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Prognostic value of preoperative neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in patients with epithelial ovarian cancer

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Summary

Purpose: The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have recently been evaluated in many cancers in prediction of survival outcomes. The purpose of this study was to investigate the impact of NLR and PLR on the prognosis of patients with epithelial ovarian cancer (EOC). *Materials and Methods:* A total of 208 patients with EOC were included in the study. Hematological parameters and clinicopathological data during diagnosis were retrospectively evaluated. The cut-off values were determined by calculating receiver operating characteristic (ROC) curve analysis of the patients. *Results:* The median overall survival (OS) of patients with low NLR was 69 months (95% CI, 43.0−94.9) whereas high NLR was 36 months (95% CI, 29.1−42.8). The median OS with low PLR patients was 76 months (95% CI, 46.4−105.5) and high PLR was 35 months (95% CI, 28.5−41.4). In serous tumors (70.7%), the median OS with low NLR and high NLR was 54 months (95% CI, 27.9−80.0) and 34 months (95% CI, 28.2−39.7), and for the median OS with low PLR and high PLR it was 51 months (95% CI, 21.2−80.7) and 35 months (95% CI, 27.8−42.1), respectively. *Conclusion:* The present findings showed that the high NLR and high PLR were associated with poor prognosis and these values are significantly remarkable in EOC patients.

Key words: Neutrophil-to-lymphocyte ratio; Platelet-to-lymphocyte ratio; Overall survival.

Introduction

Ovarian cancer is the second most common gynecological malignancy and the most leading cause of death among gynecological malignancies [1]. The majority of ovarian cancers are derived from epithelial cells and its proportion is about 95%. The clinical presentation of epithelial ovarian cancer (EOC) patients may be either acute or subacute symptoms. The EOC patients present in an acute fashion are typically those with advanced disease that requires urgent care and evaluation (e.g. bowel obstruction, respiratory distress causing pleural effusion). The subacute form of EOC involves adnexal mass or abdominal unrest. There are no effective screening and early specific symptoms in this disease and as a result, the five-year overall survival (OS) rate is generally less than 50%. Although there have been good advances in cancer treatment, the survival rate of EOC has not substantially improved. The outcome primarily depends on the stage of the disease, the histological type, and the tumor grade. Although the prognostic value of clinicopathological factors has been established in EOC, the role of molecular markers are still controversial.

Inflammation which is a consequence of immune response has a considerable role in carcinogenesis and disease progression [2]. The important markers of immune response are serum C-reactive protein, serum albumin level, and Glasgow Prognostic Score [3]. Furthermore, hematologic markers such as absolute white-cell count or its components [neutrophils, neutrophil-to-lymphocyte ratio (NLR)] and platelets, and platelet-to-lymphocyte ratio (PLR) are also prognostic markers for cancer clinical outcomes [4-6]. Recently, this systemic inflammatory response has been found to be an independent marker of prognosis in several types of cancer [4, 6-8]. NLR and PLR can be used as a simple index of systemic inflammatory response in cancer patients [9] and correlates with disease severity and prognosis for many different malignant diseases [4, 6, 9, 10]. At the same time, NLR as a cancer related inflammation marker is associated with resistance to the treatment [11]. However, data about the predictive power of NLR and PLR to predict the outcomes of patients with EOC were very limited.

In this study, the authors aimed to assess the importance of these hematological parameters (NLR and PLR) in terms of survival outcomes of the patients with EOC.

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Table 1. — *Clinical characteristics of the patients with EOC.*

Characteristics of the patients	n (%)
Age (years), Median (range)	56 (24-89)
Histopathological findings	
Serous	147 (70.7)
Non-serous	61(29.3)
Disease stage at initial diagnosis	
Stage 1-2	49 (23.6)
Stage 3-4	159 (76.4)
Grade	
Grade 1-2	62 (29.8)
Grade 3	146 (70.2)
Debulking status	
Optimal resection	120 (57.7)
Suboptimal resection	88 (42.3)
Disease status at last follow-up	
No evidence of disease (NED)	65 (31.3)
Evidence of disease (ED)	30 (14.4)
Dead	113 (54.3)
Median hemoglobin (gr/dl, range)	12 (8-18.3)
Initial serum CA-125 level (U/ml;median, range)	374 (8-8709)

Materials and Methods

Patient selection

The data of 208 patients diagnosed with EOC and presenting at the Medical Oncology Outpatient Clinic of Izmir Katip Celebi University Ataturk Training and Research Hospital, between January 2002 and December 2012, were evaluated retrospectively. The levels of NLR and PLR were recorded preoperatively. Patients with active infection (high fever, classical symptoms, and signs of the infection as of the upper and lower respiratory system, urinary system, etc, identification of the microorganisms in cultures of serous effusions and radiologic signs of the infection), active bleeding, blood transfusion within the last three months, chronic inflammatory or autoimmune disease, and steroid treatment were excluded from the study.

