Utility of preoperative neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios to distinguish malignant from benign ovarian masses

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Abstract

Objective: We aimed to investigate the utility of preoperative neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte count as biomarkers to distinguish malignant from benign ovarian masses.

Material and Methods: We retrospectively reviewed the histopathological results of 185 benign and 33 malignant cases following surgery for an initial diagnosis of adnexal mass and confirmed ovarian masses. Age, cancer antigen 125 (CA-125), white blood cell (WBC) count, hemoglobin (Hb), hematocrit (Hct), mean platelet volume (MPV), platelet distribution width (PDW), NLR, PLR, and lymphocyte counts were compared between groups.

Results: The significant diagnostic factors to distinguish malignant from benign disease were age (35.5±22 vs. 62±13 years; p<0.001) and CA-125 levels (16.6±21 vs. 98±366 U/mL; p<0.001). No significant difference was observed in WBC count, Hct, Hb, platelet count, PDW, and MPV between groups. To distinguish malignant from benign masses, lymphocyte count (1.29±0.91 vs. 1.80±0.67×10^3 cells/μL, p<0.001), NLR (4.95±5.36 vs. 3.32±2.72, p=0.024), and PLR (203.41±107.84 vs. 160.75±70.84, p<0.001) were identified as markers. The cutoff values were lymphocyte count of >1500 cells/μL (p<0.001), NLR of 3.4732 (p=0.033), PLR of 161.13 (p<0.001), CA-125 of >40 U/mL (p<0.001), and age of >53 years (p<0.001); their respective sensitivity and specificity were 66.7% and 77.8% [area under the curve (AUC), 0.723±0.055], 68.8% and 54.1% (AUC, 0.624±0.058), 81.8% and 50.8% (AUC, 0.683±0.052), 78.8% and 77.8% (AUC, 0.797±0.057), and 81.8% and 82.2% (AUC, 0.888±0.025). Multiple logistic regression analysis revealed cutoff explanatory and accuracy values of 68.2% and 94.9%, respectively, for lymphocyte count, NLR, PLR, CA-125, and age as independent parameters to distinguish malignant from benign ovarian masses.

Conclusion: In combination with age and CA-125 levels, NLR, PLR, and lymphocyte count may be helpful to preoperatively distinguish malignant from benign ovarian masses. (J Turk Ger Gynecol Assoc 2016; 17: 21-5)

Keywords: Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, malignant ovarian mass, benign ovarian mass

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Introduction

Ovarian cancer is a gynecological malignancy with the highest cancer-related mortality rate observed among women worldwide (1). Because there are limited sensitive and specific markers for prognosis of ovarian cancer in the early stages of disease and many patients are asymptomatic before diagnosis, most cases are detected in the advanced stages when there are only few treatment options available (2).

When identifying potential adnexal masses, it is challenging to distinguish benign ovarian masses from ovarian cancer before surgery. However, prognosis is excellent in cases where the diagnosis is established in the early stages of the disease incidentally or because of the symptoms presented, and also, the 5-year survival rate can exceed up to 90% (3).

Numerous prognostic factors have been established to effectively estimate patient outcomes. No diagnostic marker superior to cancer antigen 125 (CA-125) has been recognized for ovarian cancer in the past 40 years. Therefore, along with the development of new technologies, identification of new biomarkers to increase the sensitivity of cancer antigen-125 (CA-125) in combination with hematological, inflammatory, or immunologic markers has become necessary (4).

Interactions between tumor cells and host immune system may promote tumor growth and progression. The immune response, which integrates both inflammatory and coagulation processes, plays a critical role in the development and progression of various cancers by upregulating various cytokines and inflammatory mediators, inhibiting apoptosis, inducing angiogenesis, stimulating DNA damage, mediating

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immunosuppression and remodeling the extracellular matrix (5, 6).

The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been gaining attention as systemic inflammatory response markers. They have been successfully applied as predictive markers or prognostic factors in various gynecological cancers (4, 7-10). Although the pathophysiological mechanisms of interactions between inflammation and carcinogenesis are yet to be completely clarified, the identification of new biomarkers with a suspected predictive value for carcinogenesis continues to draw attention. Therefore, we assessed the utility of NLR and PLR as preoperative inflammatory markers, which are cost effective, to better distinguish malignant from benign ovarian masses in the preoperative period.

Here, we mainly aimed to compare patient age with CA-125 levels and with preoperatively defined white blood cell (WBC) count, lymphocyte count, NLR, hemoglobin (Hb), hematocrit (Hct), platelet count, platelet distribution width (PDW), mean platelet volume (MPV), and PLR to identify new biomarkers to distinguish between benign and malignant ovarian masses.

