konya, Turkey
E-mail: dr46sedakurtulus@hotmail.com
Received: December 16, 2022; Revised: March 24, 2023; Accepted: April 27, 2023
DOI: https://doi.org/10.29271/jcpsp.2023.05.539

TTP is a life-threatening TMA caused by deficiency of ADAMTS13 (Congenital TTP) and the development of antibodies against ADAMTS13 (acquired TTP). Treatment is urgently required with upto 90% mortality if plasmapheresis is not performed.[2] Treatment differs in each of the primary TMA syndromes, whereas in acquired TTP, the treatment is plasma exchange, steroid, and rituximab;[3-5] complement inhibitors, such as eculizumab, are life-saving treatments for complement-related TMA.[6,7] It is important to distinguish between primary and other TMA, especially TTP from the primary TMA group. In daily practice, tests results of ADAMTS activity level and presence of antibodies are delayed.[8] Therefore, considering the high mortality rate, the presence of unexplained thrombocytopenia accompanied by hemolytic anaemia with a negative Coombs test is considered TTP and treatment is started rapidly.

According to the International Society on Thrombosis and Haemostasis guideline, if the French and plasmic scores are high risk, it is recommended to start plasma exchange and steroids until ADAMTS activity is concluded.[9] Prognostic scores used in malignancies provide information about the survival rate and prognosis of the diseases and determine the scope of

treatment strategy. In dynamic and benign clinical conditions such as disseminated intravascular syndrome, scoring is informative about the likelihood of disease. Bentley and plasmic risk scores are the fundamental rating systems developed to predict the diagnosis of TTP.[10] The aim of this study was to examine the diagnostic role of these scores in TMA patients, especially TTP.

METHODOLOGY

Patients with MAHA and thrombocytopenia, who were evaluated using ADAMTS-13 test between February 2013 and February 2020 at the Medical Faculty, Department of Internal Medicine, Division of Hematology, were retrospectively analysed. The files of patients who were found to have non-immune hemolytic anaemia and thrombocytopenia at the time of admission and whose ADAMTS enzyme levels were studied were retrospectively scanned. Those, whose ADAMTS enzyme levels were not studied were not included in the study. Peripheral smear was evaluated by a haematologist. Epidemiologic characteristics of the patients (age and gender), clinical findings (fever and neurologic findings), leukocyte, haemoglobin, platelet (PLT), D-dimer, INR, aPTT, fibrinogen, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), sodium, potassium, calcium, total and direct bilirubin, reticulocyte (%), and haptoglobulin values at admission were recorded from the electronic patient follow-up file. ADAMTS-13 activity and inhibitor levels were also recorded.

Bentley and plasmic scores were calculated retrospectively. In Bentley score, creatinine (>2 µg/mL, −11.5 points), PLT (>35.00/µL, −30 points), D-dimer (>4.0 µg/mL, −10 points), reticulocyte (>3%, 21 points), and indirect bilirubin (>1.5 µg/mL, 20.5 points) parameters were used. Bentley score was classified as <20 low, 20–30 moderate, and >30 high. In the plasmic score, absence of active cancer, absence of solid/stem cell transplantation history, and presence of hemolysis (reticulocyte count >2.5%, indirect bilirubin >2 mg/dL, and low haptoglobulin), platelet (<30.00/µL), MCV (<90 fL), INR (<1.5), creatinine (<2.0 mg/dL) parameters were evaluated and each parameter was calculated as 1 point. Plasmic score was classified as low (0-4), moderate (5), and high risk (6-7). Patients were grouped as primary and secondary TMA according to TMA diagnosis and <10% and >10% according to ADAMTS-13 level. The groups were compared in terms of laboratory data and scoring. In addition, the primary TMA group was analysed and compared within itself.

Statistical analysis of the study was performed with SPSS IBM software version 25.0. The distribution of continuous numerical variables was analysed by Kolmogorov–Smirnov test. In group comparisons, independent sample t-test was used for normally distributed data and Mann–Whitney U test was used for non-normally distributed data. Categorical variables were expressed as counts and percentages (%). Pearson's chi-square and Fisher's exact chi-square tests were used. Results with $p < 0.05$ were considered statistically significant.

