Neutrophil Lymphocyte Ratio, Platelet Lymphocyte Ratio and Mean Platelet Volume; which one is More Predictive in the Diagnosis of Pelvic Inflammatory Disease?

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ABSTRACT

OBJECTIVE: In the present study, we aimed to assess and compare the utility of complete blood count (CBC) parameters and C-reactive protein (CRP) in the diagnosis of pelvic inflammatory disease (PID).

STUDY DESIGN: Sixty-six patients diagnosed with PID, and 200 healthy control subjects were included in this case-control study. The groups were compared in terms of demographic properties such as age, parity, body mass index (BMI), hemoglobin value, neutrophil count, platelet count, neutrophil/ lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), mean platelet volume (MPV) and CRP.

RESULTS: The groups were similar in terms of age, parity, BMI, hemoglobin and platelet count values ($p>0.05$). Neutrophil counts, CRP values, NLR and PLR were significantly higher and the MPV values were significantly lower in the study group ($p<0.05$). The parameter with highest sensitivity and specificity was NLR, which had similar diagnostic sensitivity and specificity as CRP.

CONCLUSIONS: While the most commonly used laboratory tests for the diagnosis of PID are WBC, neutrophil and CRP, NLR should be considered as an even more sensitive marker. It was concluded that NLR could be used in addition to other CBC parameters for the diagnosis of PID.

Keywords: Mean platelet volume, Neutrophil lymphocyte ratio, Platelet lymphocyte ratio, Pelvic inflammatory disease, C-reactive protein

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Introduction

Pelvic inflammatory disease (PID) is an inflammatory disease spectrum that effects upper female genital system, and includes endometritis, salphingitis, oophoritis and pelvic peritonitis. Hospitalization rates have been steadily increasing for reproductive age women diagnosed with PID.[1] Although young age, early age at first sexual intercourse, multiple sexual partners, presence of bacterial vaginosis, vaginal douching, intrauterine contraceptive device use, and sexually transmitted disease are considered the risk factors most frequently associated with PID, it may also be a consequence of dissemination of an infection localized in another organ system via lymphatic or hematogenous route, or post-abortal and post-partum genital microbial colonizations.[2,3] In clinical practice, the most frequently encountered symptoms are acute pelvic pain, fever and vaginal discharge.[4] During pelvic examination, acute abdomen findings and cervical motion tenderness may be noted.[5] The diagnostic sensitivity and specificity of these clinical findings have been reported to be 87 and 50 percent, respectively.[6] Particularly useful laboratory parameters in diagnosis are infection markers such as leukocytosis and increased erythrocyte sedimentation rate. For the diagnosis of PID, the sensitivity and specificity for white blood cell (WBC) count is 57 and 88 percent, respectively; whereas for C-reactive protein (CRP), it is 93 and 83 percent, respectively.[7,8] Laparoscopy is referred to as the gold standard diagnostic tool, however it is undoubtedly an expensive and invasive intervention.[9]

In the recent years, mean platelet volume (MPV) has gained increasing acceptance as an adjunctive diagnostic marker. In previous studies, MPV has been found to be associated with diseases such as ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, and PID.[10-12] In inflammatory processes, it has been noted that thrombocyte functions increase, thereby leading to a decrease in MPV. On the other

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hand, neutrophil/lymphocyte ratio (NLR) has been proposed as a significant marker for diagnosis in PID.[13] Platelet/lymphocyte ratio (PLR) has also been shown to have utility as a marker in inflammatory processes such as familial mediterranian fever (FMF) and ankylosing spondylitis.[14,15]

In the present study, we aimed to investigate and compare the efficacies of the inflammatory markers MPV, NLR, PLR and CRP in PID diagnosis.