Material and Methods

This retrospective study included 221 patients who underwent surgery for a suspected adnexal mass and had an ovarian mass, as identified by the School of Medicine, Department of Obstetrics and Gynecology, Kahramanmaraş Sütçü İmam University, between April 2007 and April 2015. Histopathological examination revealed that 185 cases were benign (52 endometriomas, 67 mature cystic teratomas, and 66 simple ovarian cysts or serous and mucinous cystadenomas) and 33 were malignant (25 serous cystadenocarcinomas, 5 mucinous cystadenocarcinomas, 1 endometrioid carcinoma, 1 granulosa cell tumor, and 1 theca cell tumor). We excluded three patients in whom borderline ovarian tumors were detected. The remaining 218 patients were divided into two groups, benign and malignant, according to the outcomes of the histopathological examination.

The preoperative complete blood count (CBC) and CA-125 levels were obtained from hospital records. The two groups were compared in terms of age, CA-125 levels, WBC count, Hb, Hct, MPV, PDW, NLR, PLR, and lymphocyte count. Further statistical analyses were performed to identify significant differences between these parameters and determine whether they were effective to distinguish malignant from benign masses. The study protocol was approved by the Science Research Ethics Committee of Kahramanmaraş Sütçü İmam University.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 22.0 statistical software (IBM-SPSS Inc.; Chicago, IL, USA). The Shapiro–Wilk test was used to define the compliance of data to normal distribution, and Levene's test was used to assess homogeneity of variance. The independent samples t-test with bootstrap results was used to compare two independent groups, whereas the Mann–Whitney U test was used with the Monte Carlo simulation technique. Correlations between classifications, which were separated by the cutoff values of the patient groups calculated according to the variables and the actual classification, were expressed as sensitivity and specificity using the receiver operating characteristic (ROC) curve analysis. Logistic regression analysis was used to identify cause–effect relationships between the categorical response variables with explanatory variables in binomial and multinomial categories. Quantitative data were expressed as means±standard deviations, whereas categorical data were expressed as numbers (n) and percentages (%). A p value of <0.05 was considered statistically significant.

Results

Patients with benign ovarian masses were significantly younger than those with malignant ovarian masses ($p<0.001$). Similarly, the CA-125 levels were significantly higher in the malignant group than in the benign group ($p<0.001$). No statistically significant difference was observed between groups with respect to WBC count, Hct, Hb, platelet count, PDW, and MPV ($p=0.122$, 0.338, 0.571, 0.327, 0.584, and 0.290, respectively). The mean lymphocyte count was significantly higher in the benign group than in the malignant group ($p<0.001$). The mean NLR was significantly higher in the malignant group than in the benign group ($p=0.024$). The mean PLR was significantly higher in the malignant group than in the benign group ($p<0.001$; Table 1).

For the ROC curve analysis, the cutoff values were calculated for lymphocyte count (1500 cells/μL, $p<0.001$), NLR (3.4732, $p=0.033$), PLR (161.13, $p<0.001$), CA-125 (40 U/mL, $p<0.001$), and age (53 years, $p<0.001$; Table 2). The lymphocyte count below the cutoff value had 66.7% sensitivity and 77.9% specificity for the diagnosis of a malignant ovarian mass. NLR above the cutoff value had a sensitivity of 68.8% and specificity of 54.1% for the diagnosis of a malignant ovarian mass. PLR showed 81.8%

Table 1. Comparison of blood components between groups

	Benign ovarian masses (n=185)	Malignant ovarian masses (n=33)	p
Age (years)	35.50±22.00	62.00±13.00	<0.001
Lymphocyte ($\times10^3$ cells/μL)	1.80±0.67	1.29±0.91	<0.001
NLR	3.32±2.72	4.95±5.36	0.024
Hb (g/dL)	12.00±1.80	11.40±1.70	0.571
Hct (%)	36.00±5.00	33.10±8.10	0.338
Plt ($\times$103/μL)	307.00±67.00	297.00±90.00	0.327
PDW	49.00±7.10	50.00±7.90	0.584
MPV (fL)	9.00±1.20	9.00±0.80	0.290
PLR	160.75±70.84	203.41±107.84	0.001
CA125 (U/mL)	16.60±21.00	98.00±366.00	<0.001
WBC ($\times10^3$ cells/μL)	8.44±1.96	9.00±3.42	0.122

WBC: white blood cells; NLR: neutrophil-to-lymphocyte ratio; Hb: hemoglobin; Plt: platelet; PDW: platelet distribution width; MPV: mean platelet volume; PLR: platelet-to-lymphocyte ratio; Hct: hematocrit; CA: cancer antigen
Mann–Whitney U test (Monte Carlo) and Independent t-test (Bootstrap). All data are expressed as means±standard deviations.

