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The Impact of Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios in Epithelial Ovarian Cancer

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ABSTRACT

OBJECTIVE: This study aims to investigate the prognostic value of the preoperative neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in patients with epithelial ovarian cancer.

STUDY DESIGN: Between January 2012 and December 2018, the data and preoperative levels of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio of 116 epithelial ovarian cancer patients were retrospectively collected. The association of these relevant markers with outcomes was analyzed.

RESULTS: The difference was observed concerning optimal and suboptimal debulking in platelet-to-lymphocyte ratio ratios (p=0.04). Lymphovascular space involvement was significantly associated with higher platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio ratios (p<0.0001). Patients with ascites and lymph node involvement had a higher platelet-to-lymphocyte ratio ratio (p=0.007 and p=0.004). In recurrences, higher ratios of platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio were observed (p=0.03 and p=0.02). The analysis revealed that platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio were not independent prognostic factors for recurrence (p=0.783 and p=0.391). Regarding mortality, platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio were not independently prognostic (p=0.621 and p=0.830). It was determined that neutrophil-to-lymphocyte ratio >2.45 (HR 0.714, CI 0.622-0.794, p<0.0001) and platelet-to-lymphocyte ratio >179.4 (HR 0.736, CI 0.646-0.814, p<0.0001) could predict the presence of recurrence with a certain sensitivity and specificity, and for predicting the death, a neutrophil-to-lymphocyte ratio of >2.45 had a sensitivity of 78.26% (95% CI: 56.3 to 92.5%) and a specificity of 54.84% (95%CI: 44.2 - 65.2) (p=0.03).

CONCLUSION: The evaluation of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio is important in obtaining prognostic information before surgery. However, no significant association between the neutrophil-to-lymphocyte ratio or platelet-to-lymphocyte ratio with survival was identified.

Keywords: Epithelial ovarian cancer, Neutrophil-to-lymphocyte ratio, Platelet-to-lymphocyte ratio, Prognostic factor, Systemic inflammatory response markers

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Introduction

Ovarian cancer has the highest mortality rate among women with gynecological malignancies affecting more than 310,000 women with 207,000 deaths annually (1,2). Among all ovarian cancers, 90% of them are epithelial, the treatment modality is based on the combination of cytoreductive surgery and chemotherapy. Despite improvements in therapeutic strategies, the prognosis of patients with epithelial ovarian cancer (EOC) remains poor. Numerous prognostic factors depend on patient characteristics, tumor status and biology, the success of surgical resection, and response to chemoradiotherapy (3). Additionally, many molecular markers have shown prognostic value in patients with EOC (4).

The inflammatory responses also play a crucial role in the carcinogenesis and progression of the disease. The ratio of neutrophil-to-lymphocyte (NLR) and platelet-to-lymphocyte (PLR) are inflammatory- and immunologic-based scores described as prognostic factors in EOC (5,6). Furthermore, the alterations in the systemic inflammatory response to tumor cell manifestation of systemic inflammation can be easily performed in daily oncologic practice with inexpensive costs.

Many laboratory systemic inflammatory response markers

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have been investigated as prognostic and predictive markers in patients with EOC. However, the association between NLR and PLR with survival in EOC required further investigations. Our study aims to assess the prognostic value of NLR and PLR in EOC.

Material and method

Patients

Between January 2012 and December 2018, 116 EOC patients who have admitted to the Department of Obstetrics and Gynecology, Mersin University, recruited in this retrospective cohort study. The study is approved by the Institutional Review Board and Ethical Committee of the study center. This study was approved by the local ethical committee of Mersin University (2018/20, 2018). Informed consent for the use of their data was obtained from the patients in the hospitalization period and the study was conducted with the Declaration of Helsinki. The inclusion criteria were the primary EOC that was diagnosed and underwent cytoreductive surgery followed by adjuvant chemotherapy. The presence of active infection, coexisting any hematological disorders including hematological malignancies, or autoimmune disorders were the exclusion criteria. Also, the patients with borderline epithelial ovarian tumors and the patients administered neoadjuvant chemotherapy were also excluded from the study.

Patients were followed up every three months for the first two years and every six months. After four years, patients were annually followed up. In every administration, the clinical, imaging examinations such as ultrasound and computerized tomography, and the serum level of CA125 were utilized. Patients were defined as optimally cytoreduced as ≤1cm of residual disease. Malign high-volume ascites were described as serous fluid (>200 mL) in the peritoneal cavity (7). Lymphovascular Space Invasion (LVSI) was diagnosed when endothelial-lined spaces with or without intraluminal red cells or lymphocytes were observed in tumor tissue. NLR and PLR were measured from total blood counts by dividing the certain neutrophil or platelet count, separately, by the absolute lymphocyte count.

