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Utility of preoperative neutrophil–lymphocyte and platelet–lymphocyte ratios in differential diagnosis of benign, borderline, and malignant ovarian tumors

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Abstract

To investigate the utility of preoperative neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) in the differential diagnosis of benign, borderline, and malignant ovarian tumors. This retrospective study was conducted on patients with adnexal masses who underwent surgical resection at Haseki Training and Research Hospital between September 2008 and September 2015. Sociodemographic characteristics, histopathological results and laboratory parameters were obtained from medical reports. Hematological parameters and calculated NLR and PLR were analyzed between tumor groups using IBM SPSS statistics version 22. 381 patients with a mean age of 40.81 (age range: 13-83 years) were included. Of those, 293 patients (76.91%) had benign ovarian tumors, 18 (4.72%) had borderline, and 70 (18.37%) had malignant ovarian tumors. The mean NLR was 2.318 ± 2.29 and the mean PLR was 134.35 ± 59 in benign ovarian tumors, the mean NLR was 4.27±5.23 and the mean PLR was 165.06±98.72 in borderline ovarian tumors, the mean NLR was 4.08±4.37 and the mean PLR was 194.72±114.85 in malign ovarian tumors. The NLR and PLR were significantly higher in malignant than benign or borderline ovarian tumors (all p= 0.0001). The diagnostic cut-off value of NLR for differentiating between benign or borderline and malignant tumors was 1.17, whereas that of PLR for distinguishing between benign/borderline and malignancy was 87.94.The present study indicated that NLR and PLR were significantly higher in ovarian cancers than in benign or borderline ovarian masses. Preoperative NLR and PLR values may help distinguish malignant from benign or borderline ovarian tumors.

Keywords: ovary tumor, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR)

1. Introduction

Ovarian cancer was the third most common gynecologic cancer with the highest mortality rate (1). The high mortality rate of ovarian cancer is attributed to its asymptomatic nature, the lack of early detection and surveillance methods, and the delayed onset of symptoms. In addition to these factors, the lack of sensitive and specific markers for the early detection of ovarian cancer results in the majority of cases being detected at an advanced stage (2, 3).

Several studies reported that inflammation plays a major role in the development of a variety of cancers by various mechanisms, including up-regulation of cytokines and inflammatory mediators, inhibiting apoptosis, triggering angiogenesis, and stimulating DNA damage (4). In addition, systemic inflammatory response mediators inhibit immune function by increasing leukocytes, neutrophils, and platelets and decreasing lymphocytes. Furthermore, platelet count may increase due to malignant disease.

Preoperative inflammatory markers, namely neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) may help to differentiate malignant from benign or borderline ovarian tumors in the preoperative period. NLR and PLR are noninvasive, easily measured, and cost-effective markers. They have been used as predictive markers or prognostic factors for a variety of cancers (5). Although the pathophysiological mechanisms underlying inflammation and oncogenesis have not yet been fully understood, the development of new biomarkers that predict cancer continues to attract attention. Therefore, we aimed to assess the utility of preoperative NLR and PLR levels to differentiate malignant from benign or borderline ovarian tumors.

2. Materials and Methods

This retrospective study included 381 patients who underwent surgery for a suspected adnexal mass between September 2008 and September 2015 in the Obstetrics and Gynecology Clinic of the Haseki Training and Research Hospital (Approval number: 299). The study protocol was approved by the Research Ethics Committee. The patient's demographic and clinical characteristics, including age, preoperative hematological parameters, and final histopathological results

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were reviewed from the hospital's electronic medical records. According to the final histopathological results, patients were divided into three groups: benign, borderline, and malignant. Preoperative complete blood count parameters were recorded and evaluated for each group, including white blood cell count, neutrophil count, lymphocyte count, monocyte count, NLR, platelet count, and PLR.

Patients with pre-existing local or systemic infection, chronic diseases, blood transfusions in the last three months, other malignancies, thrombolytic drugs, and those diagnosed with para tubal cyst, para ovarian cyst, leiomyoma, and tuba ovarian abscess were excluded from the study.

2.1. Statistical Analyses

The data were analyzed using IBM SPSS statistics version 22 (IBM, Armonk, NY, USA) with a significance of 0.05. Categorical data were presented as numbers (n) and percentages (%), while quantitative data were presented as means and standard deviations. Hematological parameters, geometric means for NLR and PLR, and 95% confidence intervals were compared according to age classification and tumor pathology using one-way analysis of variance (ANOVA). The optimal cut-off value was determined via ROC curve analysis. To determine the optimal cut-off value for the NLR and PLR, we found a cut-off level that maximizes Youden's J statistic. The area under the curve (AUC), specificity, and sensitivity were calculated. A p-value of <0.05 was considered statistically significant.