Table 2. Sensitivity and specificity of lymphocyte count, neutrophil-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, cancer antigen 125, and age parameters in benign–malignant distinction of ovarian masses at cutoff values defined by receiver operating characteristic curve analysis

	Benign ovarian masses (n=185)	Malignant ovarian masses (n=33)	AUC±SE	p
Lymphocyte >1500 cells/μL	144 (77.8)**	11 (33.3)	0.723±0.055	<0.001
Lymphocyte ≤1500 cells/μL	41 (22.2)	22 (66.7)*		
NLR ≤3.4732	100 (54.1)**	10 (31.3)	0.624±0.058	0.033
NLR >3.4732	85 (45.9)	22 (68.8)*		
PLR ≤161.13	94 (50.8)**	6 (18.2)	0.683±0.052	<0.001
PLR >161.13	91 (49.2)	27 (81.8)*		
CA-125 ≤40 U/mL	144 (77.8)**	7 (21.2)	0.797±0.057	<0.001
CA-125 >40 U/mL	41 (22.2)	26 (78.8)*		
Age ≤53 years	152 (82.2)**	6 (18.2)	0.888±0.025	<0.001
Age >53 years	33 (17.8)	27 (81.8)*		

ROC Analysis (Honley and McNell - Youden index J)
Sensitivity*, Specificity**
AUC: area under the ROC curve; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SE: standard error; CA: cancer antigen

Table 3. Significance of lymphocyte count, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, cancer antigen 125, and age as independent variables

Independent Variables	B±SE	p	Odds ratio (95% CI)
Lymphocyte >1500 cells/μL	-2.52±0.88	0.111	12.37 (2.20–69.64)
NLR >3.4732	-1.39±0.87	0.004	4.01 (0.73–22.06)
PLR (>161.13)	-0.54±0.84	0.519	1.72 (0.33–8.94)
CA-125 >40 U/mL	3.82±0.79	<0.001	45.51 (9.60–215.72)
Age >53 years	4.05±0.80	<0.001	57.30 (12.03–272.95)
Constant	-3.26±1.03	<0.001	
Dependent Variable Groups	Nagelkerke R^2=0.682	Predicted (%) =94.9	p <0.001

Multiple logistic regression
B: set of coefficients estimated for the model; CI: confidence interval; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SE: standard error

sensitivity and 50.0% specificity at values above the cutoff for the diagnosis of a malignant ovarian mass. For CA-125, levels higher than the cutoff value had 78.8% sensitivity and 77.8% specificity for the diagnosis of a malignant ovarian mass. Finally, age greater than the optimal cutoff value (53 years) had 81.8% sensitivity and 82.2% specificity for the diagnosis of a malignant ovarian mass (Table 2). Lymphocyte count, NLR, PLR, CA-125 levels, and age were identified as independent variables and further assessed using multiple logistic regression analysis to distinguish malignant from benign ovarian masses (Table 3). Because the created model had an explanatory value of 68.2% and considering the cutoff values, the accuracy to distinguish malignant from benign ovarian masses using these markers was 94.9%.

Discussion

Because the majority of pelvic masses are benign and only ~20% are malignant, the identification of novel markers for use in the preoperative period to determine whether suspected adnexal masses are malignant or benign has become necessary (4, 11). In this study, we observed that age and CA-125 levels were higher in the malignant group. In addition, we observed that NLR, PLR, and lymphocyte count were significantly higher in the malignant group than in the benign group. The effectiveness of these five independent parameters to distinguish ovarian malignancy from benign masses reached 94.9%.

Inflammation contributes to the development and progression of various cancers. The wide intracellular array of signaling pathways is often deregulated during inflammation, thereby resulting in malignant transformation through genomic instability induction, DNA damage, and cell proliferation and angiogenesis promotion (12). Furthermore, inflammatory mediators located in the tumor microenvironment, including cytokines and interleukins, are associated with chemoresistance in various types of tumors, including ovarian cancer (13). Consequently, the interest in blood parameters such as NLR and PLR, which is based on neutrophil, lymphocyte, and platelet counts obtained from CBC in the peripheral blood, has increased. CBC is a basic preoperative laboratory test to evaluate the concentrations of blood components in epithelial ovarian cancers (8, 10, 14). In a study of 136 patients, Bishara et al. (15) studied whether pre-treatment WBC subtypes are prognostic markers in the follow-up course in epithelial ovarian cancers and observed a correlation between low lymphocyte fractions and mortality and also between high numbers of monocytes and recurrence. In a study by Yildirim et al. (16), the neutrophil and platelet counts were higher and lymphocyte counts were lower in patients with malignant tumors than in those with benign

