Ann Med Res

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Annals of Medical Research

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# Subclinical inflammation markers and their impact on obstetric outcomes in abortus imminens: A case-control study

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ARTICLE INFO

**Keywords:**
Abortus imminens
Inflammation
Platelet crit
Neutrophil to lymphocyte ratio
Platelet to lymphocyte ratio
Monocytes to lymphocyte ratio

Received: Aug 01, 2022
Accepted: Jul 25, 2023
Available Online: 27.11.2023

DOI:
10.5455/annalsmedres.2022.07.226

## Abstract

**Aim:** The aim of the study is to investigate the relationship of subclinical inflammatory factors Platelet crit (PCT), Neutrophil-lymphocyte ratio (NLR), Monocyte-lymphocyte ratio (MLR), Platelet-lymphocyte ratio (PLR) obtained from complete blood count (CBC) with Abortion Immunes (AI) and obstetric results.

In recent years, studies reveal that subclinical inflammatory markers can be used as an indicator of the inflammatory process in many diseases. Few studies have evaluated indicators of inflammation and postpartum outcomes in abortion imminent patients.

**Materials and Methods:** The study was conducted between January 2020 and January 2021. A total of 429 pregnant women, 203 of whom were pregnant with AI and 226 who were healthy, were included in the study.

**Results:** PCT, NLR, and MLR values were significantly higher and PLR values were low in the AI group ($p<0.05$). PCT $>$ 0.22, NLR $>$ 2.29, and MLR $>$ 0.20 were significantly associated with an increased risk of AI ($p<0.05$). PLR value above 135.5 was associated with the normal group. There was a significant difference between the group whose pregnancy was terminated by abortion and the group who gave birth in terms of PCT, NLR, MLR, and PLR values. PCT, NLR, and MLR values were high in the abortion group, and PLR values were low ($p<0.05$). Premature birth was developed in 11.3% (n=15) of AI patients. There was a significant difference between the preterm and term pregnancy in terms of PCT, NLR, MLR, and PLR levels ($p<0.005$). PCT, NLR, and MLR values were high and PLR levels were low in pregnant women who gave birth prematurely.

**Conclusion:** We think that close follow-up of abortion imminent patients with high levels of these inflammatory factors is appropriate.



## Introduction

Bleeding in the first half of pregnancy is defined as imminent abortion (AI). Imminent abortion is an important pregnancy complication observed in 20-50% of all pregnancies [1]. Inflammation has an important role in the prognosis of pregnancy and in determining the pathophysiology of AI [2]. At the same time, there are studies stating that there is a relationship between inflammation and uterine contractions, cervical dilatation, and preterm delivery [3]. It has been reported that many reasons such as genetic diseases, chromosomal abnormalities, and endocrinological and immunological factors are important in the pathogenesis of low immunity [4].

CBC is an easy and inexpensive blood test. The parameters used in CBC are used in the diagnosis of many diseases. It has been known that NLR, PCT, and MLR, which are among the CBC parameters, reflect disease activity [5,6]. Platelet lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR) are complete blood count parameters that indicate inflammation and/or ischemia [7]. The neutrophil-lymphocyte ratio is the ratio of the absolute neutrophil count to the absolute lymphocyte count. It is considered a marker of the body's immune response to culprit agents. It is also considered a quick and simple parameter that is an indicator of systemic inflammation and stress. Another parameter that is known to increase during thrombosis and inflammation is the platelet-lymphocyte ratio. Mean platelet volume has been associated with platelet volume, function, and activation, and its increase is associated with the presence and prognosis of vascular diseases, including peripheral, cerebrovascular, and coronary artery disease [8,9].

Recent studies reveal that NLR and PLR values can be

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used as indicators of the inflammatory process in many diseases [10]. While neutrophils can be used as an important indicator of active inflammation, lymphocytes play an important role in the regulation of the inflammatory response. Platelet values are known to be an important indicator of thrombosis. It is thought that PLR values may increase inflammation [11,12].