RESULTS

A total of 55 patients were included in this study. Twenty-seven (49%) patients had primary TMA (TTP = 21, complement-mediated = 6) and 28 (51%) were in the secondary TMA group (malignancy-associated = 10, infection-associated disseminated intravascular coagulation = 8, Vit. B12 vitamin deficiency = 5, systemic lupus erythematous-related = 2, and pregnancy complication, malignant hypertension, and renal transplantation-associated = 1 each). The age was median 38.0 (18-63) years in the primary TMA group and 49.5 (20-84) years in the secondary TMA group. Laboratory data of the groups are given in Table I. When clinical findings were analysed, the incidence of fever was not significantly different between the groups, whereas neurologic findings were more frequent in the primary TMA group (51.9% *vs.* 17.9%, $p = 0.008$). No significant difference was found between the groups in terms of blood groups and gender.

When all patients were classified according to ADAMTS 13 activation level, the frequency of ADAMTS activity below 10% was high in the primary TMA group (OR: 118.8, 95% CI: 12.90–1093.39, $p < 0.001$). Patients with ADAMTS13 ratio <10% had high calcium levels and low PLT levels ($p < 0.006$). There was no significant difference in LDH/AST ratios between the two groups (Table II).

When risk scores were compared, the ratio of patients with high plasmic score was high in the primary TMA group (59.3% vs. 32.1%, $p < 0.009$). According to the Bentley score, all secondary TMAs were low risk, while 44% of primary TMAs were moderate and high risk ($p < 0.001$).

Intra-group comparison of 27 patients in the primary TMA group (TTP and complement-mediated TMA) showed female dominance in both diagnoses (F/M ratio 1.6 and 2, respectively). In addition, statistically significant differences were found in platelet, urea, creatinine, sodium, ADAMTS13 activity, and inhibitor levels between the two diseases (Table III). When primary TMA patients were analysed according to the Bentley risk score, among the TTP patients, 10 (47.6%) were in the low-risk group, 8 (38.1%) were in the moderate-risk group, 3 (14.3%) were in the high-risk group and among the atypical hemolytic uremic syndrome patients, 5 (83.3%) were in the low-risk group, and 1 (16.7%) was in the high-risk group. No difference was found between diseases in terms of the frequency of low or high-risk ($p < 0.929$ and $p < 0.335$, respectively).

DISCUSSION

TTP was first described in 1925 and the classical pentad (fever, renal failure, neurological findings, microangiopathic hemolytic anaemia, and thrombocytopenia), which was defined in 1966, was seen in some of the patients.[11-14] Although ADAMTS enzyme activity level is the most important parameter in the diagnosis of primary TMA, the lack of immediate results has led to detailed evaluation of clinical and laboratory parameters and clinical scoring. The diagnosis of primary TMA should be made quickly and treatment should be planned rapidly, otherwise, fatal consequences may occur.

Table I: Data of primary and secondary TMA groups.

	Primary TMA (n = 27)	Secondary TMA (n = 28)	p-value
Age	39,7±13,9	48,0±19,7	0.8[a]
Urea (mg/dL)	50(7-253)	45(17-225)	0.6[b]
Creatinine (mg/dl)	0.9(0.5-9)	0.9(0.5-6.3)	0.6[b]
Total bilirubin (mg/dL)	2.5(0.4-9.4)	1.3(0.1-7.0)	0.003[b]
Indirect bilirubin (mg/dL)	1.7(0.4-8.8)	0.7(0.05-5.5)	0.001[b]
LDH (U/L)	1327±675	949±677	0.04[a]
LDH/AST	28.2(4.4-87.8)	18.0(2.0-119.5)	0.18[b]
Calcium (mg/dL)	8.6±0.6	8.2±0.9	0.4[a]
Sodium (mEq/L)	138.7±3.2	137.9±3.7	0.6[a]
Haemoglobin (g/dl)	8.6(5.9-12.4)	8.5(4.7-16.9)	0.9[b]
MCV (fL)	88.5±6.0	88.8±11.0	0.9[a]
Platelet (10^3/µL)	21400(1000-127000)	43000(15000-131000)	0.05[b]
D-dimer (ng/mL)	2.2(0.5-22.5)	8.0(0.01-20)	0.012[b]
ADAMTS13 activity level (%)	0.5(0-84)	58.2(0.2-85.3)	<0.001[b]
ADAMTS13 inhibitor level (U/mL)	27.9(2.0-90.0)	4.2(2.0-90)	0.019[b]

[a]Independent Sample t-test, [b]Mann Whitney U-test.

Table II: Separation and comparison of groups according to ADAMTS activity level.

