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Increased neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios can be used to distinguish ovarian masses

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Summary

Objective: The present study aimed to determine whether platelet count, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) can be used to distinguish between benign and malignant ovarian lesions. *Materials and Methods:* This is a retrospective review of 200 women who underwent laparoscopy or laparotomy due to adnexal masses at the Gynecology Department of the study center between January 2012 and January 2015. *Results:* Ovarian endometrioma was detected in 58 patients (29.0%), epithelial ovarian cancer was diagnosed in 57 patients (28.5%), benign ovarian tumors (serous cystadenoma and mucinous cystadenoma) were identified in 44 patients (22.0%), and dermoid cysts were found in 41 patients (20.5%). When compared to the patients with ovarian endometrioma, the patients with ovarian cancer had significantly older age ($p = 0.001$), higher NLR ($p = 0.003$), and higher platelet count ($p = 0.001$). The women with ovarian cancer had significantly lower lymphocyte count ($p = 0.012$), higher PLR (p=0.001), and higher serum CA-125 concentrations ($p = 0.001$) than the women with benign ovarian tumors. The cut-off value of 338,500/mm^3 for platelet count had a sensitivity of 95% and specificity of 85% in predicting ovarian cancer. The cut-off value of 3.75 for NLR had a sensitivity of 85% and specificity of 88% in predicting ovarian cancer. The cut-off value of 182.9 for PLR had a sensitivity of 88% and specificity of 82% in predicting ovarian cancer. *Conclusion:* The elevated thrombocyte count, NLR, and PLR values can be used to distinguish between benign and malignant ovarian lesions.

Key words: Adnexal mass; Epithelial ovarian cancer; Neutrophil-to-lymphocyte ratio; Platelet count; Platelet-to-lymphocyte ratio.

Introduction

Epithelial ovarian cancer is the fifth leading cause of cancer-related mortality among women and the most lethal gynecological malignancy worldwide. There are no sensitive and specific markers for epithelial ovarian cancer, since the early stages of this disease are completely asymptomatic. In addition, it is very difficult to make an accurate preoperative differentiation between benign and malignant ovarian lesions [1-3].

It has been shown that inflammation is the main factor that contributes to the development and spread of cancer in the human body. Inflammatory response against tumor cells may lead to irreversible DNA damage by inducing angiogenesis and suppressing apoptosis of the cancer cells. This process allows the steady growth of the tumor, the invasion of the neighboring tissues, and the subsequent spread to distant sites [4-6].

Inflammatory markers, such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have been the focus of previously published studies on cancer. It had has been reported that inflammatory markers may reach significant blood concentrations levels in various malignancies. Therefore, it was hypothesized that these inflammatory markers may help to predict the nature of the ovarian lesions during the preoperative evaluation of the affected individuals [7-9].

Thrombocytosis has been addressed as an indicator for poor prognosis in women with ovarian cancer. The main reason for this observation is that a rise in the number of thrombocytes may lead to an increase in the release of growth factors from these cells. These factors including platelet-derived growth factor, platelet factor 4, transforming growth factor β, vascular endothelial growth factor, and thrombospondin, which may accelerate the growth and spread of ovarian tumors [10-12].

The present study aimed to determine whether platelet count, NLR, and PLR can be used to distinguish between benign and malignant ovarian lesions.

Materials and Methods

The present study was approved by the Institutional Review Board and Ethical Committee of Afyon Kocatepe University Hospital. This was a retrospective review of 200 women who underwent laparoscopy or laparotomy due to adnexal masses at the gynecology department of the study center between January 2012 and January 2015. The demographic, clinicopathological, and biochemical characteristics of the patients with adnexal masses were obtained from medical files.

