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Mean platelet volume and platelet distribution width in the prediction of treatment response in immune thrombotic thrombocytopenic purpura with severe ADAMTS13 deficiency: a multicenter study

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ABSTRACT

Aims: Lactate dehydrogenase (LDH) and platelet count are routinely used to evaluate response to treatment and discontinuation of treatment in thrombotic thrombocytopenic purpura (TTP). This study aimed to evaluate the mean platelet volume (MPV) and platelet distribution width (PDW) in immune TTP (iTTP) as markers of treatment response.

Methods: This retrospective, multicenter study included patients diagnosed with iTTP with severe ADAMTS13 deficiency. We studied the correlations of MPV and PDW values with platelet count, LDH, total bilirubin hematocrit and mean corpuscular volume, which are used to evaluate the response to total plasma exchange (TPE) or relapse in iTTP. The study variables were recorded at the time of diagnosis, 1st week of TPE treatment, and the time of the last TPE. The correlation analyses were performed between the values before the initial TPE, and after the first week and last TPE.

Results: The study included 28 patients, 20 females with iTTP [median age (minimum-maximum): 45 (23-74) years]. MPV correlated positively with LDH (r=0.533, p=0.002) and negatively with hematocrit (r=-0.445, p=0.002) and platelet count (r=-0.560, p=0.002). PDW also correlated positively with LDH (r=0.339, p=0.008) and negatively with hematocrit (r=-0.244, p=0.032) and platelet count (r=-0.285, p=0.022).

Conclusions: The results showed that MPV and PDW correlated with LDH and platelet count, which are currently used to evaluate the response to treatment in iTTP. Changes in MPV and PDW may serve as a surrogate of treatment response in these patients as an indicator of response to plasmapheresis.

Introduction

Platelets are the main component of blood that plays a role in primary hemostasis; thus, the biological functions of platelets are far beyond hemostasis and thrombosis. They are associated with inflammation, atherosclerosis, autoimmunity, and tumor immunology (1-4). Platelet indices such as mean platelet volume (MPV), plateletcrite (PCT), platelet-large cell ratio (P-LCR), platelet distribution width (PDW), and immature platelet fraction (IPF) are widely used in the investigation of the etiology of thrombocytopenia because of the low cost of the procedure, non-invasiveness, and faster results (4,5).

Genetic and acquired factors such as race, age, smoking status, alcohol consumption, and physical activity can alter platelet count and MPV (5). Platelet size correlates with cell activity and can be assessed using volume indices. Immature/young platelets are released from the bone marrow into the circulation, with a larger size and greater RNA content than mature platelets (6). The release of immature platelets increases when platelet consumption increases, which manifests as a higher MPV and IPF ratio in the whole blood count (7,8). Some platelet indices have been sought as potential indicators of platelet recovery with clinical improvement in patients who undergo bone marrow transplantation, and it was observed that MPV and PCT values decreased after thrombocyte engraftment was achieved (9-11).

In many studies, MPV value was found to decrease in thrombocytopenia that develops due to low production, and on the contrary, it increases in thrombocytopenia that develops due to increased consumption of platelets (6,8). Thrombocytopenia with high MPV is observed in patients with immune thrombocytopenic purpura (iTTP), disseminated intravascular coagulation, sepsis, preeclampsia, thrombocytopenia with low MPV, aplastic anemia, B12 deficiency, and myelodysplastic syndrome (6,12,13).

PDW is a parameter that defines the differences in platelet volume due to increased production and/or platelet activation. It has been reported that the normal reference range for PDW varies between 10-18% in healthy individuals and between 8.3% and 56% in individuals with various diseases (5,14-20). MPV and PDW show a proportional relationship with each other. The distribution of the PDW value in sick people is much above the standard deviation compared with normal individuals. Therefore, it was investigated as a useful parameter in the follow-up of diabetes, coronary artery disease, sickle cell anemia crises, acute cholecystitis, appendicitis, Crohn's disease, and non-malignant tumors (14-20).

Thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy (TMA) caused by the accumulation of ultra-large von Willebrand factor with platelets due to significantly reduced ADAMTS activity. Many patients do not have a distinct TTP clinic until the signs and symptoms of specific organ damage caused by microthrombotic ischemia occur; therefore, many clinicians have difficulty diagnosing TMA/TTP at first admission (21). The first laboratory findings of the disease were thrombocytopenia, Coombs-negative hemolytic anemia, and platelet-rich thrombi in small vessels. During the treatment of patients presenting with microangiopathy, it is desirable to find laboratory parameters that can assist in management and follow-up (21,22).

The fact that platelet indices are cheap and very easy to measure has enabled them useful in research in various fields, such as autoimmune diseases, inflammation, malignancies, and cardiovascular diseases. In microangiopathic hemolytic anemia, including TTP, thrombocytopenia develops through consumption. Changes caused by TTP in platelet parameters in the acute and remission periods and their relationship with the need for plasmapheresis have not been investigated before. The primary purpose of this study was to evaluate the significance of decreases in MPV and PDW to follow the treatment response in iTTP.

Methods

Study type and patients

This was a retrospective, multicenter study that included patients diagnosed with iTTP by three different hematology units and underwent total plasma exchange (TPE) between January 2011 and June 2020. Patients with congenital TTP, secondary TTP, pregnancy, missing data or who died within 1 week after the initiation of treatment were excluded.

This study was approved by the Etlik Zübeyde Hanım Training and Research Hospital Ethics Committee (decision no: 2021/9, date: 13.01.2021).

Data collection

Hospital records and patient files were screened in all centers. MPV and PDW measurements and other laboratory results were recorded before the first TPE and after the 1st week and last TPE separately. PDW and MPV were measured using a fully automated analyzer (Sysmex automated hematology analyzer) at all centers. Platelet counts, hemoglobin, hematocrit, mean corpuscular volume (MCV), lactate dehydrogenase (LDH), and total/indirect bilirubin were also recorded.

ADAMTS13 activity and ADAMTS13 antibody measurements were performed before the first TPE in all centers. ADAMT13 activities were <10% and ADAMT13 antibodies were positive (≥15 U/mL) in all patients.

TPE protocol

All patients received TPE with a preliminary clinical diagnosis of TTP without waiting for the ADAMTS13 activity test result. TPE procedures were performed using Fresenius COM. TEC and/or Spectra Optia apheresis systems at all centers. Following the

same protocol, daily TPE was continued with 1-2 volumes until the platelet count exceeded 150,000/mm^3 for 2 consecutive days and the LDH level returned to the normal range. Fresh frozen plasma specific to the ABO type was used as the replacement fluid in all procedures. The frequency of TPE was reduced and completed according to the response.

Statistical Analysis

Statistical analyses were performed using R 3.5.0 (R Core Team, 2018) software. Because TTP is very rare, a sufficient sample size could not be reached. Previous literature has reported that parametric tests lose their strength, and permutation tests produce more reliable results in small sample sizes and under assumptions that cannot be provided (23,24). Therefore, we used permutation test equivalents instead of the t-test for dual or multiple comparisons of continuous and categorical variables. Correlation coefficients between MPV and PDW values and platelet count, LDH, total bilirubin, hemoglobin/hematocrit, and MCV were also calculated using permutation tests. The type 1 error rate was accepted as alpha 0.05.

Results

Clinical and laboratory features

We identified 30 patients (20 females and 10 males; median age 45 years; range, 23 to 74 years). Two patients were excluded because of early death. Therefore, 28 patients had available data at the time of diagnosis, after the 7th TPE, and after the last TPE (Table 1). ADAMTS13 activity was below 5% [mean 0.2% (0-5)] and ADAMTS13 antibodies were positive [mean 56 U/mL (26.9-90)] in the whole sample. Neurological symptoms, fever, renal involvement, and cardiac involvement were observed in 16 (57.1%), 14 (50.0%), 6 (21.4%), and 3 (10.7%) patients, respectively.

