

# Predictive value of neutrophil to lymphocyte ratio, lymphocyte to monocyte ratio and mean platelet volume for pelvic inflammatory disease

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## Summary

**Purpose:** The aim of this study was to investigate the efficacies of neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR) and mean platelet volume (MPV) as early markers in patients with pelvic inflammatory disease (PID) compared with healthy women. **Materials And Methods:** The study included 48 patients diagnosed with PID and 50 healthy individuals. NLR, LMR and MPV values were compared between patients with PID and the control group. **Results:** NLR, LMR and MPV were found to be significantly different in patients with PID when compared to healthy women ( $p < 0,005$ ). **Conclusion:** To our knowledge, this study is the first to assess the role of LMR as an inflammatory marker in patients with PID. Both NLR, LMR and MPV may be considered as useful markers of PID. **Content:** A retrospective controlled study to evaluate and demonstrate the predictive value of NLR, LMR and MPV measurements in diagnosis of PID.

**Key words:** Pelvic inflammatory disease; Neutrophil; Lymphocyte; Monocyte; Mean platelet volume; C reactive protein; Erythrocyte sedimentation rate; Diagnosis

## Introduction

Pelvic inflammatory disease (PID) refers to acute and subclinical infection of the upper genital tract in women, involving any or all the uterus, fallopian tubes, and ovaries; this is often accompanied by involvement of the neighboring pelvic organs. Involvement of these structures leads to salpingitis, endometritis, oophoritis, peritonitis, and tubo-ovarian abscess. In the United States, 750,000 cases of PID are seen each year among sexually active women aged between 15 and 29 years [1]. Clinical symptoms include fever, lower abdominal-pelvic pain, and abnormal vaginal discharge.

Prompt diagnosis of PID and rapid initiation of antimicrobial therapy are very important to reduce the risk of inflammatory sequelae in female reproductive tract. Chronic pelvic pain, infertility, and ectopic pregnancy account for much of the morbidity, suffering, and cost of PID [2]. Early treatment helps avoid both the need for surgical treatment and reduce the risk of sequelae due to tubo-ovarian abscess (TOA).

Diagnosis of PID is usually made by clinical assessment; however, there is no specific physical finding or laboratory test to accurately identify PID [3, 4]. Gold standard method

for the diagnosis of PID is laparoscopy. However laparoscopy cannot be suggested as a first-line tool for PID diagnosis as it is an invasive and expensive procedure. Currently, no single test or a combination of tests have been found to detect PID reliably. White blood cell count (WBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels are often measured in case of suspicion of PID. Unfortunately, these parameters can be in normal ranges and lead clinicians to omit the disease or misdiagnose it unintentionally [5]. Accordingly, it is reasonable to introduce inexpensive, practical, and simple tests with high sensitivity and specificity for early diagnosis of PID.

Systemic inflammation can be measured using a variety of biochemical and hematological markers. Nowadays, it is claimed that measurement of the ratio of sub types of blood cells might have diagnostic significance for diseases related to inflammation. Neutrophil to lymphocyte ratio (NLR), an inflammatory marker, has been found to be predictive in the preoperative diagnosis of TOA [5] and treatment result of PID [6]. Lymphocyte to monocyte ratio (LMR) has been proposed as a surrogate marker for endothelial dysfunction and inflammation and has prognostic and predictive values [7]. Mean platelet volume (MPV) is

Table 1. — Baseline characteristics of patient groups.

Variables	Patient group (n=48)		Control group (n=50)		p
	median (IQR)	Min; max	Median (IQR)	Min; max	
Age (years)	35 (10.25)	20; 51	37 (17.75)	19; 51	0.915
Lymphocytes	2.25 (1.15)	0.4; 5.2	2.3 (0.975)	1.2; 3.9	0.757
Platelets	257 (75.5)	121; 574	273 (79)	150; 392	0.500
Monocytes	0.6 (0.325)	0.20; 2.10	0.4 (0.2)	0.2; 0.8	<0.001*
Hematocrit %	37 (4.25)	20.6; 45	37.85 (5.28)	25; 42.5	0.6158
Hemoglobin, gr/dl	12.35 (1.73)	5.7; 15.5	12.25 (1.88)	7.6; 14.4	0.8256
NLR	2.75 (3.1)	0.9; 19.5	1.75 (1.00)	0.9; 19.5	<0.001*
LMR	4 (3.48)	0.3; 8.5	5.6 (2.45)	2.4; 10.5	<0.001*
MPV	6.8 (1.6)	5.3; 13.6	7.7 (0.8)	5.8; 11.3	0.004*