	ADAMTS13 Activity level <10	ADAMTS13 Activity level >10	p-value
Female, n (%)	15 (65.2%)	17 (53.1%)	0.3[a]
Male, n (%)	8 (34.8%)	15 (46.9%)	
Age (years)	40.9±12.7	46.1±20.1	0.2[b]
Presence of fever	17.4%	28.1%	0.3[a]
Presence of neurological symptoms/signs, n (%)	13 (56.5%)	6 (18.8%)	0.004[a]
Calcium (mg/dL)	8.7±0.5	8.1±0.8	0.006[b]
Total bilirubin (mg/dL)	2.5 (0.2-9.4)	1.3(0.1-7.0)	0.009[c]
Indirect bilirubin (mg/dL)	1.7 (0.1-8.8)	0.7 (0.05-5.5)	0.004[c]
D-dimer (ng/mL)	2.2 (0.5-22.5)	8.0 (0.01-20)	0.036[c]
Bentley Score			<0.001[d]
Low (n)	55.5 % (15)	100 % (28)	
Moderate and High (n)	44.5% (12)	0 %	
Plasmic Skor			<0.001[d]
Low (n)	3.7 % (1)	35.7% (10)	
Medium (n)	37 % (10)	32.1 % (9)	
High (n)	59.2 % (16)	32.1 % (9)	

[a]Pearson Chi-square. [b]Independent t-test. [c]Mann Whitney U-test. [d]Fisher's exact

Table III: Subgroup analysis of the primary TMA group.

	TTP (n = 21)	Complement-mediated TMA (n = 6)	p-value*
Platelet (10^3/µL)	29430±8407	62333±33193	0.025
Urea (mg/dL)	59.1±11.9	103.5±65.2	0.04
Creatinine (mg/dl)	1.2±0.2	3.6±2.6	0.009
Sodium (mEq/L)	140±0.7	136±1.1	0.01
ADAMTS13 activity level (%)	6.7±5.9	48.5±24.2	0.027
ADAMTS13 inhibitor level (U/mL)	46.3±8.2	16.5±14.4	0.016

**Independent t-test.*

Plasmic and Bentley scores are used to estimate the probability of TTP diagnosis.[15] These scores have been reported to predict the diagnosis of TTP with a high rate.[16,17] In a study by Upadhyay *et al.*, it was stated that the plasmic risk score can prevent unnecessary ADAMTS test requests and that it would be cost-effective to apply plasma exchange therapy only to high-risk patients.[18] In a study in which 117 patients were evaluated, severe ADAMTS deficiency was found in 53% of the patients and sensitivity for high plasmic score was 81.7% and specificity was 71.4%, while sensitivity for moderate-high Bentley score was 59.5% and specificity was 93.9%.[19] In this study, severe ADAMTS13 deficiency was detected in 11 (36%) of 30 patients with low-to-moderate risk plasmic score. Out of the 25 patients with high plasmic score, 16 (64%) were in the primary TMA group. According to Bentley score, the entire secondary TMA group had low risk. A high plasmic score (≥6) predicted severe ADAMTS deficiency with 64% sensitivity, 63% specificity, 59% positive predictive value, and 32% negative predictive value. A moderate-to-high (≥20) Bentley score predicted severe

ADAMTS deficiency with 100% sensitivity, 34.8% specificity, and 40% positive predictive value. This study successfully predicted patients with a high-risk plasmic score as well as moderate-high-risk Bentley score. The authors, therefore, recommend evaluating the two scores together.

Although the D-dimer level is also increased in TTP, it has been shown to increase greatly in disseminated intravascular coagulation.[20] Similarly, D-dimer was found to be high in the secondary TMA group in this study. In the literature, high D-dimer levels in TTP were associated with in-hospital mortality, thromboembolic events, and lack of remission and were defined as a prognostic factor.[21] However, there was no study investigating D-dimer levels in the differentiation of primary and other TMA. The authors believe that further studies are needed on this subject.

In another study, it was emphasised that the plasmic score accompanied by the ratio of LDH to the upper limit of normal would have greater significance.[22] In the present study, LDH levels were statistically significantly higher in the primary TMA group. The present result supports the literature in this aspect.

LDH/AST ratios have been used to differentiate TTP in patients with pregnancy TMA.[22,23] In this study, no significant difference was found between the two groups in LDH/AST ratios. However, further studies are needed to elucidate the relationship between the parameters.