Material and Method

The study group consisted of 66 patients who were diagnosed with PID according to Center for Disease Control and Prevention (CDC) criteria.[16] The study patients were hospitalized, treated and discharged within the study period between June 2012 and February 2015. Following approval from the institutional review board, the study data were retrospectively collected from patient charts. The control group consisted of women who applied to our department for routine gynecological examination, matched for age, parity, and BMI with the study group. For both groups, patients using non-steroidal anti-inflammatory drugs (NSAID), anticoagulants and oral contraceptives, in addition to patients who had a chronic medical condition such as hepatic, renal, hematological and cardiac disease, or with a malignancy were excluded. For the control group, patients who applied to our clinics for routine gynecological examination that were similar with the study group in terms of age, parity and body mass index (BMI) were included. For both groups, patients with regular drug use (non-steroidal anti-inflammatory drugs, anticoagulants, oral contraceptives), chronic disease (hepatic, renal, hematological or cardiac diseases, anemia) or a malignancy were excluded from the study, as these could interfere with the study results. Additionally, patients diagnosed with a tuba-ovarian abscess, which is a severe form of PID, were excluded from the study, which could also affect study findings. PID was diagnosed clinically according to CDC criteria; symptoms such as fever, foul smelling vaginal discharge, pelvic pain with an acute onset, nausea and vomiting, and signs such as cervical motion tenderness, bilateral pelvic tenderness and demonstration of vaginal discharge during speculum examination were used for diagnosis. In terms of laboratory findings, white blood cell (WBC) count and C-reactive protein (CRP) were used as confirmatory tests. Urinary system infections were excluded by performing urinalysis and urine culture. Trans-vaginal ultrasound was performed to rule out cysts (not complicated with tuba-ovarian abscess) and a quantitative serum beta-HCG test was performed to rule out pregnancy. CBC parameters such as MPV, WBC, NLR, PLR, neutrophil and platelet counts, and serum CRP levels were compared between the study and control groups.

Statistical analyses were performed using SPSS for Windows 15.0 computer software (Statistical Package for Social Sciences, Chicago, IL, USA). Parameters were expressed as mean and standard deviation. Independent sample t-test was used to compare groups in terms of study parameters. Pearson correlation test was used to investigate the correlation between CRP and other parameters. ROC analyses were performed to assess the diagnostic accuracy and to determine optimal cut-off values of CRP, NLR, PLR, MPV values and leukocyte, neutrophil, lymphocyte and platelet counts. P values less than 0.05 were considered statistically significant.

Results

The study group comprised 66 patients diagnosed with PID. Using a 1:3 ratio, a control group was constructed that included 200 healthy control subjects. The groups were similar in terms of age (29.6±4.2 vs 28.1±5.5 yrs), parity (3.9±1.3 - 2.9±2.2), BMI (22.1±2.3 vs 23.6±3. kg/m^2), hemoglobin (11.9±1.5 vs 12.2±1.0 gr/dL) and platelet (314.9±116.6 - 121.2±40.2) values ($p>0.05$). Although mean leukocyte counts, neutrophil counts, NLR, PLR and CRP were higher in the study group, and MPV values were significantly lower ($p<0.05$) (Table 1).

Correlation analyses of the study variables were performed with CRP, as it is an infection marker with highest sensitivity and specificity. A positive correlation with NLR (rho=0.469),

Table 1: Comparison of study and control groups in terms of demographic and blood values

Parameters	Study group (n=66)	Control group (n=200)	p value
Age (years)	29.65±4.23	28.18±5.55	0.970
Parity	3.92±1.39	2.97±2.23	0.083
BMIa (kg/m^2)	22.18±2.36	23.63±3.11	0.345
Hemoglobin (gr/dL)	11.98±1.58	12.25±1.07	0.762
Platelet	314.90±116.67	272.57±72.13	0.069
Neutrophil	10.88±5.23	4.83±1.69	0.002
CRP	18.56±8.16	3.89±2.45	0.000
NLRb	6.28±5.12	2.13±0.83	0.001
PLRc	172.305±84.17	121.27±40.20	0.002
MPVd	7.47±1.94	8.49±1.44	0.025

[a]BMI: Body mass index. [b]NLR: Neutrophil/lymphocyte ratio. [c]PLR: Platelet/lymphocyte ratio. [d]MPV: Mean platelet volume

PLR (rho=0.383) ve leukocyte (rho=0.598), neutrophil (rho=0.598), platelet (rho=0.383) was observed (p<0.05). In contrast, a negative correlation with CRP was observed for MPV (rho=-0.273) ve lymphocyte counts (rho=-0.157) (p<0.05) (Table 2). In ROC curve analyses (Figure 1), sensitivity values for CRP, NLR, PLR, MPV, leukocyte, neutrophil, lymphocyte and platelet counts were 90%, 87%, 65%, 60%, 82%, 78%, 63%, 64%, respectively; and specificity values were 85%, 82%, 66%, 19%, 69%, 68%, 14%, 57%, respectively (Table 3).