\* $p < 0.05$  was considered statistically significant. IQR: interquartile range NLR, neutrophil to lymphocyte ratio; LMR: lymphocyte to monocyte ratio; MPV: mean platelet volume.

a marker derived from megakaryocytes during platelet production. It is known that platelets have a regulatory function in inflammation. MPV has been concluded to be a useful marker in the diagnosis of PID [8].

In this study, the authors aimed to investigate the efficacies of NLR, LMR, and MPV as inflammatory markers in patients with PID compared with healthy women.

## Materials and Methods

This retrospective study was carried out at the Department of Obstetrics and Gynecology of Istanbul Medeniyet University, Goztepe Education and Research Hospital and was approved by the Institutional Review Board and Ethics Committee. Forty-eight patients, who were diagnosed with PID and treated in inpatient or outpatient setting between December 2016 and January 2015, were included in the study. The control group, consisted of 50 healthy women who applied to the gynecology clinic for a routine checkup. Forty-eight patients clinically diagnosed with PID based on Centers for Disease Control and Prevention (CDC) criteria, had no pelvic abscess [9]. Transvaginal ultrasonography (TVS) was performed on both groups during gynecological examination. TOA is defined as PID with newly-found unilateral or bilateral adnexal mass [9] and patients diagnosed with TOA were excluded from the study, as they could also affect study findings.

The data of the cases were collected from hospital records and patients' files, Data including age, other systemic diseases, drug use, complete blood count parameters (WBC, neutrophil, lymphocyte, monocyte, platelet count, MPV, hemoglobin, hematocrit) were collected from both groups. NLR and LMR were calculated for both the patient and control groups. NLR was calculated by dividing the absolute neutrophil count, by the absolute lymphocyte count. LMR value was calculated by dividing the absolute lymphocyte count to absolute monocyte count. CRP values of patients with PID were also noted. As a routine, blood samples were collected in EDTA-contained tubes and processed using a hematology analyzer for complete blood count analysis. CRP levels were measured using an Architect c8000.

Exclusion criteria were women aged <18 years, pregnancy, diagnosis of TOA, chronic diseases such as hematologic, cardiac, kidney and liver diseases, prediabetes, diabetes mellitus, hypertension, hyperlipidemia, asthma, connective tissue disorders, previous thrombosis, neoplastic diseases, acute-chronic inflammatory disorders, use of glucocorticoids, antineoplastic agents, anticoagulants, non-steroidal anti-inflammatory drugs, oral contraceptives, smoking, and alcohol consumption.

Statistical analyses were performed using R Statistical Software (www.r-project.org), a free software environment for statistical computing and graphics [10]. Baseline characteristics of the groups were presented as median, interquartile range (IQR), with minimum and maximum values. The Shapiro-Wilk's test was used to analyze the data distribution. Baseline characteristics, age, lymphocyte, neutrophil, platelet, glucose, and RDW were compared by Mann-Whitney U test and the associated  $p$  values were given. Correlations of NLR and MPV between WBC, neutrophil, lymphocyte, platelet, and CRP were assessed by Spearman's rank correlation test. Receiver operating curve (ROC) analyses were constructed to evaluate diagnostic performances and optimal cut-off values for NLR, LMR, and MPV biomarkers in PID patients. Youden's index, which is Maximum=Sensitivity + Specificity - 1 was used as an optimization criterion for cut-off values [11]. The area under the receiver operating characteristic (ROC) curves was used to assess the discriminative ability of NLR, LMR, and MPV in pelvic inflammatory disease (PID) [12-14]. Epi and verification packages were used for ROC curve estimations [15]. The area underneath a ROC curve is calculated following the process outlined in Mason and Graham [13]. Standard error of area under curve (AUC) was calculated based on the Hanley and McNeil paper [14]. The p-value produced for AUC is related to the Mann-Whitney U statistics. pROC package of R was employed for comparing the ROC curves [12]. For all analyses, the  $p$  value of <0.05 was considered statistically significant.