Platelet (PLT) volume is directly related to increased PLT synthesis resulting in PLT aggregation with increased PLT distribution width (PDW). However, platelet crit (PCT), a measure of mean platelet volume (MPV) × PLT number, may be more predictive of PLT aggregation [13].

Mean platelet volume (MPV), platelet criticality, and platelet distribution width (PDW) have been investigated as markers of platelet activation and predictors of thrombophilic disorders [14].

In this study, we worked on PCT, PLR, NLR, and MLR. We aimed to examine the roles of inflammatory factors in predicting the diagnostic values of AI and investigate their effects on pregnancy outcomes.

## Materials and Methods

The case-control type study was conducted by retrospectively collecting the data of patients hospitalized with the diagnosis of imminent abortion to the obstetrics clinic between January 01, 2020, and 2021. Ethics committee approval was obtained for the study from the Van Ministry of Health University Training and Research Hospital Clinical Research and Ethics Committee with the date 05.01 2021. Verbal consent was obtained from the patients or their legal representatives included in the study. Our study was carried out in accordance with the principles of the Declaration of Helsinki. A total of 429 pregnant women, 226 of whom were healthy and 203 of whom had AI, participated in the study.

Pregnant women between 6-14 weeks of gestation, whose head-hip distance could be measured in sonographic examination and fetal cardiac activity were observed, were included in the AI group. The diagnosis of patients who had bleeding in vaginal examination and no cervical dilatation was made by obstetrician and gynecologist. Ultrasonographic examination was performed with an integrated 7.5 MHz Toshiba Xario 100 ("Toshiba Medical Systems Corporation, Nasu, Japan") vaginal probe.

CBC values were recorded in the electronic system. The delivery process of the patients was evaluated through the hospital system.

Pregnant women with subchorionic hematoma, abortion incipience, history of abortion, drug or smoking use, systemic disease, thyroid disorder, inflammatory disease, no fetal heartbeat, more than 14 weeks of pregnancy, and delivered in a different center were not included in the study.

### *Statistical analysis*

The licensed SPSS 22.0 program was used for statistical analysis. The Shapiro-Wilk test was used to evaluate whether the data conformed to the normal distribution. The Mann Whitney U test was used to compare the data of independent groups that did not fit the normal distribution. Receiver operator curve (ROC) analysis was performed to evaluate the prediction of AI diagnosis by inflammatory markers. The relationship between AI and inflammatory markers was evaluated by Spearman correlation analysis. The effect of independent risk factors on AI development was evaluated by binary logistic regression analysis. The limit of statistical significance was determined as $\alpha = 0.05$.

## Results

There was no significant difference between the groups in terms of age, gestational age, gravida, parity, and BMI ($p>0.05$). PCT, PLR, NLR, MLR, and White blood cell (WBC) values were significantly higher in the AI group ($p<0.05$).

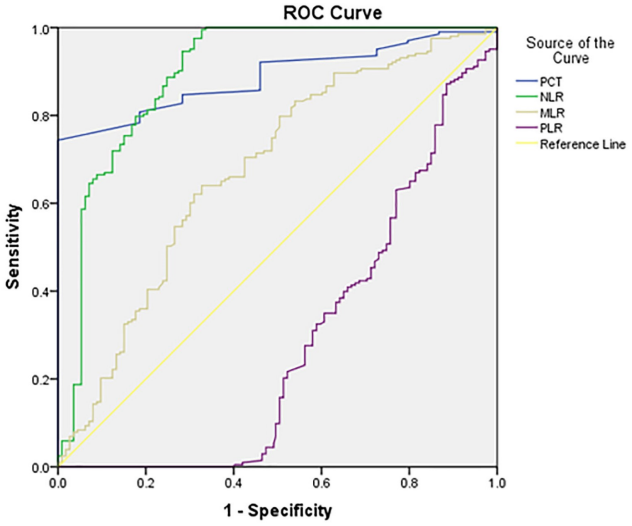


**Figure 1.** Receiver operating characteristic curves. Platelet crit (PCT), Neutrophil-to-lymphocyte ratio (NLR), Monocytes-to-lymphocyte ratio (MLR), Platelet to lymphocyte ratio (PLR), for the diagnosis of AI.

