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Can Platelet Mass Index Be Used As A Prognostic Marker In The Diagnosis of Missed Abortion Patients?

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ABSTRACT

This study aims to evaluate the effectiveness of PCT (Platelet crit), NLR (Neutrophil-to-lymphocyte ratio), and PMI (Platelet Mass Index), which are among the complete blood count parameters, in predicting missed abortion (MA).
The case-control study was conducted between January 1, 2020, and January 2022. A total of 926 pregnant women, including 474 MA and 452 normal patients, were included in the study.
There were no significant differences between the patient and control groups in terms of age, gestational week, body mass index (BMI), gravida and parity, and thyroid functions ($p>0.05$). PMI, PCT, and NLR values were significantly higher in the MA group ($p<0.05$). While there was a strong positive relationship between PMI and PCT, there was a negative relationship between PMI and NLR ($p<0.05$). In the ROC analysis, PCT>0.24, NLR>2.99, and PMI>2430.9 were significantly associated with an increased risk of missed abortion ($P<0.05$). Logistic regression analysis revealed that a one-unit increase in PCT resulted in a statistically significant 3.41-fold increase in the risk of missed abortion, a one-unit increase in NLR resulted in a 2.56-fold increase, and a one-unit increase in PMI resulted in a 1.004-fold increase ($p< 0.05$).
We think that PMI, NLR, and PCT values obtained from complete blood count parameters are important predictors of missed abortion.

Keywords: Missed abortion, Platelet crit, Neutrophil-to-lymphocyte ratio, Platelet Mass Index

Introduction

Missed abortion (MA) is known as an unpredictable early pregnancy complication that can be seen commonly in all pregnancies (1). The underlying causes in the pathophysiology of MA have not yet been clearly explained. Its common pathophysiological mechanism is known as chromosomal abnormalities, disorders in the immune system, acquired thrombophilia, diabetes, and radiation exposure (2,3). Pregnancy itself is a prothrombotic state. Natural prothrombotic events observed during pregnancy are physiological variations. One of the main causes of MA is the disruption of the hemostatic balance in the placental vessels due to the prothrombotic state that changes too much. It has been reported that women with a history of unexplained recurrent miscarriage may have changes in platelet functions (4).

Fetal development in the early stages of pregnancy takes place in a low-oxygen environment. To keep oxygen levels low, extravillous trophoblasts form a cell barrier at the ends of the uteroplacental arteries (5). This cell barrier protects the placenta from the harmful effects of free oxygen radicals in the early stages of pregnancy. Increasing oxygen radicals cause necrosis and apoptosis in the placental villous structure. Lipid peroxidation, which is also harmful, invades trophoblastic tissue and activates biochemical events by providing leukocyte adhesion, activation, and aggregation of plaques (6). With the activation of leukocytes, the increase in inflammatory parameters in the blood and the formation of thrombosis cause ischemia in the pregnancy tissues. It has been reported that there is an increase in maternal systemic inflammatory response as a result of this placentation defect (7).

Complete blood count includes parameters used in the follow-up of many diseases and its application is simple and inexpensive. Changes in platelet count (PLT), PCT, mean platelet volume (MPV), and platelet distribution width (PDW), which are among the platelet parameters, are associated with physiological and pathological function changes in various diseases (8). MPV is a simple marker of platelet function and has been associated with adverse obstetric outcomes such as systemic inflammation and first-trimester miscarriages (9).

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RDW measures erythrocyte distribution based on diameter or volume. It has an important role in immunological and inflammatory events (10). NLR and platelet-lymphocyte ratio (PLR) are inexpensive and simple to calculate as predictors of the prognosis of systemic inflammatory diseases. It has been reported that it can be used especially in inflammatory, heart, and cancer diseases (11-13).

Platelet mass index (PMI) is a new parameter that has been used recently and is calculated with the formula (Platelet number) x (MPV/1000) fl/nl (14). The parameters in the complete blood count are widely used in diagnosing many inflammatory diseases and for the prediction of pregnancy complications (15,16).

There are very few studies in which subclinical parameters acquired from complete blood count parameters related to missed abortion are studied. This study aimed to evaluate the effectiveness of parameters obtained from complete blood count in predicting missed abortions.

Materials and Methods

This case-control study was conducted with pregnant women who were hospitalized with the diagnosis of missed abortion between January 1, 2020, and January 1, 2022. Data were obtained by retrospectively reviewing patient records. Ethical approval dated 30.03.2022 and numbered 2022/07-01 was obtained for the study. Verbal assent was acquired from the participants or their legal representatives in the study, which was managed in accordance with the principles of the declaration of Helsinki. A total of 926 pregnant women, including 474 pregnant women diagnosed with missed abortion and 452 healthy pregnant women, were included in the study.

