PREDICTIVE SIGNIFICANCE OF MEAN PLATELET VOLUME AND PLATELET DİSTRİBUTİON WİDTH LEVEL IN IMMUNE THROMBOCYTOPENIA PATIENTS TREATED WITH STEROIDS

Ahmet Kaya
Inonu University, Turgut Ozal Medical Center, Department of Hematology, Malatya, Turkey
İrfan Kuku
Inonu University, Turgut Ozal Medical Center, Department of Hematology, Malatya, Turkey
Mehmet Ali Erkurt
Inonu University, Turgut Ozal Medical Center, Department of Hematology, Malatya, Turkey
Emin Kaya
Inonu University, Turgut Ozal Medical Center, Department of Hematology, Malatya, Turkey
İlhami Berber
Inonu University, Turgut Ozal Medical Center, Department of Hematology, Malatya, Turkey
Ahmet Sarıcı
Inonu University, Turgut Ozal Medical Center, Department of Hematology, Malatya, Turkey
Soykan Biçim
Inonu University, Turgut Ozal Medical Center, Department of Hematology, Malatya, Turkey
Emine Hidayet
Inonu University, Turgut Ozal Medical Center, Department of Hematology, Malatya, Turkey
Fatma Hilal YAĞIN
Inonu University, Faculty of Medicine, Department of Biostatistics and Medical Informatics, Malatya, Turkey
Ayşe Uysal
Fırat University, Faculty of Medicine, Department of Hematology, Malatya, Turkey
Corresponding author:

Mehmet Ali Erkurt
Inonu University, Turgut Ozal Medical Center, Department of Hematology, Malatya, Turkey

ABSTRACT:

Background: Immune thrombocytopenia is an acquired thrombocytopenia caused by autoantibodies against platelet antigens. Immune thrombocytopenia is usually observed more common in famale. Many patients with Immune thrombocytopenia are asymptomatic. Those with symptoms are primarily related to thrombocytopenia and bleeding, but patients may also

experience fatigue and reduced quality of life. The purpose of treatment in an Immune thrombocytopenia patient is not to normalize the platelet count, but to treat or prevent bleeding. For this purpose, steroids are an important part of the treatment in the first place. In our study, pretreatment hemogram parameters, especially Mean Corpuscular Volume and platelet distribution width values, were investigated in patients with immune thrombocytopenia, whether they were predictive values for immune thrombocytopenia.

Materials and Methods: Hemogram parameters of 222 Immune thrombocytopenia patients who received steroids as first line therapy were retrospectively scanned.

Result: A statistically significant difference was determined between the first and last measurements in terms of hemoglobin, mean corpuscular volüme, white blood cell, neutrophil and platelet variables. There is an increase in hemoglobin, mean corpuscular volüme, white blood cell, neutrophil and platelet values after the procedure (ie at the last measurement) compared to the first measurement. It can be said that there is a very high level of positive correlation between neutrophil and white blood cell. After the treatment a negative correlation was detected between platelet value and mean platelet volüme, platelet distribution width values. According to the results of the correlation analysis before the treatment, a positive corr elation was found between the platelet value and the mean platelet volüme value. While there is a positive correlation between platelet and mean platelet volüme values before the treatment, it is seen that there is a negative correlation between these values after the treatment

Conclusion: It has been concluded that mean platelet volüme and platelet distribution width values cannot be used as a predictive value in the response of disease before steroid treatment in Immune thrombocytopenia patients.

KEY WORDS: Steroid treated, immune thrombocytopenıa, Hemogram platelet parameters

INTRODUCTION:

Immune thrombocytopenia (ITP), also called idiopathic thrombocytopenic purpura, immune thrombocytopenic purpura (1). It is an acquired thrombocytopenia caused by autoantibodies against platelet antigens (2). It is one of the common causes of asymptomatic