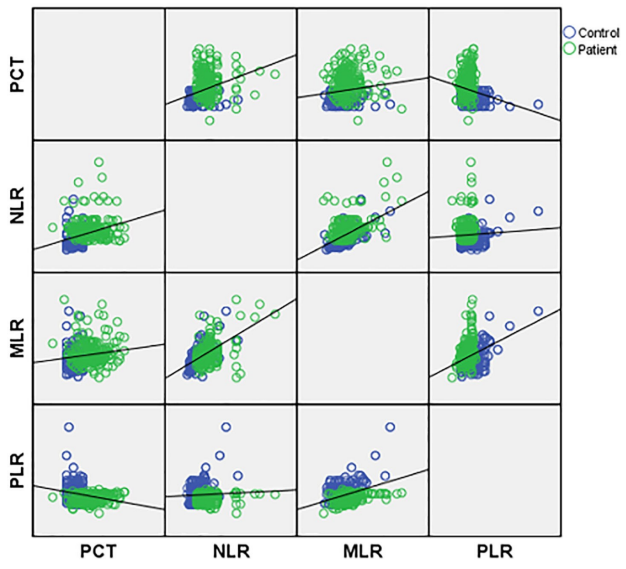


**Figure 2.** Scatter matrix plot of the laboratory parameters by the groups.

**Table 1.** Comparison of demographic and the laboratory parameters between the groups.

| | Control group (n=226) | | AI group (n=203) | | |
|---|---|---|---|---|---|
| | Mean | Min-Max | Mean | Min-Max | p |
| Age | 29.38 | 18.00-42.00 | 29.82 | 18.00-44.00 | 0.55 |
| Gravida(n) | 2 | (1-4) | 2 | (1-4) | 0.67[a] |
| Gestational age (week) | 10.53 | (7–12) | 10.34 | (7.00-12) | 0.43[a] |
| Parity (n) | 1 | (0:5) | 1 | (0:5) | 0.30[a] |
| BMI (kg/m$^2$) | 26.70 | (22.10-30.10) | 26.60 | (22.10-30.10) | 0.65[a] |
| TSH (U/L) | 0.32 | 0.28-3.6 | 0.31 | 0.29-3.4 | 0.23[a] |
| fT4 (pmol/L) | 13.43 | 13-18 | 13.39 | 12-19 | 0.34[a] |
| WBC (10$^9$/L) | 6.55 | 5.30-8.20 | 10.19 | 5.34-20.90 | **0.001**[a] |
| Hb (g/dL) | 12.92 | ±1.06 | 13.02 | ±1.41 | 0.44[b] |
| MCV (fL) | 92.21 | 90.50-96.00 | 92.83 | 88.20-98.50 | 0.42[a] |
| PC (10$^3$/µL) | 265.48 | 195.00-355.00 | 268.96 | 122.00-440.00 | 0.67[a] |
| RDW (%) | 13.95 | 12.10-14.60 | 14.06 | 11.50-22.00 | 0.09[a] |
| PCT (%) | 0.19 | 0.16-0.23 | 0.26 | 0.10-0.41 | **0.001**[a] |
| MPV (%) | 10.52 | 8.11-88.20 | 10.59 | 7.90-115.00 | 0.32[a] |
| NLR (%) | 1.84 | 0.42-8.07 | 3.50 | 0.91-13.70 | **0.001**[a] |
| MLR (%) | 0.19 | 0.06-0.56 | 0.24 | 0.05-0.64 | **0.001**[a] |
| HRR (%) | 0.98 | 0.79-1.17 | 0.94 | 0.44-1.26 | 0.31[a] |
| PLR (%) | 142.69 | 62.10-581.97 | 128.38 | 21.99-279.66 | **0.03**[a] |
| ELR (%) | 0.06 | 0.00-0.53 | 0.06 | 0.00-0.49 | 0.453[a] |

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: TSH; Thyroid Stimulating Hormone, fT4; free T4, WBC; White Blood Cell, Hb; hemoglobin, MCV; mean corpuscular volume, PC; Platelet count, PLT; Platelet count, 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. a Mann–Whitney U test, and b independent sample t test.