It is also important to distinguish the primary TMA group within itself (such as TTP, complement-associated TMA). Because treatment approach and delays in treatment are of vital importance. There is no large-scale study using these scores, especially in TTP and complement-related TMA. In a case report, it was emphasised that plasmic score would be useful in the differentiation of TTP and complement-related TMA, and that complement inhibitor therapy could be started without delay if it was low-intermediate risk.[24] In this study, it was found that platelet level, creatinine, sodium, and urea values may provide guidance in the differentiation of primary TMAs, but plasmic and Bentley scoring were not useful. The reason that the scoring systems were not significantly predictive may be due to the small sample size and the difference in the sample size between groups. Therefore, studies with a larger patient population are needed to differentiate primary TMA.

CONCLUSION

Treatment of TTP is urgent and can be fatal without timely intervention. It is important to differentiate the condition and ensure the appropriate treatment until the ADAMTS level is determined. In this study, plasmic score and Bentley score as well as LDH and D-dimer levels were helpful in the differentiation of primary and secondary TMA. In the differentiation of primary TMAs, studies with large populations are necessary.

ETHICAL APPROVAL:
The ethical approval for the study was obtained from the Ethics Committee of Medical Faculty (Decision Date: 22.07.2022 and No. 2022/3888) before the study.

PATIENTS' CONSENT:
Not applicable as the data were obtained retrospectively.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
SY: Conception and design, drafting of the manuscript, material preparation, and data collection.
AT: Data analysis.
AT, OC: Guidance and revision of the manuscript.
All the authors have approved the final version of the manuscript to be published.

REFERENCES

1. George JN, Nester CM. Syndromes of thrombotic microangiopathy. *N Eng J Med* 2014; **371(7)**:654-66. doi: 10.1056/NEJMra1312353.
2. Amorosi EL, Ultmann JE. Thrombotic thrombocytopenic purpura report of 16 cases and review of the literature. *Med* 1966; **45(2)**:139-60. doi: 10029532483.
3. Rock GA, Shumak KH, Buskard NA, Blanchette VS, Kelton JG, Nair RC, *et al*. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian apheresis study group. *N Engl J Med* 1991; **325(6)**:393-7. doi: 10.1056/NEJM199108083250604.
4. Saha M, McDaniel JK, Zheng XL. Thrombotic thrombocytopenic purpura: Pathogenesis, diagnosis and potential novel therapeutics. *J Thromb Haemost* 2017; **15(10)**: 1889-1900. doi: 10.1111/jth.13764.
5. Coppo P, Cuker A, George JN. Thrombotic thrombocytopenic purpura: Toward targeted therapy and precision medicine. *Res Pract Thromb Haemost* 2019; **3(1)**:26-37. doi: 10. 1002/rth2.12160.
6. Legendre CM, Licht C, Muus P, Greenbaum LA, Babu S, Bedrosian C, *et al*. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. *N Engl J Med* 2013; **368(23)**:2169-2181. doi: 10.1056/NEJMoa1208981.
7. Fakhouri F, Hourmant M, Campistol JM, Cataland SR, Espinosa M, Gaber AO, *et al*. Terminal complement inhibitor eculizumab in adult patients with atypical hemolytic uremic syndrome: A single-arm, open-label trial. *Am J Kidney Dis* 2016; **68(1)**:84-93. doi: 10.1053/j.ajkd.2015.12.034.
8. Stratmann J, Ward JN, Miesbach W. Evaluation of a rapid turn-over, fully-automated ADAMTS13 activity assay: A method comparison study. *J Thromb Thrombolysis* 2020; **50(3)**:628-631. doi: 10.1007/s11239-020-02086-8.
9. Zheng XL, Vesely SK, Cataland SR, Coppo P, Geldziler B, Iorio A, *et al*. ISTH guidelines for the diagnosis of thrombotic thrombocytopenic purpura. *J Thromb Haemost* 2020; **18(10)**:2486-95. doi: 10.1111/jth.15006.