thrombocytopenia in adults (3). The lack of a sensitive or specific diagnostic test for ITP and the many other potential causes of thrombocytopenia that may be missed (eg, drug-induced thrombocytopenia, hereditary thrombocytopenia) contribute to the difficulties in diagnosing ITP (4). Other common causes of thrombocytopenia include drug-induced thrombocytopenia, chronic liver disease, hypersplenism, and temporary decreases in platelet count due to bone marrow suppression or an infection. Hereditary thrombocytopenias are less common, may be mistakenly diagnosed as ITP when first identified in adulthood (5). ITP usually occurs in healthy women, and many have their platelet count first noticed during pregnancy (6). Severe ITP refers to ITP with bleeding symptoms sufficient to require treatment; this typically occurs when the platelet count is below 20,000/ microliter (7). The pathogenesis of ITP is not fully understood. The reduced platelet lifespan due to antibody-mediated destruction is the dominant hypothesis. The basic mechanism is thought to involve specific autoantibodies directed against platelet membrane glycoproteins such as IgG against GPIIb/IIIa by the patient's B cells (8,9). Some patients with ITP may have triggering events. Genetic and acquired factors may contribute it (10). Changes in immune homeostasis can lead to a loss of peripheral tolerance and promote the development of self-reactive antibodies (11). With the widespread use of routine complete blood counts, the incidence of ITP is about 1 to 6 per 100,000 adults per year, but has increased to as much as 10 per 100,000 in recent studies (12). Many patients with ITP are asymptomatic. Those with symptoms are primarily related to thrombocytopenia and bleeding, but patients may also experience fatigue and reduced quality of life. Bleeding due to thrombocytopenia may occur in two-thirds of patients. Typically, bleeding occurs on the skin or mucous membranes, more often it is insidious, although sometimes it can be sudden (13). Diagnostic evaluation in ITP is a diagnosis of exclusion made in patients with isolated thrombocytopenia (ie without anemia or leukopenia). Therefore, important components of diagnostic evaluation include excluding other possible causes of thrombocytopenia and identifying secondary causes of thrombocytopenia (11). Differential diagnosis of ITP includes various inherited and acquired conditions. Drug-induced thrombocytopenia can cause thrombocytopenia by various non-immune mechanisms, including various infections, bone marrow suppression, hypersplenism, and platelet depletion. Liver disease and/or other causes of hypersplenism often cause mild thrombocytopenia by accumulation of platelets in the spleen. Microangiopathic processes include hereditary and acquired conditions associated with extensive microvascular coagulation and/or thrombosis. There are mild clinical phenotypes of various hereditary thrombocytopenia and they occur only in the case of a hemostatic problem in adulthood or during routine platelet counting. Like

ITP, these disorders may be characterized by mild clinical bleeding or isolated thrombocytopenia. Unlike ITP, these conditions may have morphological abnormalities of platelets in the peripheral blood smear. Examples include giant platelets (the size of red blood cells) in May Hegglin anomaly or Bernard Soulier syndrome, or absence of platelet granules in gray platelet syndrome (14). The goal of treatment in the ITP patient is to treat or prevent bleeding, not to normalize the platelet number. For this purpose, steroids are an important part of first line therapy. Patients with a platelet count ≥ 30,000/ microliter per microliter without bleeding can be monitored without medical treatment with certain periods (15). The use of platelet transfusion is recommended in all patients with critical bleeding causing hemodynamic or respiratory failure. Glucocorticoids plus intravenous immunoglobulin constitute medical therapy in patients with bleeding (16). Plus dexamethasone produces a faster effect. The typical dose is 40 mg orally or intravenously once a day for four days. Plus methylprednisolone is typically administered intravenously at 1 g once a day for three days. The dose of prednisone is 1 mg/kg orally once a day for one to two weeks. IVIG is 1 g/kg per day for one or two days. Anti-D immunoglobulin can be used as an alternative in RhD positive patients. However, many clinicians hesitate to use it because of the risk of serious hemolytic transfusion reactions (17). For some patients, glucocorticoids or IVIG do not produce a stable, safe platelet number. If the platelet count does not increase within a few days, it is necessary to reassess the diagnosis. If ITP is strongly suspected, the add of a thrombopoietin receptor agonist is recommended. Other options for second line therapy include rituximab, splenectomy, and various immunosuppressive agents. Since spontaneous remission may occur in the first year in some people, it is usually necessary to postpone splenectomy until at least a year has elapsed (17).