**Table 2.** Roc analysis results for inflammatory variables.

| Variables | AUC | SE | p | Predictive value | Sensitivity | Specificity | 95% | Confidence interval |
|---|---|---|---|---|---|---|---|---|
| PCT | 0.88 | 0.01 | **0.001** | 0.22 | 80.3 | 81.4 | 0.84 | 0.92 |
| NLR | 0.84 | 0.02 | **0.001** | 2.29 | 77.8 | 74.3 | 0.79 | 0.89 |
| MLR | 0.67 | 0.03 | **0.001** | 0.20 | 64.6 | 62.8 | 0.61 | 0.73 |
| PLR* | 0.71 | 0.02 | **0.01** | 135.5 | 0.64 | 0.63 | 0.66 | 0.76 |

Abbreviations: AUC; Area under the curve, SE; Standard error, PCT; Platelet crit, NLR: neutrophil-to-lymphocyte ratio, MLR: monocytes-to-lymphocyte ratio, PLR: platelet to lymphocyte ratio. Bold p values indicate statistically significant. *According to control group.

**Table 3.** Distribution of inflammatory factors according to birth and abortion status in AI patients.

| | Abortion group (n=71) | | Birth group (n=132) | | |
|---|---|---|---|---|---|
| | Mean | Min-Max | Mean | Min-Max | p |
| PCT | 0.28 | 0.10-0.41 | 0.24 | 0.18-0.41 | **0.01** |
| NLR | 5.31 | 3.69-13.70 | 2.53 | 0.91-3.64 | **0.001** |
| MLR | 0.31 | 0.13-0.64 | 0.20 | 0.05-0.53 | **0.001** |
| PLR | 109.88 | 21.99-207.59 | 162.96 | 79.13-279.66 | **0.001** |

Abbreviations: PCT; Platelet crit, NLR: neutrophil-to-lymphocyte ratio, MLR: monocytes-to-lymphocyte ratio, PLR: Platelet to lymphocyte ratio. Bold p values indicate statistically significant.

There was no significant difference between the two groups in terms of Hemoglobin (Hb), Platelet count (PC), Red Cell Distribution Width (RDW), Mean platelet volume (MPV), Hemoglobin to red cell distribution width ratio (HRR), and Eosinophil to lymphocyte ratio (ELR) values. There was no difference (p>0.05), (Table 1).

The distribution matrix of PCT, NLR, MLR, and PLR values by groups is shown in Figure 1. While there was a negative correlation between PCT and PLR, there was a positive correlation between other parameters (p<0.001).

The effect of inflammatory markers in the diagnosis of AI was evaluated with the ROC curve (Figure 2). Areas under the curve were 0.88, 0.84, and 0.67 for PCT, NLR, and MLR, respectively (p<0.05). PCT>0.22, NLR>2.29, and MLR>0.20 were significantly associated with an increased risk of AI (P<0.05). ROC analysis for PLR was performed relative to the control group. The area under the curve was 0.71 for PLR (p<0.05). PLR value above 135.5 was associated with the normal group (Table 2).