10. Bendapudi PK, Hurwitz S, Fry A, Marques MB, Waldo SW, Li A, *et al.* Derivation and external validation of the plasmic score for rapid assessment of adults with thrombotic microangiopathies: A cohort study. *Lancet Haematol* 2017; **4(4)**:e157-e64. doi: 10.1016/S2352-3026(17)30026-1.
11. Moschcowitz E. An acute febrile pleiochromic anaemia with hyaline thrombosis of the terminal arterioles and capillaries; an undescribed disease. *Am J Med* 1952; **13(5)**:567-9. doi: 10.1016/0002-9343(52)90022-3.
12. Tekgündüz E, Yılmaz M, Erkurt MA, Kiki I, Kaya AH, Kaynar L, *et al*. A multicenter experience of thrombotic microangiopathies in Turkey: The Turkish hematology research and education group (ThREG)-TMA01 study. *Transfus Apher Sci* 2018; **57(1)**:27-30. doi: 10.1016/j.transci.2018.02.012.
13. Jang MJ, Chong SY, Kim IH, Kim JH, Jung CW, Kim JY, *et al*. Clinical features of severe acquired ADAMTS13 deficiency in thrombotic thrombocytopenic purpura: The Korean TTP registry experience. *Int J Hematol* 2011; **93(2)**:163-9. doi: 10.1007/s12185-011-0771-5.
14. Scully M, Yarranton H, Liesner R, Cavenagh J, Hunt B, Benjamin S, *et al*. Regional UK TTP Registry: Correlation with laboratory ADAMTS 13 analysis and clinical features. *Br J Haematol* 2008; **142(5)**:819-26. doi: 10.1111/j.1365-2141.2008.07276.x.
15. Sakai K, Wada H, Nakatsuka Y, Kubo M, Hayakawa M, Matsumoto M. Characteristics behaviors of coagulation and fibrinolysis markers in acquired thrombotic thrombocytopenic purpura. *J Intensive Care Med* 2021; **36(4)**:436-42. doi: 10.1177/0885066619899637.
16. Li A, Khalighi PR, Wu Q, Garcia DA. External validation of the plasmic score: A clinical prediction tool for thrombotic thrombocytopenic purpura diagnosis and treatment. *J Thromb Haemost* 2018; **16(1)**:164-9. doi: 10.1111/jth.13882.
17. Jajosky R, Floyd M, Thompson T, Shikle J. Validation of the plasmic score at a University Medical Center. *Transfus Apher Sci* 2017; **56(4)**:591-4. doi: 10.1016/j.transci.2017.06.006.
18. Upadhyay VA, Geisler BP, Sun L, Uhl L, Kaufman RM, Stowell C, *et al*. Utilizing a plasmic score-based approach in the management of suspected immune thrombotic thrombocytopenic purpura: A cost minimization analysis within the Harvard TMA Research Collaborative. *Br J Haematol* 2019; **186(3)**:490-8. doi: 10.1111/bjh.15932.
19. Wynick C, Britto J, Sawler D, Parker A, Karkhaneh M, Goodyear MD, *et al*. Validation of the plasmic score for predicting ADAMTS13 activity < 10% in patients with suspected thrombotic thrombocytopenic purpura in Alberta, Canada. *Thromb Res* 2020: **196**:335-9. doi: 10.1016/j.thromres.2020.09.012.
20. Zhao N, Zhou L, Hu X, Sun G, Chen C, Fan C, *et al*. A modified plasmic score including the lactate dehydrogenase/the upper limit of normal ratio more accurately identifies Chinese thrombotic thrombocytopenic purpura patients than the original plasmic score. *J Clin Apher* 2020; **35(2)**:79-85. doi: 10.1002/jca.21760.
21. Wang HX, Han B, Zhao YY, Kou L, Guo LL, Sun TW, *et al*. Serum D-dimer as a potential new biomarker for prognosis in patients with thrombotic thrombocytopenic purpura. *Med* 2020; **99(13)**:19563. doi: 10.1097/MD.0000000000019563.
22. Tang N, Wang X, Li D, Sun Z. Validation of the plasmic score, a clinical prediction tool for thrombotic thrombocytopenic purpura diagnosis, in Chinese patients. *Thromb Res* 2018; **172**: 9-13. doi: 10.1016/j.thromres.2018.10.010.
23. Keiser SD, Boyd KW, Rehberg JF, Elkins S, Owens MY, Sunesara I, *et al*. A high LDH to AST ratio helps to differentiate pregnancy-associated thrombotic thrombocytopenic purpura (TTP) from HELLP syndrome. *J Matern Fetal Neonatal Med* 2012; **25(7)**:1059-63. doi: 10.3109/14767058.2011.619603.
24. Lu E and Moore W. The plasmic score may be useful in the early diagnosis of complement-mediated thrombotic microangiopathy *via* early exclusion of thrombotic thrombocytopenic purpura. *Case Rep Med* 2019; 1-3. doi:10.1155/2019/9180810.