The final diagnoses were confirmed by pathological assessment. The patients were classified into four different groups based on their pathological diagnosis of adnexal masses. Ovarian endometrioma was detected in 58 patients (29.0%), epithelial ovarian cancer was diagnosed in 57 patients (28.5%), benign ovarian tumors (serous

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Table 1. — *Clinical characteristics of the participants.*

	Mean ± standard deviation (Minimum−maximum)
Age (years)	41.7 ± 15.1 (16−80)
Hemoglobin (g/dl)	11.8 ± 2.5 (9.3−14.1)
Hematocrit (%)	35.4 ± 7.6 (27.9−42.3)
Leukocyte count (/mm^3)	9621.9 ± 4424.1 (650−15800)
Neutrophil count (/mm^3)	8000.5 ± 2450.0 (100−4850)
Lymphocyte count (/mm^3)	3536.5 ± 2288.9 (310−5110)
Neutrophil/lymphocyte ratio	3.1 ± 3.1 (0.1−21.8)
Platelet count (/mm^3)	293614.5 ± 93196.4 (139100−653000)
Platelet/lymphocyte ratio	171.9 ± 140.9 (38.1−1641.9)

cystadenoma and mucinous cystadenoma) were identified in 44 patients (22.0%), and dermoid cysts were found in 41 patients (20.5%).

The type and Stage of epithelial ovarian tumors were classified using the staging guidelines of the International Federation of Gynecology and Obstetrics. Since almost all of the patients with ovarian epithelial cancer had advanced stage disease (Stage III or IV), ovarian tumors were not further classified into subgroups based on stage. Dermoid cysts were categorized as a different entity than benign ovarian tumors because they had easily recognizable and distinct clinical or sonographic characteristics.

During the preoperative period, two venous blood samples of ten ml were drawn by standard phlebotomy from all women with an adnexal mass. After the first samples were conveyed into sodium citrate tubes, they were transported in temperature-controlled containers and collected in plastic test tubes (Falcon blue cap) containing three ml of 3.8% sodium citrate dehydrate and 136 mmol glucosium. These samples were then analyzed by means of an automated commercial counter. The preoperative complete blood count parameters of the patients were recorded for each patient, including hemoglobin, hematocrit, neutrophil count, lymphocyte count, and platelet count.

As for the second sample, serum CA-125 concentrations were measured with commercial microparticle enzyme immunoassay (MEIA) kits. The intra-assay coefficient of variation (CV) changed between 1.14% and 5.87% while the inter-assay CV differed between 6.67% and 9.58% for CA-125. The CA-125 value of 35 IU/ml was considered as the upper normal limit.

Collected data were analyzed by the Statistical Package for Social Sciences version 16.0 (SPSS). Continuous variables were expressed as mean ± standard deviation (range: minimum-maximum) whereas categorical variables were denoted as numbers or percentages. The normality of distribution for variables was assessed using the Shapiro-Wilk test. In order to assess the differences in the variables among groups, the Kruskal-Wallis test was used, followed by evaluation with the Mann-Whitney U test for multiple comparisons. A post hoc analysis was then made to determine the two variables between which there was a statistically significant difference.

Receiver operating characteristic (ROC) curve was drawn to determine the sensitivity and specificity of platelet, NLR, and PLR values in distinguishing the ovarian cancer form benign lesions. The area under the curve and 95% confidence intervals (CI) were estimated for the defined variables. The cut-off values of the preoperative variables that predicted ovarian cancer were computed using the ROC curve analyses. The optimal cut-off values for the platelet count, NLR, and PLR depended on the most prominent point on the ROC curve for sensitivity and specificity. Two-tailed *p* values less than 0.05 were accepted to be statistically significant.

Results

This was a retrospective review of 200 patients who were diagnosed with adnexal mass. The clinical characteristics of the participants are demonstrated in Table 1. A total of 99 patients (49.5%) had serum CA-125 levels less than 35 IU/ml and the remaining 101 patients (50.5%) had serum CA-125 concentrations above 35 IU/ml.

Table 2 shows the clinical characteristics of the participants according to the pathological diagnoses, including ovarian endometrioma (n=58), epithelial ovarian cancer (n=57), benign ovarian tumors (n=44), and dermoid cysts (n=41). When compared to the patients with ovarian endometrioma, the patients with ovarian cancer had significantly older age ($p = 0.001$), higher NLR ($p = 0.003$), and higher platelet count ($p = 0.001$). The women with ovarian cancer have significantly lower lymphocyte count ($p = 0.012$), higher PLR ($p = 0.001$), and higher serum CA-125 concentrations ($p = 0.001$) than the women with benign ovarian tumors.