Statistical analysis

Collected data were analyzed by Statistical Package for Social Sciences version 22.0 (SPSS IBM Inc., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (range: minimum-maximum) and categorical variables were expressed as numbers or percentages where appropriate. The distribution of data was assessed by the Kolmogorov-Smirnov test. Student t-test, chi-square test, Kruskal-Wallis H test, and Mann-Whitney U test were used for the statistical comparisons. Pearson correlation test was used to detect the correlations among variables. Receivers operating characteristic (ROC) curves were drawn to specify the power of NLR and PLR values for predicting lymphovascular invasion, omentum involvement, tumor recurrence, and lymph node involvement. A value of $p<0.05$ was confirmed to indicate a statistically significant difference.

Results

The mean participants' age was 53.3±12.6 years (range 26– 75 years). The median level of Ca-125 was 725.5 U/mL. A total of 116 EOC were distributed as follows: serous 63.8% and the remaining were non-serous (mucinous, endometrioid, clear cell, etc.). The optimal debulking was achieved in 101 patients (77.1%) in primary surgery and the suboptimal debulking rate was reported as 22.9%. Following the review of pathological results, the final stages were found to be I in 50 patients (43.1%), II in 22 patients (18.9%), III in 44 (37.9%) patients, and IV in a patient (0.1%). Twenty-nine patients (25%) had LVSI positivity and the remaining were negative for LVSI. Ascites were detected in 40 patients (34.4%) and lymph node involvement was detected in 23 patients (19.8%). At the end of follow-up time (median: 42 months), 35 (30.2%) recurrences and 23 deaths (19.8%) were recorded. The baseline characteristics of the patients are summarized in table I.

Table I: *Clinicopathologic characteristics, demographics, and outcomes of all patients (n= 116)*

Characteristics	Value, n (%)
Age (years), mean±standard deviation	53.3±12.6
CA-125 (U/mL), median	725.5
Histologies	
High-grade serous	74 (63.8)
Other than high-grade serous	42 (36.2)
Residual tumor	
Optimal debulked	101 (77.1)
Suboptimal debulked	15 (22.9)
FIGO Stage	
Stage I	50 (43.1)
Stage II	22 (18.9)
Stage III	44 (37.9)
Stage IV	1 (0.1)
LVSI	
Yes	29 (25)
No	87 (75)
Ascites	
Yes	40 (34.4)
No	76 (64.6)
Lymph Node Involvement	
Yes	23 (19.8)
No	93 (80.2)
Recurrences	
No	81 (69.8)
Yes	**35 (30.2)**
Died of Disease	
No	93 (80.2)
Yes	23 (19.8)

LVSI; Lymph-vascular space invasion

Table II shows the correlations between preoperative PLR and NLR ratios with clinicopathological characteristics. Among age and tumor histology subgroups, no statistically significant differences were observed in PLR and NLR ratios. Surgical success was not the variable affecting NLR ratios. Besides, there was a significant difference concerning optimal and suboptimal debulking in PLR ratios (p=0.04). The patients with stage I EOC had significantly lower PLR and NLR ratios than the patients with remaining stages (p=0.007 and p<0.0001). LVSI positivity was significantly associated with higher PLR and NLR ratios (p<0.0001). Patients with ascites and lymph node involvement had higher PLR ratios (p=0.007 and p=0.004), and with this respect, no significant difference was observed in NLR ratios. In patients with recurrences, higher ratios of PLR and NLR were observed (p=0.03 and p=0.02). PLR and NLR ratios have no association with cancer deaths. A significant positive correlation was found between preoperative CA 125 level and NLR and PLR (correlation coefficients and p values 0.335, <0.0001 and 0.480, <0.0001, respectively) (Spearman's rho correlation test).