MATERIALS AND METHODS:

Our study was approve by the İnönü University Ethics Committee with the number 2021/2727. Electronic files in the system of patients hospitalized in the adult hematology clinic of İnönü University Turgut Özal Medical Center between January 2009 and December 2021 were analyzed retrospectively. Patients over 18 years of age with thrombocytopenia and diagnosed with clinical, laboratory and bone marrow biopsy (if necessary) ITP were included

in our study. Patients who were started on 1 mg/kg/day prednisolone or 40 mg/day dexamethasone for four days were included in the study. Patients with a thrombocyte count over 30,000/ microliter after steroid therapy are included in the study, thinking to be responsible to steroid therapy Hemoglobin(HGB), Mean Corpuscular Volüme(MCV), White Blood Cell(WBC), Neutrophıl(NE), Platelet(PLT), Platelet Distribution Width(PDW), Mean Platelet Volume(MPV) values of hemogram parameters before and after treatment were recorded.

Data analysis

Normally distributed data were summarized as mean ± standard deviation and non-normally distributed data were summarized as median (minimum-maximum). Paired Samples t-test and Wilcoxon test were used where appropriate for statistical analysis. Spearman's rank correlation coefficient for the last measurements was calculated for the correlation analysis in which the relationship between variables was examined. $p < 0.05$ was considered statistically significant. IBM SPSS Statistics 26.0 program was used in the analysis.

RESULT:

Table 1: Demographic distribution of patients

	n	%	Mean ± SD.

GENDER	Male	79	35.6	-
	Female	143	64.4	-
AGE				50.84 ± 17.46

SD: Standard deviation

According to Table 1; 79 (35.6%) of the patients were male and 143 (64.4%) were female. The mean age of the patients was calculated as 50,84.

Table 2: Comparison of the first and last measurements of blood parameters

Variables	first		last		effect size	p value
	Mean ± SD	Median (Min-Max)	Mean ± SD	Median (Min-Max)		
HGB	-	13.25(4.6-18.7)	-	13.5(6.9-18.1)	12.059	0.004**
MCV	-	85.4(49.3-114.5)	-	86(8.9-112)	12.058	0.033**
WBC	-	8.2(2.27-27.3)	-	12.2(1.4-29.9)	12.074	0.0001**
NE	-	5.2(0-52)	-	9.25(0.51-26.2)	12.073	0.0001**
PLT	-	17(2-338)	-	89(3-560)	12.078	0.0001**
PDW	-	16.7(0-78.7)	-	16.6(0-21.8)	-	0.655*
MPV	10.074±2.053	-	9.865±1.904	-	-	0.091*

Abbreviations: HGB: Hemoglobin, MCV: Mean Corpuscular Volüme, WBC: White Blood Cell, NE: Neutrophıl, PLT: Platelet, PDW: Platelet Distribution Width, MPV: Mean Platelet Volume

According to the results in Table 2; a statistically significant difference was found between the first and last measurements in terms of HGB. MCV. WBC. NE and PLT variables. HGB. MCV. WBC. NE and PLT values increased after the procedure (ie at the last measurement) compared to the first measurement. Paired Samples t test and Wilcoxon test were used for statistical analysis of the table2.

Table 3: Correlation coefficients between blood values for last measurements

Abbreviations: HGB: Hemoglobin, MCV: Mean Corpuscular Volüme, WBC: White Blood Cell, NE: Neutrophıl, PLT: Platelet, PDW: Platelet Distribution Width, MPV: Mean Platelet Volume

Variables	Statistics	HGB_ last	MCV_ last	WBC_ last	NE_ last	PLT_ last	MPV_ last	PDW_ last
HGB_last	**ρ**	1.000	**0.135**	**0.254**	**0.223**	0.081	-0.031	-0.056
	p value	-	**0.044**	**0.0001**	**0.001**	0.232	0.645	0.406
MCV_ last	**ρ**	**0.135**	1.000	-0.084	-0.086	-0.012	-0.058	-0.020
	p value	**0.044**	-	0.212	0.200	0.863	0.387	0.763
WBC_ last	**ρ**	**0.254**	-0.084	1.000	**0.919**	**0.199**	-0.089	0.052
	p value	**0.0001**	0.212	-	**0.0001**	**0.003**	0.185	0.442
NE_ last	**ρ**	**0.223**	-0.086	**0.919****	1.000	0.105	-0.071	0.039
	p value	**0.001**	0.200	**0.0001**	-	0.119	0.290	0.561
PLT_ last	**ρ**	0.081	-0.012	**0.199****	0.105	1.000	**-0.275**	**-0.156**
	p value	0.232	0.863	**0.003**	0.119	-	**0.0001**	**0.020**
MPV_ last	**ρ**	-0.031	-0.058	-0.089	-0.071	**-0.275**	1.000	**-0.169**
	p value	0.645	0.387	0.185	0.290	**0.0001**	-	**0.012**
PDW_ last	**ρ**	-0.056	-0.020	0.052	0.039	**-0.156***	**-0.169***	1.000
	p value	0.406	0.763	0.442	0.561	**0.020**	**0.012**	-