The mean response time of the patients to TPE was 9 (4-23) days, and 21.7% (n=5) of the patients responded in the first week. The mean number of TPEs was 21.5 and the mean length of hospital stay was 28.5 days. All patients were administered standard oral prednisone (1 mg/kg/day) because of ADAMTS13 antibody positivity. Intravenous methylprednisolone 500/1000 mg/day for three days was administered to 2 patients with serious neurological involvement. Thirteen (46.4%) patients received weekly rituximab (375 mg/m^2) for 4 consecutive weeks. Of the patients who received rituximab, 5 relapsed and 8 showed exacerbation under TPE treatment. Other therapeutic approaches were recorded much less and only 2 patients received vincristine treatment before rituximab, but rituximab was also added to these patients' treatment because of insufficient response. The median follow-up period was 48.5 months.

Correlations between MPV and PDW values and laboratory variables

MPV showed a positive correlation with LDH, total bilirubin, and indirect bilirubin reduction during the treatment. In addition, MPV reduction negatively correlated with increases in hemoglobin/hematocrit and platelet counts. There was a positive correlation between MPV and PDW, but it did not reach statistical significance. There was no correlation between MPV and MCV.

There was a positive correlation between the decrease in PDW and LDH and a negative correlation between hemoglobin/hematocrit and platelet count (Table 2). The changes in MPV and PDW values by week are shown in Figures 1 and 2.

Because the mean MPV of the patients at the time of diagnosis was within normal limits, no cut-off value could be established for the diagnosis of the disease. We observed that the decrease in MPV during treatment in patients who benefited from the treatment according to the baseline value was significant and correlated with other response parameters. Similarly, the mean PDW value was above the normal limits even when the treatment was completed, and we determined that the decrease in the PDW value was a correlation of response to the treatment.

Table 1. The laboratory results of patients; at the time of diagnosis, after the 7th and last TPE

Variable*	At the time of diagnosis	After 7th TPE	After last TPE
Hb (gr/dL)	8.55 (5.3-12.8)	9.8 (7.6-12.6)	11.5 (8.6-15.7)
Hct (%)	24.75 (15.5-35.1)	29.1 (22.9-36.8)	33.9 (25.1-46.3)
MCV (fL)	88 (76.6-129.3)	92.3 (82-103.2)	92.2 (83.9-104)
LDH (U/L)	1103 (311-3200)	354 (177-945)	197.5 (150-374)
Plt (/mm^3)	11000 (3000-74000)	107500 (10000-463000)	304500 (195000-604000)
Total bilirubin (mg/dL)	2.7 (1.2-5.2)	1.3 (0.2-7.9)	0.7 (0.2-1.4)
Indirect bilirubin (mg/dL)	2.2 (0.4-4.6)	0.9 (0.1-2.9)	0.3 (0.1-0.8)
MPV (fL)	10.4 (7.3-14.6)	8.8 (6.1-12.8)	7.9 (5.9-11.4)
PDW (%)	21.9 (15.2-44)	17.5 (12.6-40)	16.1 (10-36)

*Data are presented as median (minimum-maximum).
TPE: Total plasma exchange, Hb: Hemoglobin, Hct: Hematocrit, MCV: Mean corpuscular volume, LDH: Lactate dehydrogenase, Plt: Platelet, MPV: Mean platelet volume, PDW: Platelet distribution width

Table 2. Correlation matrix of MPV and PDW

	MPV	PDW	Hct	MCV	PLT	LDH	Total bilirubin
MPV	1.000						
PDW	0.082 p=0.494	1.000					
Hct	-0.455 **p=0.002**	-0.244 **p=0.032**	1.000				
MCV	0.066 p=0.538	-0.148 p=0.204	0.019 p=0.898	1.000			
Plt	-0.560 **p=0.002**	-0.285 **p=0.022**	0.633 **p=0.002**	0.176 p=0.096	1.000		
LDH	0.533 **p=0.002**	0.339 **p=0.008**	-0.563 **p=0.002**	0.036 p=0.65	-0.587 **p=0.002**	1.000	
Total bilirubin	0.462 **p=0.002**	0.242 p=0.064	-0.514 **p=0.002**	-0.283 **p=0.008**	-0.626 **p=0.002**	0.622 **p=0.002**	1.000