To predict the presence of recurrence, regression analysis was used to determine whether there were independent variables that could affect the threshold PLR and NLR value. The analysis revealed that PLR (HR 1.012, 95% CI 0.796-1.034) and NLR (HR 1.023, 95% CI 0.759-1.540) were not independent prognostic factors for recurrence among all other significant factors (p=0.783 and p=0.391). The stage of the disease (HR 1.092, 95% CI 1.890-8.112) was found to be the only factor that had a statistically significant relationship with recurrence (p=0.02). Regarding mortality, the results of the study showed that PLR (HR 1.001, 95% CI 0.996-1.007) and NLR (HR 1.053, 95% CI 0.656-1.690) were not independently prognostic (p=0.621 and p=0.830). The 1-, and 5-year cumulative survivals were 93% and 74%. In the presence of recurrence stage (HR 60.536, 95% CI 8.702-421.133) and age (HR 1.053, 95% CI 1.004-1.103) were found to be significant prediction factors with survival (p<0.0001 and p=0.03).

The cutoff values for NLR, and PLR were not uniform in the previous reports for EOC. On account of curve analysis for finding optimal cutoff points for the NLR and PLR. The mean NLR was 2.38±1.45 (range 1.08-10.46), and the mean PLR was 216.13±143.39 (range 34.8-797.73). In the ROC curve analysis performed to find a threshold value that alone could predict the presence of recurrence in the preoperative period, it was determined that NLR >2.45 (HR 0.714, CI 0.622-0.794, p<0.0001) and PLR >179.4 (HR 0.736, CI 0.646-0.814, p<0.0001) could predict the presence of recurrence with a certain sensitivity and specificity (Figure 1). In the ROC curve analysis performed to find a threshold value that alone could predict the death, an NLR of >2.45 had a sensitivity of 78.26% (95% CI: 56.3 to 92.5%) and a specificity of 54.84% (95%CI: 44.2-65.2) (p=0.06).

***Table II. C**orrelations between preoperative PLR and NLR ratios with clinicopathological characteristics*

Variables	PLR mean (SD)	p	NLR mean (SD)	p
Age				
≤50 years	199.4 (95.7)	NS	2.09 (1.7)	NS
>50 years	204.9 (118)		2.12 (1.4)	
Histologies				
High-grade serous	189.8 (68)	NS	2.29 (1.2)	NS
Others	204.3 (156)		2.32 (1.3)	
Residual tumor				
Optimal debulked	159.4 (102.8)	0.04	2.45 (1.6)	NS
Suboptimal debulked	224.9 (313)		3.11 (4.0)	
FIGO Stage				
Stage I	139.1 (60)	0.007	2.2 (1.3)	<0.0001
Stage II-IV	220 (166.9)		2.9 (1.6)	
LVSI				
Yes	224.9 (91.1)	<0.0001	3.57 (2.9)	<0.0001
No	152.6 (51.8)		2.33 (1.3)	
Ascites				
Yes	202.2 (287.2)	0.007	2.55 (2.3)	NS
No	156.2 (102.9)		2.41 (1.8)	
LN Involvement				
Yes	228.3 (365.1)	0.004	3.17 (4.0)	NS
No	156.3 (90.9)		2.45 (1.7)	
Recurrences				
Yes	281.4 (264.3)	0.03	3.36 (3.9)	0.02
No	159.39 (163.9)		2.23 (2.2)	
Died of Disease				
Yes	202.7 (258.3)	NS	2.98 (2.7)	NS
No	158.2 (105.2)		2.4 (1.7)	

NS = Not significant, LVSI; Lymphovascular Space Involvement, LN; Lymph Node, p<0.05 is statistically significant.