According to Table 3; it can be said that there is a very high level of positive correlation between NE and WBC. In other words, WBC value increases as NE increases or WBC value decreases as NE decreases.

There was a negative correlation between PLT value and MPV, PDW values after treatment. In other words, we can say that as the PLT value increases after the treatment, the MPV and PDW values decrease, or the MPV and PDW values increase as the PLT value decreases. Spearman's rank correlation coefficient were used for statistical analysis of the table 3.

Table 4: Correlation coefficients of the first and last measurements

Variables	Statistics	MPV_first	PDW_first	PLT_last
MPV_first	**ρ**	1.000	-0.051	0.104
	p value	-	0.449	0.122
PDW_first	**ρ**	-0.051	1.000	0.011
	p value	0.449	-	0.873
PLT_last	**ρ**	0.104	0.011	1.000
	p value	0.122	0.873	-

Abbreviations: PLT: Platelet, PDW: Platelet Distribution Width, MPV: Mean Platelet Volume

According to Table 4; there was no correlation between the MPV, PDW values before the treatment and the PLT value after the treatment. Spearman's rank correlation coefficient were used for statistical analysis of the table 4.

Table 5. Correlation coefficients between blood values for first measurements

Variables	Statistics	HGB	MCV	WBC	NE	PLT	MPV	PDW

HGB	**ρ**	1.000	0.118	**0.326****	**0.248****	0.062	0.030	0.093
	p value	-	0.078	**0.0001**	**0.0001**	0.358	0.654	0.166
MCV	**ρ**	0.118	1.000	-0.106	-0.130	0.064	0.040	**0.135***
	p value	0.078	-	0.115	0.054	0.339	0.554	**0.044**
WBC	**ρ**	**0.326****	-0.106	1.000	**0.883****	-0.010	-0.054	**0.169***
	p value	**0.0001**	0.115	-	**0.0001**	0.882	0.420	**0.011**
NE	**ρ**	**0.248****	-0.130	**0.883****	1.000	-0.032	-0.047	**0.153***
	p value	**0.0001**	0.054	**0.0001**	-	0.637	0.488	**0.022**
PLT	**ρ**	0.062	0.064	-0.010	-0.032	1.000	**0.276****	0.043
	p value	0.358	0.339	0.882	0.637	-	**0.0001**	0.526
MPV	**ρ**	0.030	0.040	-0.054	-0.047	**0.276****	1.000	-0.051
	p value	0.654	0.554	0.420	0.488	**0.0001**	-	0.449
PDW	**ρ**	0.093	**0.135***	**0.169***	**0.153***	0.043	-0.051	1.000
	p value	0.166	**0.044**	**0.011**	**0.022**	0.526	0.449	-

Abbreviations: HGB: Hemoglobin, MCV: Mean Corpuscular Volüme, WBC: White Blood Cell, NE: Neutrophıl, PLT: Platelet, PDW: Platelet Distribution Width, MPV: Mean Platelet Volume

According to Table 5; The correlation analysis before the treatment, a positive correlation was found between the PLT value and the MPV value. it can be said that as the PLT value increases, the MPV value also increases. (or against, as the PLT drops, so does the MPV.)

In addition, according to the pre- and post-treatment correlation analysis; While there is a positive correlation between PLT and MPV values before the treatment, it is seen that there is a negative correlation between these values after the treatment. Spearman's rank correlation coefficient were used for statistical analysis of the table 5.