Table 2. — *Clinical characteristics of the participants based on pathological diagnosis.*

	Ovarian endometrioma (n=58)	Ovarian cancer (n=57)	Benign ovarian tumors (n=44)	Dermoid cysts (n=41)	*p*
Age (years)	33.6 ± 1.2	54.3 ± 1.8	41.2 ± 2.1	35.6 ± 2.2	0.001*
Hemoglobin (g/dl)	11.9 ± 1.5	12.0 ± 1.6	11.8 ± 1.7	11.8 ± 1.3	0.966
Hematocrit (%)	35.7 ± 4.5	36.0 ± 4.8	35.5 ± 5.1	35.4 ± 3.9	0.887
Leukocyte count (/mm^3)	7551.6 ± 250.2	8708.1 ± 414.3	7878.0 ± 334.4	7546.8 ± 316.7	0.074
Neutrophil count (/mm^3)	4929.3 ± 1768.7	5947.7 ± 2705.0	14180.7 ± 6078.2	1647.6 ± 750.2	0.068
Lymphocyte count (/mm^3)	2118.6 ± 555.6	1799.5 ± 855.2	7397.3 ± 3315.5	2108.3 ± 597.8	0.012†
Neutrophil/lymphocyte	2.5 ± 1.2	4.8 ± 4.4	2.5 ± 1.2	2.7 ± 1.7	0.003*
Platelet count (/mm^3)	288224.1 ± 78300.2	340719.3 ± 110285.6	266227.3 ± 59916.9	265144.1 ± 93417.6	0.001*
Platelet/lymphocyte	146.7 ± 59.9	252.8 ± 229.0	128.6 ± 52.1	141.3 ± 63.3	0.001†
Serum CA-125 (IU/ml)	121.5 ± 82.2	1099.9 ± 565.4	26.7 ± 19.8	24.0 ± 20.9	0.001†

*Statistically significant difference between the ovarian endometrioma and cancer groups.
†Statistically significant difference between the ovarian cancer and benign ovarian tumor groups.

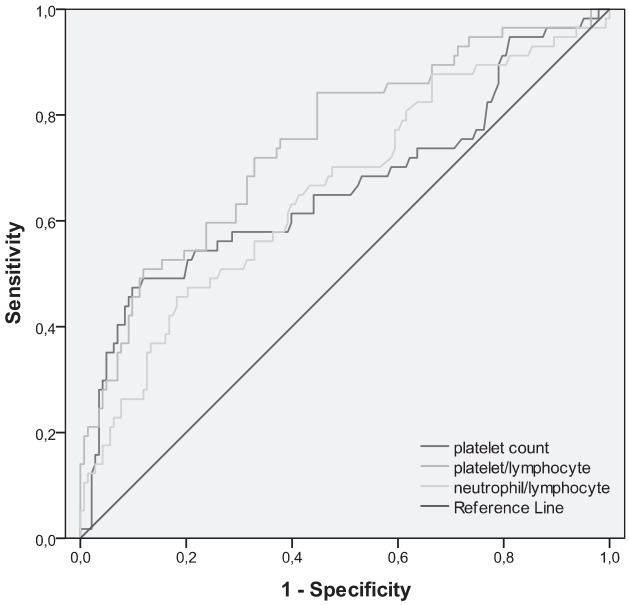

Figure 1. — ROC curves for platelet count, platelet/lymphocyte ratio, and neutrophil/lymphocyte ratio in distinguishing ovarian cancer from benign ovarian lesions.

Figure 1 displays the ROC curves for platelet count, NLR, and PLR values. The ROC curve analysis indicates that the area under curve for platelet count was 0.665 ± 0.047 (95% CI: 0.572−0.757) (p = 0.001). A cut-off value for platelet count was recommended as 338,500/mm^3. This value had a sensitivity of 95%, specificity of 85%, positive predictive value of 86.4% and negative predictive value of 94.4% in predicting ovarian cancer.

ROC curve analysis indicated that the area under curve for NLR was 0.658 ± 0.044 (95% CI: 0.571−0.744) (p = 0.001). The cut-off value for NLR was assigned as 3.75. This value had a sensitivity of 85%, specificity of 88%, positive predictive value of 87.6%, and negative predictive value of 85.4% in predicting ovarian cancer.

ROC curve analysis indicated that the area under curve for PLR was 0.748 ± 0.040 (95% CI: 0.671−0.826) (p = 0.001). A cut-off value for PLR was calculated as 182.9. This value had a sensitivity of 88%, specificity of 82%, positive predictive value of 83%, and negative predictive value of 87.2% in predicting ovarian cancer.