3. Results

A total of 381 patients with a mean age of 40.81 (13-83) years were included in the study. The final histopathological reports revealed that 293 patients (76.91%) had benign ovarian tumors, 18 (4.72%) had borderline, and 70 (18.37%) had malignant ovarian tumors. The mean age of patients with benign, borderline, and malignant tumors was 37.76, 50.72, and 51.02, respectively.

The histopathological characteristics of patients with benign ovarian tumors (n=293) were as follows: serous cystadenoma (n=95), mature cystic teratoma (n=79), endometrioma (n=56), mucinous cystadenoma (n=28), corpus luteum (n=14), serous cystadenofibrom (n=7), fibroma-fibrothecoma (n=7), struma ovarii (n=2), and benign Brenner tumor (n = 1).

The histopathological characteristics of patients with malignant ovarian tumors (n=70) were as follows: serous papillary carcinoma (n=39), mucinous carcinoma (n=13), endometrioid carcinoma (n=4), Kruckenberg tumor (n=3), granulosa cell tumor (n=3), and dysgerminoma (n=2). Borderline pathologies (n = 18) included mucinous borderline tumors (n = 11) and serous borderline tumors (n=7).

Patients with benign ovarian tumors were significantly younger than those with borderline and malignant tumors (p <0.001).

In benign ovarian tumors, the mean neutrophil/lymphocyte ratio (NLR) was found to be 2.318 ± 2.29 (0.05-20.62) and the mean PLR was 134.35 ± 59 (0.93-588.33), in borderline ovarian tumors mean NLR was 4.27±5.23 (0.79-17.03) and mean PLR was 165.06±98.72 (51.85±391.53), in malignant ovarian tumors mean NLR count was 4.08 ± 4.37 (1-28.29) and mean PLR count was 194.72 ± 114.85 (56.32-623.44).

There was no statistically significant difference between age groups and NLR and PLR of patients (p= 0.93, 0.95, respectively). The geometric means of NLR and PLR by age groups are shown in Table 1.

Table 1. Comparison of geometric mean neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) by age groups

Age	n	NLR	PLR
<45	235	2.06 (1.92-2.25)	127.91 (117.98-136.73)
45-54	75	2.06 (1.76-2.43)	134.74 (122.07-149.69)
55-64	38	2.15 (1.79-2.60)	124.08 (92.90-154.31)
≥65	33	2.38 (2.04-2.88)	133.25 (112.97-159.93)
Total	381	2.10 (1.97-2.24)	129.29 (121.39-136.36)
ANOVA p		0.93	0.95

Table 2. Appropriate cut-off value, sensitivity and specificity for differentiating benign or borderline and malignant ovarian tumor using ROC curve analysis

	Cut-off value	AUC	95% CI	P-value	Sensitivity (%)	Specificity (%)
NLR (Benign or borderline vs malignancy)	1.17	0.66	0.59-0.73	<0.001	91	13
PLR (Benign or borderline vs malignancy)	87.94	0.64	0.57-0.71	<0.001	90	16

Abbreviations; ROC: Receiver operating characteristic, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, vs: versus, AUC: area under the curve; CI: confidence interval

Patients with benign, borderline, and malignant ovarian tumors were evaluated using ROC curve analysis (Table 2 and Fig. 1). The diagnostic cut-off value, sensitivity, and specificity for NLR and PLR were calculated. The diagnostic cut-off value that maximized Youden's J statistic of NLR and PLR was used for differentiating. The diagnostic cut-off value of NLR (AUC=0.66, p<0.001) for differentiating between malign and benign/borderline ovarian tumors was 1.17, with a sensitivity of 91% and a specificity of 13% (Fig. 1A). The diagnostic cut-off value of PLR (AUC= 0.64, p<0.001) for differentiating between malign and benign/borderline ovarian tumors was 87.94, with a sensitivity of 90% and specificity of 16% (Fig. 1B).

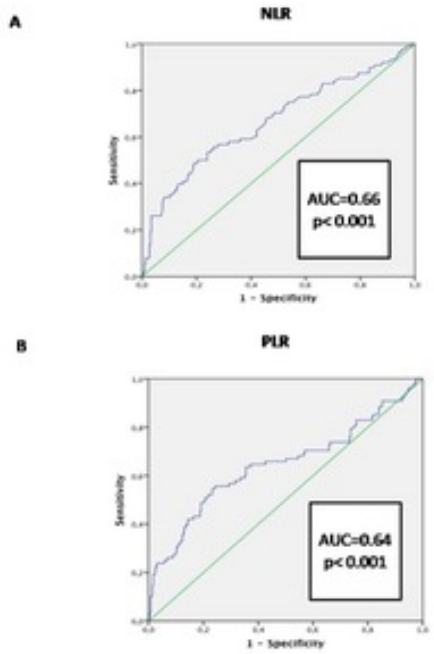

Fig 1: Receiver operating characteristic (ROC) curves analysis of neutrophil-lymphocyte ratio (NLR) (A) and platelet-lymphocyte ratio (PLR) (B) in patients with benign or borderline versus malignant ovarian tumor