The control group was selected from healthy pregnant women who did not have any systemic disease that could affect the complete blood count and who had a positive fetal heart rate between 6 and 20 weeks. Gestational age was defined according to the last menstrual period and was confirmed using ultrasonographic findings.

Blood specimens were taken from the antecubital vein. Blood tubes with ethylene-diamine tetra-acetic acid (EDTA) were used and samples were analyzed within two hours at the latest. Gestational age, age, gravida, parity, body mass index (BMI), height, and laboratory values were obtained from patient records. PMI of each patient at the time of hospitalization was calculated and recorded using the formula [Platelet count] × [MPV / 1000] fl/nl.

Exclusion criteria: multiple pregnancies, a history of recurrent miscarriage, uterine structural abnormalities, chromosomal abnormality, insufficient data on patients, acute or chronic infectious diseases, malignancy, autoimmune diseases, thyroid dysfunctions, and chronic inflammatory conditions, smoking during pregnancy, infertility, inadequate data.

Statistical Analysis: Statistical analysis was done with a licensed SPSS 22.0 program. The data of independent paired groups that were not normally distributed were evaluated with the Mann-Whitney U test. The prediction of inflammatory markers for the diagnosis of MA was evaluated by receiver operator curve (ROC) analysis. Spearman correlation test was used to determine the relationship between inflammatory markers. Binary logistic regression analysis was used to determine the effect of inflammatory markers on the development of MA. The statistical significance level was determined as $\alpha = 0.05$.

Results

Table 1 shows the clinical features and laboratory values of the patients. There was no differentiation between MA and control groups in terms of age, gestational week, gravida and parity, thyroid functions, and, body mass index ($P>0.05$). WBC, HB, MCV, PLT, PCT, NLR, and PMI values were significantly high in the patient group ($P<0.05$).

The relationship between PMI and PCT and NLR values is shown in Table 2. There was a strong positive relationship between PMI and PCT. There was a negative relationship between PMI and NLR ($P<0.05$). In other words, as PMI values increase, PCT values increase and NLR values decrease. The scatter matrix distribution plot of PMI, PCT, and NLR values by groups is shown in figure 1.

The effect of inflammatory markers in the diagnosis of late abortion was defined by the ROC curve (Figure 2). ROC analysis results are shown in Table 3. Areas under the curve for PCT, NLR, and PMI were 0.62.0.85 and 0.61, respectively ($P<0.05$). PCT>0.24, NLR>2.99, and PMI>2430.9 were significantly related to a high risk of miscarriage ($P<0.05$).

According to logistic regression analysis, a one-unit rise in PCT resulted in a statistically

Table 1. Comparison of Demographic and the Laboratory Parameters between the Groups

	Control group (n=452)		Missed group (n=474)		p
Age	28.49	(18.00-42.00)	28.89	(18-42)	0.65
Gravida	3	(1-4)	3	(1-4)	0.69
Gestational age	10.53	(7–12)	10.34	(7.00-12)	0.44
Parity (number)	3	(0:5)	3	(0:5)	0.32
Body mass index	26.80	(18.20-30.10)	26.70	(19.15-30.20)	0.18
TSH (U/L)	0.32	0.28-3.6	0.31	0.29-3.4	0.24
fT4 (pmol/L)	13.43	13-18	13.39	12-19	0.33
WBC	7.33	3.16-5.19	10.62	7.90-15.80	0.001
HB(g/dl)	13.05	5.19-16.60	13.43	7.90-15.80	0.03
MCV	83.85	75.5-95.98	86.08	68.50-96.90	0.02
PLT(103/mm³)	249.52	101.0-488.0	263.00	160.00-442.00	0.005
PMI(fl/nl)	2116.48	716.88-4148.0	2576.61	1537.9-3964.4	0.001
PCT(%)	0.23	0.12-0.42	0.26	0.15-0.94	0.001
PDW(%)	16.52	6.21-18.54	16.23	6.11-18.21	0.232
RDW(%)	14.15	10.50-23.50	13.85	11.80-21.40	0.16
MPV(fl)	9.70	2.06-13.10	9.70	7.20-12.50	0.99
HRR(%)	7.37	1.70-30.26	7.00	3.00-17.11	0.30
PLR(%)	137.95	114.43-546.15	136.29	157.36-327.71	0.79
NLR(%)	2.63	1.01	4.42	1.70-39.41	0.001
MLR(%)	0.23	0.03-1.62	0.24	0.12-0.47	0.39
ELR(%)	0.057	0.01-0.38	0.04	0.03-0.04	0.08

The levels of categories are presented as the mean standard deviation for parametric variables and median (min-max) for nonparametric variables. Values in bold represent statistically significant out comes.; Abbreviations: Thyroid Stimulating Hormone (TSH), free T4 (fT4), WBC; White Blood Cell, Hb; hemoglobin, MCV; mean corpuscular volume, PLT; platelet count, PMI; Platelet Mass Index, PCT; platelet crit, RDW; red cell distribution width, MPV; mean platelet volume; HRR; Hemoglobin to red cell distribution width ratio, , PLR: platelet to lymphocyte ratio, NLR: neutrophil to lymphocyte ratio, MLR: monocytes to lymphocyte ratio, ELR: eosinophil to lymphocyte ratio and a Mann–Whitney U test

significant 3.41-fold rise, a one-unit rise in NLR resulted in a statistically significant 2.56-fold rise and a one-unit rise in PMI resulted in a 1.004-fold rise in the risk of MA (P<0.05) (Table 4).