Of the pregnancies in the imminent abortion group, 35% (n=71) resulted in miscarriage, 40% (n=81) resulted in normal delivery, and 25% (n=51) resulted in cesarean sec-

**Table 4.** Distribution of inflammatory factors according to term labor and preterm labor status in birth group.

| | Preterm labor (n=15) | | | Term labor (n=117) | | | |
|---|---|---|---|---|---|---|---|
| | Mean | Minimum | Maximum | Mean | Minimum | Maximum | p |
| PCT | 0.29 | 0.24 | 0.38 | 0.27 | 0.18 | 0.41 | **0.03** |
| NLR | 4.19 | 1.79 | 8.45 | 2.78 | 2.67 | 2.87 | **0.04** |
| MLR | 0.34 | 0.10 | 0.31 | 0.21 | 0.05 | 0.53 | **0.02** |
| PLR | 107.88 | 21.99 | 207.59 | 126.29 | 73.67 | 184.31 | **0.04** |

Abbreviations: PCT; Platelet crit, NLR: neutrophil-to-lymphocyte ratio, MLR: monocytes-to-lymphocyte ratio, PLR: Platelet to lymphocyte ratio. Bold p values indicate statistically significant.

**Table 5.** The effects of PCT, NLR, MLR and PLR on AI development by binary logistic regression analysis.

| | B | OR | 95% CI | p |
|---|---|---|---|---|
| PCT | 0.50 | 1.65 | 1.42-1.92 | **0.001** |
| NLR | 1.89 | 6.65 | 3.82-11.59 | **0.03** |
| MLR | 0.16 | 1.17 | 1.06-1.29 | **0.001** |
| PLR | -0.06 | 0.93 | 0.91-0.95 | **0.01** |

Abbreviations: PCT; Platelet crit, NLR: neutrophil-to-lymphocyte ratio, MLR: monocytes-to-lymphocyte ratio, PLR: platelet to lymphocyte ratio. Bold p values indicate statistically significant.

tion. AI patients were divided into two groups those whose pregnancy was terminated and those who gave birth. The distribution of inflammatory factors according to these groups is presented in Table 3. Among AI patients, there was a significant difference in PCT, NLR, MLR, and PLR values between the group whose pregnancy was terminated and the group who gave birth ($p<0.05$).

Premature birth developed in 11.3% (n=15) of the patients who gave birth. Preterm and term pregnant groups were different in terms of PLR, PCT, NLR, and MLR values ($p<0.005$). PCT, NLR, and MLR values were higher in pregnant women who delivered prematurely, and PLR values were lower (Table 4).

In logistic regression analysis, a one-unit increase in PCT, NLR, and MLR results in a 1.65, 6.65, and 1.17-fold increase in AI risk, respectively (Table 5).

## Discussion

AI is vaginal bleeding during early pregnancy despite fetal heartbeat and a non-dilated cervix. In AI, 10-14% of pregnancies end in miscarriage [15,16]. Many different molecular and laboratory tests are being investigated to estimate this possibility [17]. The pathogenesis of AI is multifactorial and inflammation plays an important role in it [18]. Many hematological and biochemical parameters are used in the evaluation of systemic infection. It is known that neutrophil levels increase and lymphocyte levels decrease in systemic inflammation. NLR and PLR scores, which include neutrophil, lymphocyte, and monocyte values, are considered to be the indicators that best reflect systemic inflammation [19,20,21]. According to recent studies, it has been reported that PLR and NLR values can be used as markers of the inflammatory process in many diseases. Neutrophils are important indicators of active inflammation. Lymphocytes have an important role in the regulation of the inflammatory response. It is known that platelet values are an important indicator of thrombosis [10,12]. NLR and PLR are thought to increase gynecological, gastrointestinal, and heart diseases associated with chronic diseases [13,14]. PCT is one of the platelet indices and can be used to foresee fetal loss [22]. It is one of the prognostic markers of inflammation-related diseases in MLR [23]. In a retrospective study, significant differences in PLR values were observed in AI patients, but no difference in NLR values [24]. In another study with AI patients, PLR values were lower than in the control group. There was no difference between the groups in terms of NLR values [25]. In a study of spontaneous abortion patients, PLR values were low and NLR values were high in the abortion group [26]. In the study in which abortion patients were compared with the control group, although there was a difference between the two groups in terms of PLR and PCT values, there was no difference in terms of NLR values. While PLR values were lower in the abortion group, PCT values were higher [27]. In a different study, although NLR and PLR values were found to be higher in the abortion group than in the control group, no difference was found in terms of MLR values [23].