MPV: Mean platelet volume, PDW: Platelet distribution width, Hct: Hematocrit, MCV: Mean corpuscular volume, Plt: Platelet, LDH: Lactate dehydrogenase

Discussion

Studies have claimed that platelet indices such as MPV and PDW can be used for discriminating hyperdestructive thrombocytopenia from hypoproductive thrombocytopenia, and they are sensitive and specific for their diagnostic predictive value. In these studies, MPV and PDW values were higher in hyperdestructive thrombocytopenias such as TTP than in hypodestructive thrombocytopenia (7,25,26). However, there is no study on MPV and/or PDW alteration due to TTP treatment. Platelet counts have been routinely used as laboratory variables with LDH to monitor clinical responses to TTP therapy; however, MPV and PDW may be more specific objective measurements to define the clinical outcomes in TTP. To the best of our knowledge, this is the first study that investigated the change in MPV and PDW in the follow-up of TPE response in patients with severe ADAMTS13 deficiency. We found that MPV and PDW were high in iTTP patients at the beginning of treatment and decreased in correlation with the response to TPE. We also found that the decrease in MPV and PDW negatively correlated with platelet count and positively correlated with LDH. In some of our cases, we observed an increase in MPV and/or PDW one or two days before the decrease in platelet count in relapses or exacerbations. However, because there were a few patients, we were unable to reach a firm conclusion in this regard.

The two main causes of thrombocytopenia in TTP are increased destruction or peripheral consumption. A decrease in platelet production is not an expected situation in TTP, except for several bone marrow diseases that can lead to secondary TTP, such as bone marrow transplantation or tumor infiltration. Immature platelets which are newly synthesized in the bone marrow are larger than the reticulocytes. They contain higher amounts of cytoplasmic RNA, and as they age, their RNA content

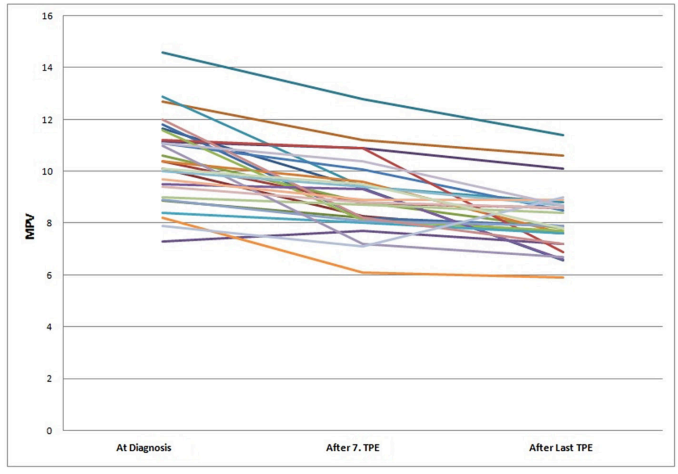

Figure 1. The change of MPV values by weeks
MPV: Mean platelet volume, TPE: Total plasma exchange

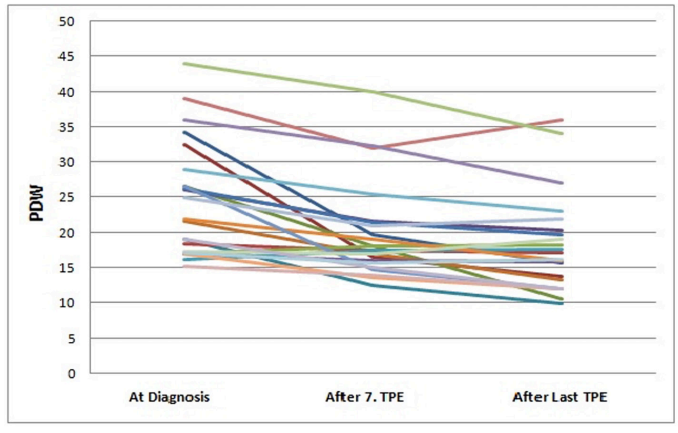

Figure 2. The change of PDW values by weeks
PDW: Platelet distribution width, TPE: Total plasma exchange

and size decrease. From this point, theoretically, in the recovery period, bone marrow platelet production reduces due to the decrease in disease activity in patients with TTP, accompanied by lower MPV and PDW. As it is known in TTP patients, a platelet count of 150,000/mm^3 is a criterion of response and termination of TPE treatment. This study was designed to determine whether MPV and PDW values that indicate an indirect reduction of platelet destruction could be a predictor of treatment response or an indication of early relapse and exacerbation.