## Results

Forty-eight patients with PID and 50 healthy women were included in the study. Baseline characteristics of the patients with PID and the control group are summarized in Table 1. There were no significant differences in terms of age, lymphocyte, platelet, hematocrit, and hemoglobin levels between the two groups. The study group consisted of 48 patients with a median age of 35 (min-max 20-51 years) years, and the control group was comprised of 50 healthy women with a median age of 37 (min-max 19-51) years (Table 1).

The number of monocytes in the PID group (median=0.6; IQR=0.325) was higher than in the control group (median=0.4; IQR=0.2). The increase in the number of monocytes in PID patients compared with the control group was statistically significant ( $p < 0.001$ ). NLR in the PID group

Table 2. — Illness-related parameters of patient group.

Variables	Patient group (n=48)		Control group (n=50)		p
	Median (IQR)	Min; max	Median (IQR)	Min; max	
CRP, mg/dl	1.30 (4.9)	0; 31			
Leukocytes, ×103/μl	9.9 (6.03)	4.6; 28.9	7 (2.08)	4, 10.6	<0.001*
Neutrophils, ×103/μl	6.15 (5.38)	2.7; 25.3	3.8 (1.58)	1.8; 6.8	<0.001*

\* $p < 0.05$  was considered statistically significant. IQR: interquartile range; CRP: C-reactive protein.

Table 3. — Spearman rank correlations between mean platelet volume, NLR and LMR values and neutrophil rate, leukocyte, platelet count, C-reactive protein (CRP) for patient group

	MPV		NLR		LMR	
	correlation	p-value	correlation	p-value	correlation	p
WBC	-0.05	0.7245	0.55	<0.001*	-0.29	0.0427*
Neutrophils	-0.18	0.2324	0.73	<0.001*	-0.43	0.0024*
Lymphocytes	0.23	0.1148	-0.57	<0.001*	0.55	<0.001*
Platelets	-0.45	0.012*	0.15	0.3051	-0.20	0.1822
CRP	-0.25	0.0902	0.51	<0.001*	-0.33	0.0212*

\* $p < 0.05$  was considered statistically significant. MPV: mean platelet volume; NLR: neutrophil to lymphocyte ratio; LMR: lymphocyte to monocyte ratio; WBC: white blood cell; CRP: C-reactive protein.

Table 4. — AUC values and cut-off points for variables.

	Cut-off point	AUC±SE	95% CI	p	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
NLR	1.9	0.78±0.047	0.688-0.872	<0.001*	79.2	60	65.5	75
LMR	3	0.69±0.054	0.585-0.795	<0.001*	39.6	96	90.5	62.3
MPV	6.9	0.67±0.055	0.563-0.777	0.002	58.3	82	75.7	67.2
WBC	8.4	0.822±0.043	0.732-0.892	<0.001*	68.8	82	78.6	73.2

\* $p < 0.05$  was considered statistically significant. CI: confidence Interval SE = standard error; PPV = positive predictive value; NPV = negative predictive value; NLR: neutrophil to lymphocyte ratio; LMR: lymphocyte to monocyte ratio; MPV: mean platelet volume; WBC: white blood cell.

(median=2.75; IQR=3.1) was higher than in the control group (median=1.75; IQR=1.00). The increase in NLR in PID patients compared with the control group was statistically significant ( $p < 0.001$ ). LMR in the PID group (median=4; IQR=3.48) was lower than in the control group (median=5.6; IQR=2.4). The reduction in LMR in PID patients compared with the control group was statistically significant ( $p < 0.001$ ). MPV values in the PID group (median=6.8; IQR=1.6) were lower than in the control group (median=7.7; IQR=0.8). The reduction of MPV in PID patients compared with the control group was statistically significant ( $p = 0.004$ ).