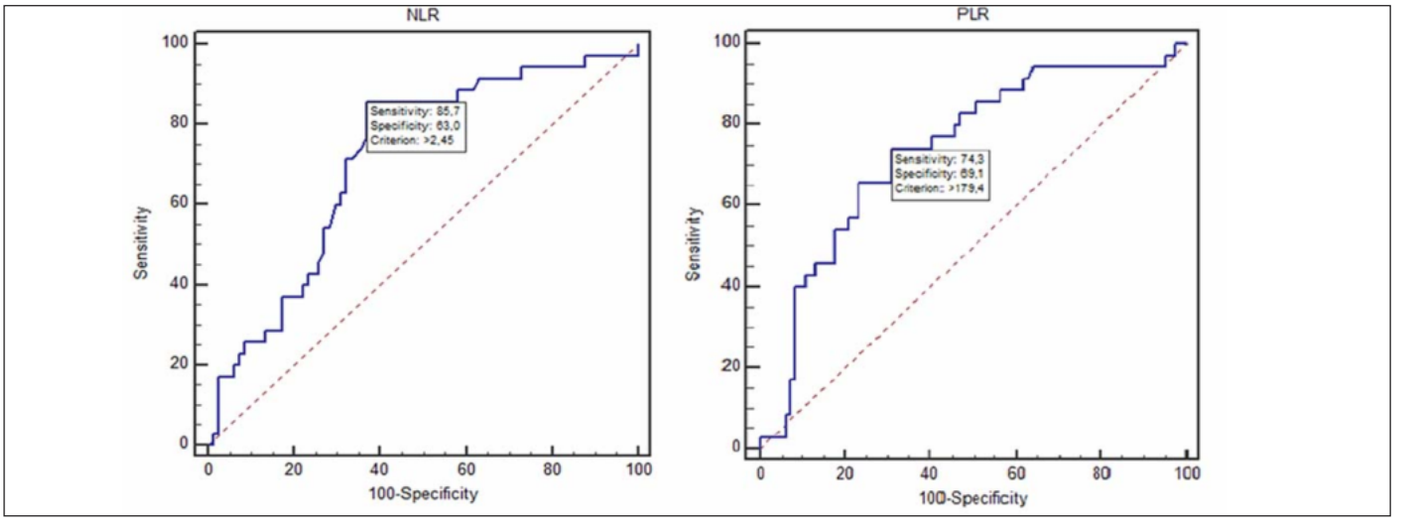

Figure 1: *Receivers operating characteristic curves of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio for predicting recurrences in epithelial ovarian cancer.*

Discussion

Inflammation plays a crucial role in the initiation and development of EOCs. Moreover, the inflammatory process contributes to the progression of EOCs (8). And there is growing evidence of the immunological profile of patients with EOCs, and the distinct immunological profile is associated with different clinical perspectives. In this context, many studies revealed a close association between increased systemic inflammatory responses assessed with immunologic-based scores such as NLR and PLR and the outcomes of EOCs (9,10). The present study showed an elevated preoperative NLR and PLR ratios signal more aggressive disease and correlates with a poor prognosis for EOC.

Reports showed that the increase in neutrophils levels results in tumor proliferation, angiogenesis, and invasion of tumor (11). It is known that the lymphocytes provide immune defense against cancer, and the decrease in lymphocytes was associated with poor prognosis in EOC (12). On the other hand, platelets were eventually turned into thrombocytosis with the immune response, and thrombocytosis formation results in invasion and metastasis. Therefore, the increase in NLR and PLR might contribute to unfavorable outcomes in EOC (13). However, some reports showed that NLR and PLR played controversial roles in EOC, and either NLR or PLR or none of them had an association with the prognosis of EOC (10,14). Our results showed higher NLR and PLR were associated with recurrences in univariate analysis, however, no significant association between the NLR or PLR with survival was identified.

The present study revealed higher median NLR and PLR ratios in terms of extra ovarian involvement. The present study revealed also higher mean NLR and PLR ratios in terms of extra ovarian involvements. The possible reasons can be the intraabdominal tumor spread might be a trigger for systemic inflammation or as described in many studies the higher tumor burden might result in elevated NLR and PLR ratios (15,16). The higher tumor burden might also be observed in patients who had suboptimal cytoreductive surgery, ascites, and LN metastases, and this proposal might be clarified by the higher rates of NLR and PLR in these relevant patients groups.

In the present study, the elevated levels of NLR and PLR run parallel to serum levels of CA 125, however, the efficacy of NLR and PLR in differentiating benign and malignant ovarian tumors was not investigated. In this context, NLR and PLR differ from CA 125 with being prognostic rather than being predictive. The fact that these immunological markers allow for better identification of patients with advanced-stage, poor prognosis, and more recurrence confirms this proposition. Moreover, a previous study reported that elevated NLR ratios predicted a poor outcome in EOC, and the combination of preoperative CA 125 with NLR could be a low-cost diagnostic tool (17).

Furthermore, NLR and PLR predict recurrence in patients with EOC with 85.7% and 74.3% sensitivity; 63% and 69.1% specificity in our study, respectively when the cut-off level for NLR and PLR were 2.45 and 179.4%. In general, a screening test requires a sensitivity of greater than 75% and greater than 75% with a specificity of at least 99.6% to reach a positive predictive value (18). However, in our study, sensitivity and specificity of regarding markers were more behind than of those were in previous studies and CA 125 (19,20).

In summary, total blood count analysis is a low-cost and easy method that is a part of preoperative workup in EOC. Therefore, the evaluating of NLR and PLR might be important in obtaining prognostic information before surgery. The fact that the present study's design is retrospective and our

cohort is relatively small, the importance of NLR and PLR in EOC should be confirmed in prospective trials with larger sample sizes.

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