Original Research Article

PREDICTIVE SIGNIFICANCE OF MPV AND PDW LEVEL IN IMMUNE THROMBOCYTOPENIA PATIENTS TREATED WITH STEROIDS

ABSTRACT:

Background: Immune thrombocytopenia (ITP) is an acquired thrombocytopenia caused by autoantibodies against platelet antigens. ITP is usually observed more common in healthy women. 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 purpose of treatment in an ITP 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. Patients with a platelet count ≥ 30,000 per microliter without bleeding can be monitored without medical treatment with certain periods. In our study, it was aimed to determine whether pre-treatment hemogram parameters, especially MPV and PDW values, are predictive values for the disease in patients with immune thrombocytopenia

Materials and Methods: Hemogram parameters of 222 ITP patients who received steroids as first-line therapy were retrospectively scanned. Statistical analyzes were performed using Paired Samples t test, Wilcoxon test, Spearman's rank correlation coefficient tests in IBM SPSS Statistics 26.0 program.

Result: A statistically significant difference was determined between the first and last measurements in terms of HGB, MCV, WBC, NE and PLT variables. There is an increase in HGB, MCV, WBC, NE and PLT 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 NE and WBC. After the treatment a negative correlation was detected

between PLT value and MPV, PDW values. According to the results of the correlation analysis before the treatment, a positive correlation was found between the PLT value and the MPV value. 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

Conclusion: It has been concluded that MPV and PDW values cannot be used as a predictive value in the response of disease before steroid treatment in ITP patients.

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

INTRODUCTION:

Immune thrombocytopenia (ITP), also called idiopathic thrombocytopenic purpura, immune thrombocytopenic purpura. It is an acquired thrombocytopenia caused by autoantibodies against platelet antigens. It is one of the common causes of asymptomatic thrombocytopenia in adults. 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. 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. ITP usually occurs in healthy women, and many have their platelet count first noticed during pregnancy. Time elapsed since diagnosis, New diagnosis of ITP (Up to three months from diagnosis), persistent (three to 12 months from diagnosis), permanent (Three to 12 months from diagnosis) or chronic (more than 12 months since diagnosis). Severe ITP refers to ITP with bleeding symptoms sufficient to require treatment; this typically occurs when the platelet count is below 20,000/microL(1). 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 (2,3). Some patients with ITP may have triggering

events. Genetic and acquired factors may contribute it (4). Changes in immune homeostasis can lead to a loss of peripheral tolerance and promote the development of self-reactive antibodies (5). 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 (6). 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 (7). 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 (5). 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 (8). 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 per microliter without bleeding can be monitored without medical treatment with certain periods (9). 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 (10). 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. (11). 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 (11).

MATERIALS AND METHODS:

Our study was approve by the İnönü University Ethics Committee with the number 2021/2727.

The records of the patients were reviewed retrospectively with the bone marrow transplant unit of İnönü University Turgut Özal Medical Center between 2009 and 2021.In our study, hemogram values of 222 patients diagnosed with ITP who received steroid (1mg/kg/day prednisolone or 40 mg/day dexamethasone for four days) as first line treatment were retrospectively scanned. Hgb, wbc, anc, plt, mpv, pdw values of hemogram parameters were recorded. Statistical analyzes were performed using Paired Samples t test, Wilcoxon test, Spearman's rank correlation coefficient tests in IBM SPSS Statistics 26.0 program.

RESULT:

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.

Table 1: 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 1; 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

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_	**ρ**	**0.135**	1.000	-0.084	-0.086	-0.012	-0.058	-0.020

statistical analysis of the table1.

last	**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**	-

Table 2: 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

According to Table 2. 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 2.

Tablo 3. 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 3, 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 3.

Table 4. 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 4. 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 4.