Discussion

In the study, the relationship between inflammatory markers and missed abortion was investigated. Unlike other studies, wider parameters and platelet mass index, a parameter that has not been studied before, were examined. In addition to other parameters, especially PCT, NLR and PMI were closely associated with missed abortion.

A balanced inflammatory environment is necessary for healthy implantation and shaping of tissues during pregnancy. Excessive inflammatory response with oxidative stress, defective implantation of the placenta, and problems in spiral artery invasion cause early pregnancy loss (17,18).

The hematologic system has an important role in the completion of implantation and the development of the placenta. The implantation of the egg in the uterus after fertilization depends on the compatibility between the fetus, placenta, and mother. Various changes that cause thrombus formation during pregnancy may affect the implantation stage and cause pregnancy loss (19).

Although the exact mechanism of MA remains unclear, inflammation has an important role in the pathophysiology of MA. It has been reported that the increase in an inflammatory reaction is high in pregnancies resulting in miscarriage (20). NLR draws attention as an important inflammatory marker used in the prediction and follow-up of many medical conditions, and its use has been

Table 2: Relationship of Platelet Mass Index with PCT, and NLR Values

Factor		PCT (%)	NLR (%)
Platelet Mass Index (fl/nl)	r	0.771	-0.193
	p	<0.001	0.001

Abbreviations: PCT; platelet crit, NLR: neutrophil to lymphocyte ratio.

Table 3. ROC Analysis Results for Inflammatory Variables

Variables	AUC	SE	p	Predictive value	Sensitivity	Specificity	95% Confidence interval	
PCT	0.62	0.03	0.001	0.24	60.3	59.3	0.55	0.68
NLR	0.81	0.02	0.001	2.99	75.2	74.0	0.76	0.86
PMI	0.61	0.33	0.001	2430.9	59.6	59.3	0.54	0.67

Abbreviations: AUC; Area under the curve*,* SE*;* Standard error*, PCT;* Platelet crit, NLR: neutrophil-to-lymphocyte ratio, PMI; Platelet Mass Index.

Table 4. The Effect of Binary Logistic Regression Analysis and PCT, NLR, and PMI on the Development of Missed Abortion

Factor	B	OR	95% C.I	p
PCT	1.29	3.41	1.92-6.06	0.001
NLR	0.94	2.56	1.95-3.37	0.001
PMI	0.03	1.004	1.002-1.004	0.001

Abbreviations: PCT*;* Platelet crit, NLR: neutrophil-to-lymphocyte ratio, PMI; Platelet Mass Index.

increasing in recent years. These markers are rapidly replacing the old parameters because they are easily accessible and do not bring additional costs (21,22).

There are few studies investigating the relationship between early pregnancy loss and NLR. Bas et al. found high NLR values in the spontaneous abortion group in their study. In addition, it was stated that NLR values determined at the 6th gestational week in the spontaneous abortion group would be useful in estimating the risk of miscarriage (23). In a study comparing spontaneous abortion and control groups, it was reported that NLR values were significantly lower in the spontaneous abortion group (24). Unlike these studies, there are studies showing that NLR does not change in patients with early pregnancy loss (25,26).

When we look at the literature, it is seen that different results are obtained in terms of NLR. In this study, significant differentiation was sighted between the two groups in terms of NLR values. NLR values were statistically significantly high in the missed abortion group. The predictive value of NLR in the diagnosis of MA was >2.99. A one-unit increase in NLR results in a statistically 2.56-fold increase in the risk of missed abortion ($p< 0.05$).

Platelets are primarily responsible for coagulation. It has an important role in thrombophilias and vascular diseases. PCT, which is one of the platelet volume indices, is one of the indicators of platelet activity and is routinely obtained from automatic complete blood counts (27).

It is seen that there are various studies investigating thrombocyte parameters in cases of missed abortion. In the study of Oglak et al. in which 137 early pregnancy loss and 148 control groups were included, no differentiation was found between the two groups in terms of PCT values (28). In another study, PCT values were high in the group with pregnancy loss. It is stated that PCT is a low-cost, easily obtainable marker that can be used to predict pregnancy loss in patients with at least one miscarriage history (29). Similarly, in another study, PCT values were high in the group with pregnancy loss. PCT was thought to be an important marker of pregnancy loss (30).