DISCUSSIONS:

Immune thrombocytopenia (ITP) is an acquired thrombocytopenia caused by autoantibodies against platelet antigens. The lack of a sensitive or specific diagnostic test for ITP and the many other potential causes of thrombocytopenia make it difficult to diagnose it. ITP is generally more common in healthy women. The pathogenesis of ITP is not fully understood. Decreased platelet lifespan due to antibody-mediated destruction is the dominant hypothesis. Many patients with ITP are asymptomatic. Those with symptoms are primarily related to thrombocytopenia and bleeding, but patients may also experience fatigue and reduced quality of life. The goal of treatment in the ITP patient is to treat or prevent bleeding, not to normalize the platelet number. For this purpose, steroids are an important part of first line therapy. The first line steroid used in the treatment of ITP may cause dose dependent effects on the hematological system (18). The effects of glucocorticoids are mediated by cytosolic glucocorticoid receptors and result from both genomic and non-genomic mechanisms that also play a role in the therapeutic effects of these agents. Genetic polymorphisms in the glucocorticoid receptor and glucocorticoid metabolism may explain the heterogeneity in observed glucocorticoid toxicities (19). Steroids decrease the rate of leukocytes in hemogram parameters, but increase the neutrophil and platelet level. Pharmacological doses of glucocorticoids usually result in increased leukocytosis mainly due to an increase in neutrophils. This phenomenon is due to the circulation of neutrophils adhering to the endothelium (20). In our study, an increase in the number of neutrophils and leukocytes was detected in accordance with the literature. If table 2 is examined, an increase in neutrophils and WBC will be seen after steroids. The size and size distribution of the cells is affected because of natural result of change hemogram cells. Steroids increase platelet levels. Increasing platelet levels result in a decrease at cell size (21). If we look at table-3 in our study, it will be seen that the platelet level has decreased in the last measurements. In our study, there was an increase in white blood cell (WBC) and neutrophil ratios in consistent with the literature, and this increase was statistically significant. FH Gardner and JD Bessman found in their studies that mean platelet volume and PDW were high in ITP (22). Looking at table 5, it is seen that there is a positive correlation between PLT and MPV before steroid treatment in ITP. It was inconsistent with FH Gardner's study. This may be because the patients received platelet apheresis during the treatment process. Table 3 a positive correlation was observed between PLT value and MPV and PDW, supporting the FH Gardner's study. As FH Gardner's study mentioned, the relationship between platelet count and MPV and PDW is the result of megakaryocyte proliferation and platelet production. Decrease in platelet destruction and a consequent increase in platelet count are expected in ITP patients who

develop remission after steroid use. Our study did not support this prediction. There is an increase in HGB values after steroid treatment.Such hematological side effects of glucocorticoids are not mentioned at the studies in the literatüre(23). In our study, increase in HGB was observed after steroids, and this increase was found to be compatible with the literature. It was detected that there was a negative correlation between PLT value and MPV and PDW values after treatment while a positive correlation before treatment. It was thought that it might be secondary to the immunosuppressive effects of steroids. Inhibition of possible antibody-mediated platelet destruction in ITP patients may have reduced peripheral outflow of new platelets in the bone marrow. As a result of the dominance of older platelets instead of younger platelets in the peripheral circulation, it results in a decrease in the value of MCV and a decrease in the value of PDW, which is its peripheral reflection. When the MPV and PDW values before the treatment and the PLT values after the treatment were examined, no correlation was found between the MPV and PDW values and the PLT values. Therefore, before the study it was thought that remission would occur in the ITP patient with steroid treatment, and that as a result of this remission, the output of platelet cells with a greater MPV value from the bone marrow would decrease and, in parallel, the PDW value would increase. However, this hypothesis, which was created before the study, is not supported by the study data. It is thought that MPV and PDW values cannot be used as a predictive value in terms of the response of the disease to steroids before steroid treatment in ITP patients. Statistically significant difference was found between the first and last measurements in terms of HGB, MCV, WBC, NE and PLT variables

CONCLUSION:

In the light of the available data in the study, it was concluded that MPV and PDW values in ITP patients could not be used as a predictive value in the response of disease before steroid treatment. It is thought that MPV and PDW values are not useful parameters in predicting treatment in ITP patients. Comprehensive studies with more cases are needed to clarify the relationship between hemogram parameters and ITP treatment. studies with larger data is needed for MPV and PDW values predictive marker use in ITP patient.

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