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. Glucocorticoids can have side effects on dermatological, ophthalmological, cardiovascular, gastrointestinal, bone and muscle, neuropsychiatric, metabolic and endocrine, immune system and hematological systems depending on the duration of use and dose. (12) 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. The side effects of glucocorticoids are both dose and duration dependent. 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 (13). The MPV value is determined from the geometric mean of the converted lognormal platelet volume data in impedance technology systems, or in some systems, the platelet volume of MPV is measured using optical technology. Therefore, MPV will vary according to the method by which it is measured. Therefore, the reference range of the laboratory to be established for that patient population should be established using a particular hematology instrument. A study examining MPV ranges in adults with normal platelet counts reported that impedance methods had normal values ranging from 6.0 to 13.2 fL, while optical methods had normal values ranging from 5.6 to 12.1 fL(14). In our study, the MPV value was measured by the impedance method in the samples taken from the patients. High MPV indicates active bone marrow production of platelets in the thrombocytopenic patient (as in immune thrombocytopenia). High MPV is also seen in some congenital thrombocytopenias (eg, gray platelet syndrome, May-Hegglin anomaly, Bernard-Soulier syndrome) and some patients with myelodysplastic syndromes. An increase in MPV over time may indicate megakaryocytic regeneration in a hypoplastic or aplastic state. Low MPV is indicative of bone marrow suppression, as in aplastic anemia in the thrombocytopenic patient. Low MPV may also be seen in some congenital thrombocytopenias (eg Wiskott-Aldrich syndrome) (15). Platelet cell distribution width (PDW) is a measure of variation in platelet size reflected in the degree of platelet anisocytosis in the peripheral blood smear. A high PDW means a large variation in platelet sizes and a low PDW means a more homogeneous platelet population. Pharmacological doses of glucocorticoids usually result in increased white blood cell counts mainly due to an increase in neutrophils. This phenomenon is due to a decrease in the

proportion of neutrophils adhering to the endothelium. 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. There is an increase in HGB values after steroid treatment. HGB increase after steroids is not consistent with the literature. Such hematological side effects of glucocorticoids are not mentioned at the studies in the literature. It was considered that this increase may be due to possible blood transfusions or dehydration of the patient. 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. There is an increase in HGB. MCV. WBC, NE and PLT values after the procedure (ie in the last measurement) compared to the first measurement. 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 decreases as NE decreases. After the treatment a negative correlation was detected between PLT value and MPV and PDW values. 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. 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 not clearly enlighten whether MPV and PDW values are useful parameters in predicting treatment in ITP patients. In order to clarify the relationship of hemogram parameters with ITP therapy, comprehensive studies with more cases are needed.

Whether MPV and PDW values can be used as a predictive marker in ITP patient needs to be clarified by studies with larger data.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

REFERENCES:

1-Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood 2009; 113:2386.

2-Nugent D, McMillan R, Nichol JL, Slichter SJ. Pathogenesis of chronic immune thrombocytopenia: increased platelet destruction and/or decreased platelet production. Br J Haematol 2009; 146:585.

3-Toltl LJ, Arnold DM. Pathophysiology and management of chronic immune thrombocytopenia: focusing on what matters. Br J Haematol 2011; 152:52.

4-Sood R, Wong W, Gotlib J, et al. Gene expression and pathway analysis of immune thrombocytopenic purpura. Br J Haematol 2008; 140:99.

5-Cines DB, Liebman H, Stasi R. Pathobiology of secondary immune thrombocytopenia. Semin Hematol 2009; 46;S2.

6-Weycker D, Hanau A, Hatfield M, et al. Primary immune thrombocytopenia in US clinical practice: incidence and healthcare burden in first 12 months following diagnosis. J Med Econ 2020; 23:184.

7-Mithoowani S, Cervi A, Shah N, et al. Management of major bleeds in patients with immune thrombocytopenia. J Thromb Haemost 2020; 18:1783.

8-Bolton-Maggs PH, Chalmers EA, Collins PW, et al. A review of inherited platelet disorders with guidelines for their management on behalf of the UKHCDO. Br J Haematol 2006; 135:603.

9- Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv 2019; 3:3829.

10- Sirotich E, Guyatt G, Gabe C, et al. Definition of a critical bleed in patients with immune thrombocytopenia: Communication from the ISTH SSC Subcommittee on Platelet Immunology. J Thromb Haemost 2021; 19:2082.

11- Provan D, Arnold DM, Bussel JB, et al. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Adv 2019; 3:3780.

12-Hoes JN, Jacobs JW, Verstappen SM, et al. Adverse events of low- to medium-dose oral glucocorticoids in inflammatory diseases: a meta-analysis. Ann Rheum Dis 2009; 68:1833.)

13-Chrousos GA, Kattah JC, Beck RW, Cleary PA. Side effects of glucocorticoid treatment. Experience of the Optic Neuritis Treatment Trial. JAMA 1993; 269:2110.

14-Hoffmann JJ. Reference range of mean platelet volume. Thromb Res 2012; 129:534.

15-Kaito K, Otsubo H, Usui N, et al. Platelet size deviation width, platelet large cell ratio, and mean platelet volume have sufficient sensitivity and specificity in the diagnosis of immune thrombocytopenia. Br J Haematol 2005; 128:698.)