Table 2: Correlation analysis of C-reactive protein (CRP) and other significant parameters

C-reactive protein	rho	P value
NLRa	0.469	0.002
PLRb	0.383	0.000
Leukocyte	0.598	0.001
Neutrophil	0.598	0.001
Platelet	0.383	0.000
Lymphocyte	-0.157	0.003
MPVc	-0.273	0.000

[a]NLR: Neutrophil/lymphocyte ratio, [b]PLR: Platelet/lymphocyte ratio, [c]MPV: Mean platelet volume

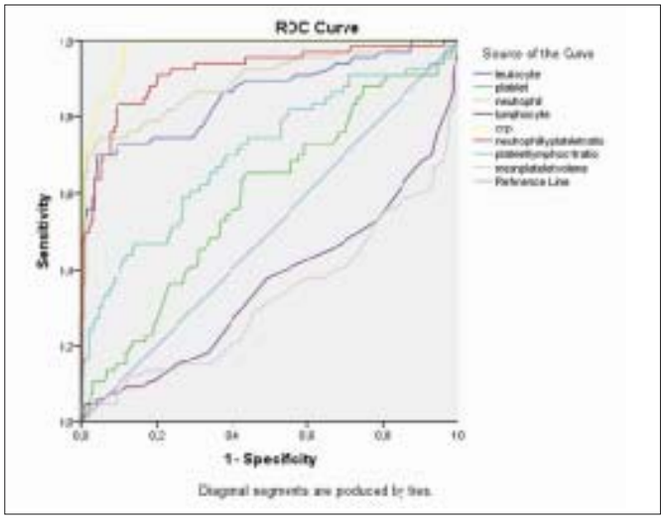

Figure 1: ROC curve for the diagnostic parameters

Discussion

In the present study, it was confirmed that MPV, NLR, PLR and CRP are significant markers of inflammatory response. It was also found that, NLR is a significant marker with high sensitivity and specificity, and thus could be used as an alternative to CRP measurement.

In general, PID is considered a polymicrobial disease, which tends to disseminate in an ascending fashion from lower genital system (i.e. vaginal-cervical) to the upper genital structures such as endometrium, myometrium, tubes and ovaries.[17] If left untreated, serious complications such as tuba-ovarian abscess, intra-abdominal infection, generalized peritonitis and even life-threatening sepsis may occur.[18] In addition, clinically silent infections may cause chronic pelvic pain, persistent pelvic mass, and infertility.[19,20] The gold standard method for the diagnosis of PID is laparoscopy. However, widespread use of laparoscopy in is restricted, mainly due to its invasive nature and high cost, besides the lack of strict indications. Because the symptoms are generally non-specific and there are no definitive laboratory tests, diagnosis is challenging. In a previous study by Blenning et al., the authors reported that there is currently no single test with adequate diagnostic power for PID diagnosis.[21] Due to the infectious stimulus, interleukins (mainly IL-3, IL-6, IL-11), granulocyte colony stimulating factor (G-CSF) and cytokines are secreted, which result in release of mature granulocytes from the bone marrow. The first cells to arrive to the area of infection are neutrophils. The increase in neutrophil count causes a decrease in lymphocyte count.[22,23] Consequently, it causes an increase in NLR, which is the main parameter that is investigated in the present study. In the study by Kopuz et al.[13] which included 65 patients with PID and 65 patients in the control group, for a NLR cut-off value of 2.92, sensitivity and specificity were determined to be 81.5 and 98.4 percent, respectively, and it was proposed that NLR was a useful marker for treatment follow-up. However, a cut-off value for PID diagnosis was not proposed in this study. In the present study, although the study group had a similar sample size, the control group included more women, which lead to a more powerful

Table 3: The diagnostic values of blood parameters in pelvic inflammatory disease

Parameter	Cut-off	AUC	Sensitiviy	Specifity	PPV	NPV
CRPa	10.5	0.915	90	85	86.32	84.35
NLRb	2.674	0.915	87	82	84.33	76.00
PLRc	131.548	0.576	65	66	41.57	52.35
MPVd	6.75	0.323	60	19	34.38	15.59
Leukocyte	8.92	0.765	82	69	73.12	52.35
Neutrophil	6.15	0.890	78	68	60.44	54.59
Lymphocyte	1.75	0.359	63	14	37.38	11.02
Platelet	277.000	0.587	64	57	38.89	47.05

aCRP: C-reactive protein, bNLR: Neutrophil/lymphocyte ratio, cPLR: Platelet/lymphocyte ratio, dMPV: Mean platelet volume

statistical analysis. In ROC curve analysis, when a NLR cut-off value of 2.67 was taken for PID diagnosis, sensitivity and specificity values were calculated to be 87 and 82 percent, respectively. It was concluded that, among all CBC parameters, NLR was the most sensitive and specific marker.