In the literature, it is seen that different results were obtained in studies evaluating subclinical inflammatory parameters in imminent abortion patients. In our study, PCT, NLR, and MLR values were significantly higher in the AI group. PLR value was higher in the control group. Areas under the curve for PCT, NLR, and MLR in ROC analysis were 0.88, 0.84, and 0.67, respectively ($p<0.05$). PCT>0.22, NLR>2.29, and MLR>0.20, values were significantly related to increased AI risk ($P<0.05$). ROC analysis for PLR value was performed relative to the control group. Areas under the curve for PLR, 0.71 ($p<0.05$), PLR value over 135.5 was related to the normal group. In logistic regression analysis, a one-unit increase in PCT, NLR, and MLR results in a 1.65, 6.65, and 1.17-fold increase in AI risk, respectively.

In the literature, there are very few studies evaluating the postnatal outcomes of AI with indicators of inflammation. In our study, we investigated both the relationship of the AI patient group with inflammatory factors and the effect of inflammatory factors on the diagnosis of AI, as well as how the pregnancy of these patients resulted and the relationship of these results with inflammatory factors. The etiology of imminent abortion is still unclear. Considering that a cause-effect relationship can be established with

pregnancy complications such as abortion, preterm labor, and IUGR in pregnancies with abortion imminence, studies on the etiology and treatment of AI are needed. In the study in which the pregnancy outcomes of imminent abortion patients were investigated, the rates of preterm labor, premature rupture of membranes, cesarean section, uterine atony, and neonatal intensive care unit need were significantly higher in the AI group [28]. Similarly, in another study, the rates of preeclampsia and premature rupture of membranes were significantly higher in AI patients [29]. Although there are studies in which the relationship between the AI group and PPROM increases, there are studies indicating that the risk does not increase [30,31]. In our study, 35% of the pregnancies of AI patients resulted in miscarriage, 40% with normal delivery, and 25% with cesarean section. AI patients were divided into two groups those whose pregnancy was terminated and those who gave birth. The two groups were statistically different in terms of PCT, NLR, MLR, and PLR values. Premature birth developed in 11.3% (n=15) of the patients who gave birth. PCT, NLR, MLR, and PLR levels were significantly different between pregnant women who had preterm delivery and those who had term delivery ($p<0.005$). PCT, NLR, and MLR values were high and PLR values were low in pregnant women who gave birth prematurely. We think that patients with high levels of these inflammatory factors in imminent abortion patients should be followed more closely.

The study has some limitations. Limitation of the study; It is retrospective, single-center, and included few cases in the study. In addition, the fact that other proven inflammation markers were not used in the same patient group is one of the points that should be kept in mind and regulated in future studies. On the other hand, the fact that the data of the included patients were complete, the patients with a history of recurrent abortion were not included in the study, and the parameters that may affect pregnancy outcomes such as age and gravida were similar between the groups are the strengths of the study.

## Conclusion

In conclusion, inflammation has an important role in AI cases. We think that these subclinical inflammatory values, which are important markers of inflammation, can be used in the follow-up of AI patients and to predict pregnancy outcomes. Patients with high PCT, NLR, MLR, and PLR values obtained from routine blood counts should be followed up more frequently.

*Conflict of interest*

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

*Financing*

The author disclosed that they did not receive any grant during conduction or writing of this study.

*Informed consent*

Informed consents were obtained from the study participants.

*Ethical approval*

Ethics committee approval was obtained for the study from the Van Ministry of Health University Training and Research Hospital Clinical Research and Ethics Committee with the date 05.01 2021 and the decision number 2022/01-01.

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