4. Discussion

The present study evaluated the association of preoperative NLR and PLR between benign, borderline and malignant ovarian tumors. The study indicated that preoperative NLR and PLR values were significantly higher in malignant ovarian tumors than those in the benign or borderline ovarian tumor group. The diagnostic cut-off value of NLR in predicting malignant ovarian tumors was set at 1.17, with a sensitivity of 91% and a specificity of 13%. The cut-off value for the PLR values was also calculated to be 87.94, with a sensitivity of 90% and specificity of 16% for distinguishing malignant ovarian tumors from benign or borderline ovarian tumors.

Recently, it has been found that patients with malignant tumors have high CRP values, neutrophilia, and lymphocytopenia secondary to the inflammatory response (6). Leukocytosis and neutrophilia have been shown to be readily available prognostic factors in non-small cell lung cancer, cervical cancer, and endometrial cancer. Furthermore, an elevated leukocyte count was associated with poor survival (7). Research has shown neutrophilia may be a critical predictive factor for oncologic outcomes in patients with persistent or recurrent cervical cancer (8). A systematic review and meta-analysis by Ahmed Ebu-Zaid et al. in 2021 found that preoperative leukocytosis correlates with unfavorable pathological and survival outcomes in endometrium cancer (9). It has also been shown that preoperative leukocytosis was related to an increased risk of recurrence and mortality in patients with non-endometrioid endometrial adenocarcinoma (10). A meta-analysis conducted by Chen et al. demonstrated that NLR was an available predictor of overall survival and progression-free survival for patients with ovarian cancer (11). Prior research reported that NLR and PLR elevation was associated with poor survival in numerous cancers (12).

Systemic inflammation plays a crucial role in oncogenesis and cancer progression. In a number of studies, biomarkers of the systemic inflammatory response, NLR and PLR, were found to predict ovarian tumor characteristics. In response to inflammation, increased neutrophil, platelet, and relatively decreased lymphocyte counts can be observed, which results in elevated NLR and PLR. Previous research has established that NLR and PLR could benefit diagnosis and prognosis prediction. A study conducted by Polat et al. demonstrated that the preoperative NLR and PLR of patients with malignant ovarian tumors were significantly higher than those of patients with benign tumors. They suggest that NLR and PLR might help predict malignant ovarian cancers (13). Cho et al. also concluded that increased NLR and PLR levels served as a quick, easy, and cost-effective method for discriminating between malignant tumors and benign masses of the ovary (14). The current study confirmed that high NLR and PLR could be used to differentiate between malignant and benign or borderline tumors. In view of all that has been mentioned so far, NLR and PLR can be used in guiding clinicians in the management of a wide range of cancers.

Elevated NLR and PLR have been associated with adverse oncological outcomes as well as reflecting advanced stage and more aggressive disease (15,16). Moreover, a recent study found that NLR could be a feasible, acceptable, and efficacious biomarker in the evaluation of sensitivity to chemotherapy in advanced serous ovarian cancer (17).

The limitations of this study include that we were unable to compare parameters according to the histological subtype of benign and malignant masses. However, statistical significance would have been difficult to establish due to the relatively small number of cases in each subtype. Another possible limitation of the study was a retrospective design. Lastly, the main findings of this study were not externally validated, and further well-designed studies in an independent cohort are needed. Notwithstanding these limitations, we could evaluate patients with borderline tumors as a separate group. We hope

that the use of novel models incorporating variables such as age, CA125, ultrasound findings, and NLR and PLR values may contribute to the early detection of ovarian masses. Future studies should be conducted with larger sample sizes to discover additional markers and incorporate them into clinical practice.

In conclusion, NLR and PLR were significantly higher in ovarian cancers than in benign or borderline ovarian masses. NLR and PLR values seem to be useful inflammatory markers in predicting malignant ovarian tumors preoperatively.

Conflict of interest

The authors declared no conflict of interest.

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None to declare.

Authors' contributions

Concept: S.S.K., G.Y., D.S.A., Design: S.S.K., E.K., R.B.T., Data Collection or Processing: S.S.K., D.S.A., Analysis or Interpretation: E.K., R.B.T., P.B.İ, P.Y., G.Y., E.M., Literature Search: S.S.K., E.K., D.S.A., P.Y., Writing: S.S.K., E.K., G.Y., E.M., R.B.T., P.B.İ.

Ethical Statement

Approval was obtained from İstanbul Haseki Training and Research Hospital Ethics Committee, the study started. The ethics committee decision date is 19/12/2018 and the number of ethical committee protocol number is 299.

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