In our study, there were no statistically significant differences between the two groups in terms of PCT values. PCT values were high in the missed abortion group. The predictive value of PCT in the diagnosis of MA was determined as PCT>0.24. According to regression analysis, a one-unit increase in PCT ensued in a statistically

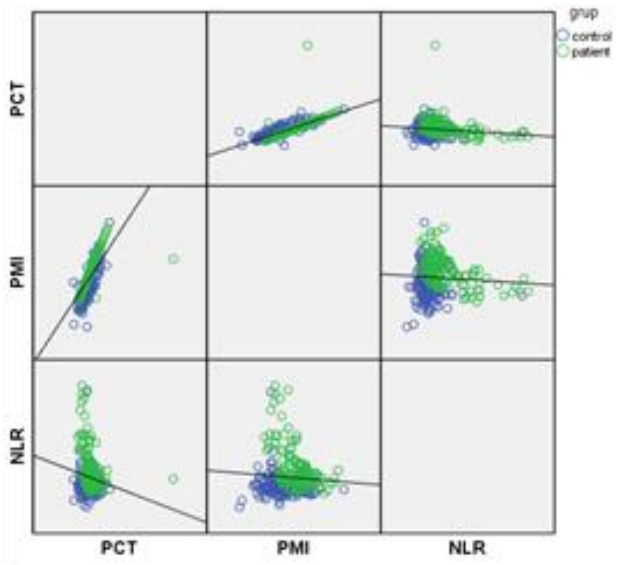

Fig. 1. Scatter Matrix Plot of PMI, PCT, and NLR Values by the Groups

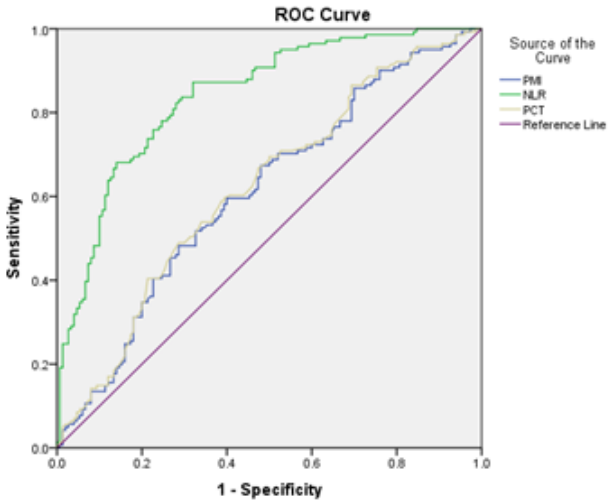

Fig. 2. Receiver Operating Characteristic Curves Platelet crit (PCT), Neutrophil-to-Lymphocyte Ratio (NLR), Platelet Mass Index (PMI) For the Diagnosis of Missed Abortus

significant 3.41-fold increase in the risk of missed abortion. These results show that platelet activation has an important role in spontaneous early pregnancy loss. There are studies in the literature with different results. Obtaining different results may be related to the insufficient number of patients and the inclusion of patients with a history of recurrent miscarriage.

There are studies on PMI (Platelet Mass Index), which is an up-to-date parameter with increasing importance recently (31,32). This is the first study in which PMI values were studied in missed abortion patients. There was a significant difference between the two groups in terms of PMI values. PMI values were higher in missed abortion group. PMI values were high in missed abortion group. While there was a strong positive relationship between PMI and PCT, there was a negative relationship between PMI and NLR ($P<0.05$). In other words, as PMI values increase, PCT values increase and NLR values decrease.

The study has some limitations that should be mentioned. Due to the single-center nature of our study, our results cannot be generalized to other female populations. In addition, the fact that other proven markers of inflammation were not used in the same patient group is one of the points that should be kept in mind and should be regulated in future studies. We consider the strengths of the article to be the study of almost all blood parameters in the complete blood count and the study of a new marker such as PMI for the first time in this patient group.

In conclusion, this study seems to be the first study in which almost all parameters included in a complete blood count were studied in missed abortion patients. We consider it important to study PMI, which is one of the current parameters, in missed abortion cases. We think that the increased maternal systemic inflammatory process plays a role in the estimation of MA due to the significantly high PMI, NLR, and PCT in the study, and we suggest that it be supported by more comprehensive studies.

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Declaration of Authorship All authors designed the study, acquired the data, analyzed and interpreted the data. All authors drafted the manuscript; all authors critically revised the manuscript for important intellectual content; all authors gave approval of the version to be submitted; all authors agree to be accountable for all aspects of the work.

Ethical Approval Ethics committee approval was obtained from Van Training and Research Hospital with the decision dated 30.03.2022 and numbered 2022/07-01.

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