Although some studies suggested cut-off values for MPV and PDW in hyperdestructive thrombocytopenias and others, their sensitivity and specificity are low (7,25,27). Previous studies also showed a statistically significant difference in MPV, PDW, and P-LCR according to race/skin color. This situation supports the idea that following up the level of MPV and PDW in the treatment process will be more valuable than determining a limit value for these in TTP patients, as in our study (26,28).

The other platelet parameters that can be measured with a fully automated hematology analyzer are P-LCR and absolute immature platelet count (A-IPC). MPV, PCT, and PDW are more frequently available parameters, and A-IPC and IPF measurements cannot be routinely performed with the automatic hematology analyzer used by all three centers. In previous studies, these platelet parameters were usually evaluated for the differentiation of immune thrombocytopenia from healthy participants or diseases in which the bone marrow production of platelets decreased (7). However, no study has examined the change in MPV and PDW in the treatment process of TTP patients and its relationship with other parameters such as platelet count and LDH level used in response to treatment. In a case report, Kier et al. (29) suggested that IPF can be used to follow the efficacy and response to treatment modalities in TMA hemolytic anemia. Additionally, Zheng et al. (30) reported that A-IPC could be useful in the prediction of clinical response in idiopathic TTP patients and serves as a potential indicator for TPE cessation.

The only study that examined A-IPC in the diagnosis and monitoring of the clinical course of TTP was performed by Hong et al. (31) who found that all iTTP patients had significantly increased IPF and decreased A-IPC and platelet count at presentation. During follow-up, their patients with TTP who responded to TPE showed a decrease in IPF in correlation with an increase in the number of platelets. Their study included 12 patients with iTTP, routine measurement of ADAMTS13 antigen during treatment, and assessment of correlations between IPF and ADAMTS13 antigen levels. They found that A-IPC positively correlated with ADAMTS13 activity at presentation but negatively correlated with ADAMTS13 activity during recovery. Another study (32) found that PDW, MPV, and P-LCR in children with iTTP were significantly higher, and, as in our study, they found that after the treatment, PLT and PCT gradually increased while PDW, MPV, and P-LCR gradually decreased.

Study Limitations

This study has several limitations. First, MPV and/or PDW could not be studied in some periods because of the change in automated hematology analyzers in the three participating centers, leading to a decrease in the number of patients included. Second, the daily change in MPV and PDW in patients with relapse or exacerbation and their relationships with platelet count could not be demonstrated due to insufficient data.

Conclusion

In conclusion**,** MPV and PDW are easily accessible, non-invasive tests of thrombopoiesis that can be used to monitor disease improvement and treatment responses of iTTP. The decrease in MPV and PDW values during treatment is an indicator of the response to plasmapheresis. They also correlate with the number of platelets and LDH levels, which are used in treatment response. Prospective clinical trials on the correlation of platelet parameters such as PCT, PDW, MPV, P-LCR, and A-IPC with disease progression and remission in patients with TTP are warranted.

Ethics

Ethics Committee Approval: This study was approved by the Etlik Zübeyde Hanım Training and Research Hospital Ethics Committee (decision no: 2021/9, date: 13.01.2021).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: S.S., M.Y., A.K.G., M.R.A., M.A., G.Ö., M.A., Concept: S.S., M.Y., Design: S.S., M.Y., M.A., G.Ö., M.A., Data Collection or Processing: M.Y., A.K.G., M.R.A., Analysis or Interpretation: E.Ş.Y., Literature Search: S.S., M.Y., Writing: S.S., M.Y.

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