Illness-related parameters of patient group is given in Table 2. Leukocyte (WBC) counts were higher in the PID group (median=9.9; IQR=6.03) compared with the control group (median= 7; IQR=2.08). A statistically significant increase in the WBC count was detected in the PID group compared with the control group ( $p < 0.001$ ). The neutrophil ratio in the PID group (median=6.15; IQR=5.38) was higher than in the control group (median=3.8; IQR=1.58). The rise in the neutrophil ratio of the patients with PID compared with the control group was statistically significant ( $p < 0.001$ ).

Correlations between mean platelet volume, NLR, and LMR values and neutrophil rate, leukocyte, platelet count, C-reactive protein (CRP) for patient group are given in Table 3. A negative correlation was discovered between platelet count and MPV values ( $p = 0.0012$ ,  $r = -0.45$ ). A positive correlation was discovered between WBC and NLR values ( $p < 0.001$ ,  $r = 0.55$ ). A positive correlation was discovered between neutrophil and NLR values ( $p < 0.001$ ,  $r = 0.73$ ). A negative correlation was discovered between lymphocyte and NLR values ( $p < 0.001$ ,  $r = -0.57$ ). A positive correlation was discovered between CRP and NLR values ( $p < 0.001$ ,  $r = 0.51$ ). A negative correlation was discovered between WBC and LMR values ( $p = 0.0427$ ,  $r = -0.29$ ). A negative correlation was discovered between neutrophil and LMR values ( $p = 0.0024$ ,  $r = -0.43$ ). A positive correlation was discovered between lymphocyte and LMR values ( $p \leq 0.001$ ,  $r = 0.55$ ). A negative correlation was discovered between CRP and LMR values ( $p = 0.0212$ ,  $r = -0.33$ ).

Table 4 describes the cutoff values of NLR, LMR, and MPV in terms of detecting PID in the study. The area under the curve for NLR is AUC = 0.78, with SE = 0.047 and 95% CI from 0.688 to 0.872. The best cut-off for NLR is

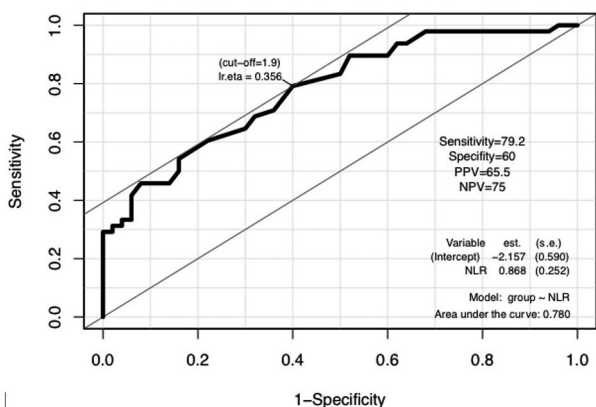


Figure 1. — ROC curve of NLR for PID classification.

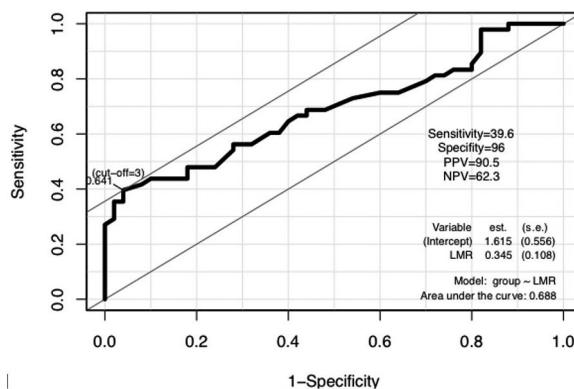


Figure 2. — ROC curve of LMR for PID classification.