Discussion

Chronic inflammation is associated with compromised immune functions and both mechanisms are closely related with the natural course of cancer. Neutrophil, lymphocyte, and platelet counts are the markers of host systemic inflammation which is precipitated by tumor formation. It is well known that inflammation leads to a pronounced increase in the number and activity of neutrophils and the proinflammatory cytokines, such as interleukins triggering megakaryocyte proliferation and thrombocytosis [13, 14].

A number of studies have focused on the alterations of preoperative NLR and PLR values in patients with various cancer types. These studies have also demonstrated that patients with advanced cancer usually have increased platelet count, elevated neutrophil count, and decreased lymphocyte count, resulting in elevated NLR and PLR values. Therefore, both NLR and PLR have been identified as two of the most easily available and effective markers of chronic inflammation and associated immune suppression in malignancy patients. Preoperative NLR values also significantly correlate with cancer stage, prognosis, and response to treatment [15-17].

Kodama *et al.* were the first to claim that the elevation in serum levels of C-reactive protein and interleukin-6 indicated poor prognosis in a cohort of 120 women with epithelial ovarian cancer [18]. Afterwards, Watanabe *et al.* evaluated how inflammatory markers change in ovarian cancer and revealed that preoperative inflammatory markers increase with disease progression [19]. Later, Asher *et al.* observed that the overall survival span was significantly shortened in association with high preoperative PLR value among 235 women with epithelial ovarian cancer. The median overall survival was 37.4 months (95% CI: 26.1−48.7) in patients with a PLR of < 300, whereas the median overall survival was 14.5 months (95% CI: 11.7−17.2) in patients with a PLR of > 300. Thus, it was concluded that PLR might be an independent prognostic marker in patients with ovarian cancer [20].

Cho *et al.* aimed to specify the diagnostic value of NLR in women with epithelial ovarian cancer. They found that preoperative NLR was significantly higher in 192 patients with ovarian cancer than in 173 patients with benign ovarian tumors and 405 healthy controls (respectively 6.02 *vs.* 2.57 *vs.* 2.55, $p < 0.001$). When the cut-off value was taken as 2.60, the sensitivity and specificity of NLR were calculated to be 66% and 83%, respectively. Moreover, NLR positivity was labeled as the most powerful predictive variable [21].

Yildirim *et al.* performed a retrospective analysis of 306 women with adnexal masses. They reported that 40 patients with epithelial ovarian cancer had significantly higher NLR and PLR values than 79 women with benign ovarian tumors. The cut-off value for NLR was set at 3.35, with a sensitivity of 55% and a specificity of 81%. On the other hand, the cut-off value for the PLR values was found to be approximately 57%, with a sensitivity of 100% for detecting ovarian cancer [22].

A Thailand study addressed PLR as a prognostic marker which would successfully predict advanced stage disease or suboptimal surgery. A PLR value of > 200 was able to predict advanced stage disease with a sensitivity of 66% and a specificity of 59% in a cohort of 166 patients with

epithelial ovarian tumors. Thus, it was concluded that PLR was a better prognostic indicator for the survival of epithelial ovarian cancer patients than thrombocytosis or increased NLR value [15].

As for the present study, patients with ovarian cancer had significantly higher NLR and platelet values than the patients with ovarian endometrioma. The women with ovarian cancer had also significantly lower lymphocyte counts and higher PLR values than the women with benign ovarian tumors. The cut-off value of 338,500/mm^3 for platelet count had a sensitivity of 95% and specificity of 85%, while the cut-off value of 3.75 for NLR had a sensitivity of 85% and a specificity of 88%, and the cut-off value of 183 for PLR had a sensitivity of 88% and a specificity of 82% in predicting ovarian cancer.

Complying with literature, the findings of the present study also indicate the significance of the elevated thrombocyte, NLR and PLR values in distinguishing between benign and malignant ovarian lesions. The variations related with the cut-off points and their predictive values can be attributed to the demographic and clinical diversities of the reviewed participants, as well as the differences in hematological assessment techniques. However, these findings should be interpreted carefully as the power of the present study is limited by its retrospective design, relatively small cohort size, relatively higher number of patients with advanced stage ovarian cancer, and the lack of patients with borderline ovarian tumors. Further research is warranted to clarify the role of inflammatory markers in the differential diagnosis of ovarian lesions.

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