In previous studies, MPV has been investigated as a marker of inflammation in the diagnosis of PID. In a study by Incebıyık et al.[12] 44 patients with PID was compared with 44 controls, MPV was reported to be significantly lower in patients with PID. The authors reported that, for a MPV cut-off value of 7.25, 73% sensitivity and 68% specificity could be reached. In the present study, which was performed on a larger sample size, the cut-off value for MPV was determined to be 6.75. However, sensitivity and specificity values were 60 and 19 percent, respectively. When a cut-off value of 7.25 was implemented as in Incebiyik et al.'s[12] study, sensitivity and specificity was found to be even lower (57 and 19%, respectively). Thus MPV was considered as an insignificant marker for PID.

Platelet lymphocyte ratio has also been reported to be significantly increased in a number of inflammatory diseases (ankylosing spondylitis, familial mediterranean fever), and was thereby suggested as a useful marker for inflammatory diseases.[14,15] However, in the present study, for a PLR cut-off value of 131.5, sensitivity and specificity was found to be 65 and 66 percent, respectively, which were lower than of NLR. In addition, for optimal cut-off values of other CBC parameters (leukocyte, lymphocyte, neutrophil and platelet counts), sensitivity and specificity were lower than of NLR. Thus, these markers were not considered as significant markers of PID.

In Hemilia et al.'s[8] study, for a CRP cut-off value of 10, sensitivity and specificity for PID detection was reported to be 93 and 83 percent, respectively. Similarly, in the present study, for a CRP cut-off value of 10.5, sensitivity and specificity was found to be 90 and 85 percent, respectively. For this reason, CRP is generally considered a good marker for infection, with quickly increasing levels at from the beginning of infection. However, in this study, its sensitivity and specificity for PID detection was very similar to NLR.

In summary, the most sensitive and specific CBC parameter was found to be NLR, with values approaching nearly as of CRP. As an inexpensive, widely available, non-invasive and quick assay, NLR is a promising marker for the diagnosis of PID.

Nötrofil Lenfosit Oranı Trombosit Lenfosit Oranı ve Ortalama Trombosit Hacmi: Pelvik Enflamatuvar Hastalık Tanısında Hangisi Daha Prediktif?

ÖZET

AMAÇ: Bu çalışmada amacımız pelvik enflamatuvar hastalık (PID) teşhisinde, tam kan ve C-reaktif protein (CRP) parametrelerini kullanarak hangi parametrenin teşhis açısından daha faydalı olduğunun tespit edilmesidir.

GEREÇ VE YÖNTEM: Bu vaka kontrol çalışmasına PID tanısı konularak yatırılmış 66 hasta ve sağlıklı 200 kadın dahil edildi. Gruplar, demografik özellikler (yaş, parite, vücut kitle indeksi), hemoglobin değerleri, nötrofil, platelet sayısı, Nötrofil/ lenfosit oranı (NLR), Platelet/lenfosit oranı (PLR), Mean platelet volüm (MPV) ve CRP düzeyleri açısından karşılaştırılmıştır.

BULGULAR: Gruplar arasında yaş, parite, vücut kitle indeksi, hemoglobin ve platelet sayıları açısından anlamlı farklılık saptanmadı (p>0,05). Çalışma grubundaki hastaların nötrofil sayısı, CRP düzeyleri, NLR oranı ve PLR oranı kontrol grubuna göre anlamlı olarak yüksek bulunmuşken, MPV düzeyleri düşük olarak tespit edildi (p<0,05). Sensitivite ve spesifitesi en yüksek olarak bulunan parametre ise CRP'ye çok yakın değerlerle NLR oranıydı.

SONUÇ: PID tanısında en sık kullanılan kan testleri WBC, nötrofil sayısı ve CRP iken, yine bir tam kan parametresi olan NLR'nin enflamatuvar yanıtta rol aldığı ve CRP gibi bir enfeksiyon markerına yakın spesifite ve sensitivitesi olan NLR'nin PID tanısında diğer tam kan parametrelerinin önüne geçebileceği gösterilmiştir.

Anahtar Kelimeler: Ortalama trombosit hacmi, Nötrofil lenfosit oranı, Trombosit lenfosit oranı, Pelvik enflamatuvar hastalık, C-reaktif protein

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