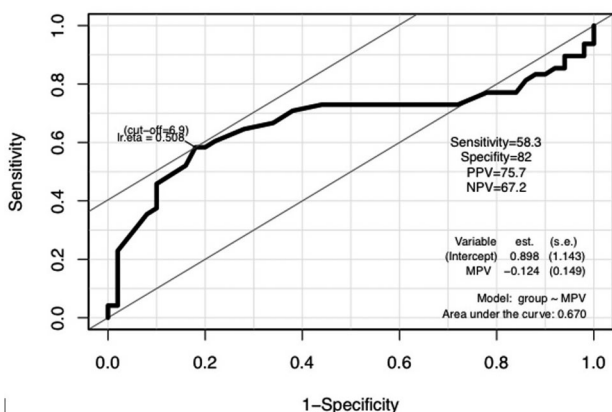


Figure 3. — ROC curve of MPV for PID classification.

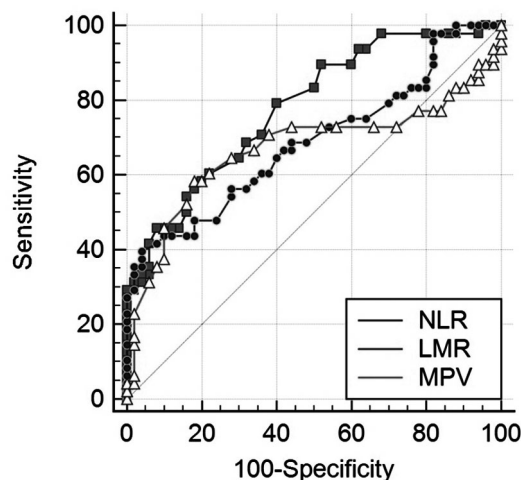


Figure 4. — ROC curves for NLR (square), LMR (circle), and MPV (triangle).

1.9. For values of NLR equal to 1.9 or greater, it is considered that the PID is estimated to occur. At this cut-off point, the sensitivity is 79.2%, specificity is 60%, positive predictive value is 65.5%, and negative predictive value is 75%. The best cut-off for LMR is 3. Of note is that there is a negative relationship between PID status and LMR and MPV. For values of LMR equal to 3 or smaller it is considered that the PID is estimated to occur. At this cut-off point, the sensitivity is 39.6%, specificity is 96%, positive predictive value is 90.5%, and negative predictive value is 62.3%. The AUC for MPV is 0.67 with SE = 0.055 and 95% CI from 0.563 to 0.777. The best cut-off for MPV is 6.9. For values of MPV equal to 6.9 or smaller, it is considered that the PID is estimated to occur. At this cut-off point, the sensitivity is 58.3%, specificity is 82%, positive predictive value is 75.7%, and negative predictive value is 67.2%.

Receiver-operating curve analysis indicated that NLR has greater AUC value than LMR and MPV (0.78, 0.69, and

0.67, respectively). It seems from the ROC analyses that the *p* values associated with NLR, LMR, and MPV are all smaller than 0.05. Thus, all AUCs are significantly different than 0.5, which shows that these biomarkers are all good indicators to anticipate PID (Figures 1-4).

### Discussion

PID is a serious infection of the female reproductive system. Early recognition of the disease and proper management of patients with PID are very important to reduce morbidity and significant sequelae. There is no single test that has adequate sensitivity and specificity to reliably detect PID, but several serum biomarkers associated with disease have been described in the literature.

Elevated CRP or ESR are accepted as findings that may



increase the specificity of the diagnosis of PID [9]. PID is known to increase CRP levels along with ESR. A study assessing the relationship between PID and CRP has shown that in patients with suspected PID, the sensitivity and specificity of CRP in determining the diagnosis of PID was 74% and 67%, respectively (cut-off level 20 mg/L; confirmed by laparoscopy and endometrial sampling) [16]. Mittinen *et al.* demonstrated that in patients with proven severe PID, CRP and ESR had specificities of 73% and 75%, sensitivities of 83% and 73%, positive predictive values of 74% and 73%, and negative predictive values of 82% and 75%, respectively [17]. They suggested that simultaneous use of CRP and ESR allows more accurate assessment of the severity than could be reached by clinical examination only (in discriminating between mild and severe PID). In the present study, the authors discovered a positive correlation between CRP and NLR values ( $p < 0.001$ ,  $r = 0.51$ ). However, they were unable to determine any cutoff point for CRP for predicting PID.