tumors. In vivo and in vitro studies have suggested that various platelet mechanisms play important roles in the progression of ovarian cancers. In one such study, tumor-related increases in interleukin-6 levels induced hepatic thrombopoietin expression; thus, thrombocytosis may support tumor growth (17). In addition, the direct proliferative effect of platelet count on cancer cells, independent from direct contact, decreased, whereas proliferation indices were increased by anti-platelet TGF-β1 blockage in ovarian cancer cells following platelet infusion (18). NLR has been established as a prognostic marker of host inflammation. Cho et al. (4) reported that NLR was greater in patients with ovarian cancer than in those with benign gynecological growths or healthy controls. Nevertheless, the sensitivity and specificity of NLR for the identification of ovarian cancer were 55% and 81%, respectively (NLR cutoff, 3.35). NLR was identified as a marker of CA-125-negative cases and to be more sensitive than CA-125 for predicting survival (4). CA-125 levels are directly correlated with increased neutrophil count and decreased lymphocyte count. Therefore, NLR can be a useful pathogenic marker of disease status, and subsets of CA-125 levels and leucocyte counts may be correlated, which may impact the inflammatory response and alter CA-125 levels (7). Among the blood components, the potential mechanism underlying the prognostic value of NLR may be the correlation between high NLR and inflammation. Neutrophilia contributes to malignant progression by releasing both related host cells such as tumor cells and leukocytes and tumoral growth factors (e.g., vascular endothelial growth factor), thereby upregulating the production of inflammatory cytokines and chemokines (19). However, neutrophilia involving immune cells as an inflammatory response against cancer will suppress the cytotoxic activities of lymphocytes and natural killer cells, thereby hindering the immune response (20). NLR reflects these inflammatory changes and therefore may be a useful prognostic marker for cancers with no reliable marker (21). NLR can help predict the prognosis of patients with ovarian cancer. Williams et al. (7) retrospectively evaluated 519 ovarian cancer patients and demonstrated that a high NLR was correlated with disease progression and poor survival in addition to other known risk factors, including familial history. When patients with malignant ovarian masses were compared with those with benign ovarian masses, CA-125 appeared to be the most important screening marker, whereas NLR and neutrophil count could be used alone or in combination with CA-125 (16).

In the present study, we also evaluated PLR as an alternative marker to NLR. PLR and cancer stage and prognosis have been reported to be correlated. PLR of 200 has a good predictive value. In a study, Asher et al. (9) reported the usefulness of NLR and PLR as prognostic markers, as evaluated in 235 ovarian cancer patients. The authors found that age, disease stage, surgical outcome, disease grade, definite neutrophil count, platelet count, NLR (≥4), and PLR (≥300) were significantly correlated with poor survival. Only stage, residual disease, and PLR were found to be independent prognostic factors for survival. Furthermore, the predictive value of PLR in the diagnosis of ovarian neoplasms has been studied. In these studies, an increased PLR was found to be correlated with poor prognosis and decreased survival (9, 10, 22). In studies to identify alternative markers, a comparison between PLR and CA-125 revealed that a significant increase in PLR was correlated with CA-125 levels ($p<0.01$). In addition, among platelet indices, PLR was found to be the only factor useful to discern early from advanced stage disease (23). In a similar study, PLR was found to be more sensitive than CA-125 to distinguish early from advanced stage ovarian cancers (24). When PLR was compared with the other blood components, such as platelet count and NLR, PLR was found to be a better prognostic marker. In addition, PLR and poor survival of patients with advanced disease are markedly correlated (9, 22, 25).

A possible limitation to this study is that we could not compare parameters according to histological subtypes in benign and malignant masses. However, because the number of the cases in each subtype was relatively small, a statistical significance would have been questionable. Furthermore, we could not assess patients with borderline tumors as a separate group because there were only three such patients. Nonetheless, we excluded these patients from the study because of insufficient histological analyses. Another limitation could be that we analyzed only CA-125 among the other tumor markers. Furthermore, the study was of a retrospective design with a relatively small sample size.

It is important to distinguish malignant from benign masses at any age. Hence, the accuracy of diagnoses can be optimized by the inclusion of additional biomarkers to the imaging modalities. CA-125 alone is insufficient. NLR, PLR, and lymphocyte count in the preoperative period in combination with age and CA-125 may be helpful to distinguish malignant from benign masses.

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