NLR, an inflammatory marker, has already been found to be associated with the inflammation. Neutrophils are the first WBC population to arrive and affect the host inflammatory response. Acute inflammatory processes or bacterial infections increase neutrophil production and inflammatory infiltration [6, 18]. NLR reflects both the lymphocyte and neutrophil counts. NLR represents both a relative decrease in the lymphocyte count and an increase in the neutrophil count.

In the present study, the authors found that there were statistically significant differences between the patient and control groups in terms of NLR ( $p < 0.001$ ). A positive correlation was discovered between CRP, WBC, neutrophil, and NLR values ( $p < 0.001$ ). Per ROC curve analysis, when cut off value was 1.9, NLR predicts PID with a 79.2% sensitivity and 60% specificity. Kopuz *et al.* investigated the relationship between PID and NLR, and they found that NLR with a cut-off value of 2.92, has a sensitivity and specificity of 81.5% and 98.4%, respectively. They proposed that NLR was a useful marker for treatment follow-up [6]. When compared to the present findings, in their study, NLR values had a higher predictive capacity. This could be explained by the fact that their study consisted of hospitalized and most probably more severe PID patients. On the other hand, the present study group consist of patients with mild from severe PID, which was diagnosed and treated in inpatient or outpatient setting. Yıldırım *et al.*, demonstrated that NLR predicts TOA with a sensitivity of 95.2% and a specificity of 99.4% [5]. The positive predictive value of NLR was found to be 99.2% and the negative predictive value was 96.7%. Due to TOA, which is a severe complication of PID, NLR might have higher sensitivity and specificity than the present study as well.

LMR has been studied as an inflammatory marker in several studies [7, 19-21]. A high monocyte count or a low lymphocyte count has separately been shown as an adverse

effect of prognosis in various disorders [19, 20, 22, 23]. Nevertheless, to the present authors' knowledge, the role of LMR as an inflammatory marker in patients with PID has not yet been studied. In the present study, LMR was found to be significantly low in patients with PID when compared to healthy women ( $p < 0.001$ ). Per ROC curve analysis, if cut off value was chosen to be 3, then LMR predicts PID with a 39.6% sensitivity and a 96% specificity. The present authors suggest that LMR may be used as a potential marker of inflammation in patient with PID.

MPV is a measurement of the average size of platelets found in blood and is considered as a significant marker and determinant of platelet function. It is reported that when there is an active inflammatory disease, platelet counts increase because of increased inflammatory cytokine activity and breakdown of these increased larger young platelets in inflammation area lowers MPV [24]. Its roles in inflammation have been investigated [25-27]. There are few studies assessing the value of MPV as an inflammatory marker in patients with PID [8]. The present authors detected lower MPV levels in patients with PID in comparison with healthy women. Significant reduction of MPV in PID patients compared with the control group was detected ( $p = 0.004$ ). Per ROC curve analysis, when cut off value was 6.9, MPV predicts PID with a 58.3% sensitivity and a 82% specificity. Incebiyik *et al.* investigated the relationship between PID and MPV, and they demonstrated that MPV cut-off value of 7.25 resulted in sensitivity and specificity of 73% and 68%, respectively [8]. Incebiyik *et al.* discovered a significant negative correlation between MPV values and platelet count, whereas there was no significant correlation between MPV values and CRP, leukocyte, and neutrophil levels. Their findings are in accordance with the present study.

The current study has some limitations. Firstly, it is a retrospective analysis. Secondly, data pertaining to NLR, LMR and MPV levels at the clinical remission period were unable to be evaluated. Thirdly, the authors were unable to assess correlation between NLR, LMR and MPV levels, and the severity of PID.

## Conclusion

The present findings support previous literature pertaining to relationship between NLR, MPV, and PID. To the authors' knowledge, this is the first study to assess the value of LMR as an inflammatory marker in patients with PID. NLR, LMR, and MPV seem to be useful markers in the diagnosis of PID. These markers deserve to be reevaluated in prospective, controlled studies in which they are handled together with clinical findings to investigate their ability to predict diagnosis, disease severity, and clinical outcome of patients with PID.

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