NLR ratio and PLR

NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. PLR was defined as the platelet count divided by the absolute lymphocyte count. Cut-off levels of NLR and PLR were determined according to receiver operating characteristic (ROC) curve analysis.

Statistical analysis

All statistical analyses were performed using SPSS version 20. All p-values < 0.05 were considered statistically significant. Survival probability was calculated using the product limit method of Kaplan Meier. Differences in survival between groups were determined using the log-rank test. ROC curves were used to determine the cut-off values of NLR and PLR.

Results

Patient characteristics

The characteristics of 208 patients are reported in Table 1. The median age of the patients was 56 years (range, 24-89). The majority of the patients had serous adenocarcinoma (70.7%) and poorly differentiated tumor (70.2%) (Table 1). Most of the patients had advanced stage disease (Stage 3-4, 76.4%). The ratio of the patients achieved optimal cytoreduction (microscopic residual disease) was 57.7% (n=120). Only 14.4% of the patients were disease-free at the last follow-up evaluation.

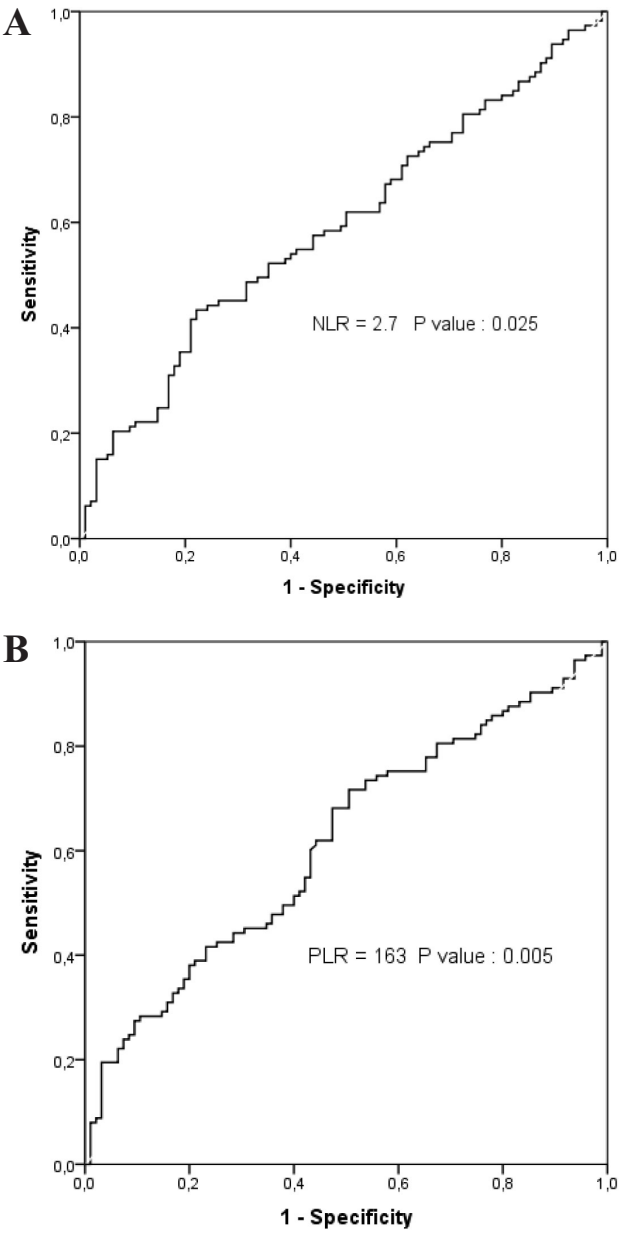

Figure 1. — A) ROC curve for the NLR. OS cut-off value of NLR: 2.7, sensitivity: 60%, specificity: 51%. B) ROC curve for the PLR. OS cut-off value of PLR: 163, sensitivity: 70%, and specificity: 50%.

Cut-off values of NLR and PLR

The median values of preoperative neutrophil, lymphocyte and platelet counts were 5.03×10^9/L, 1.85×19^9/L, and

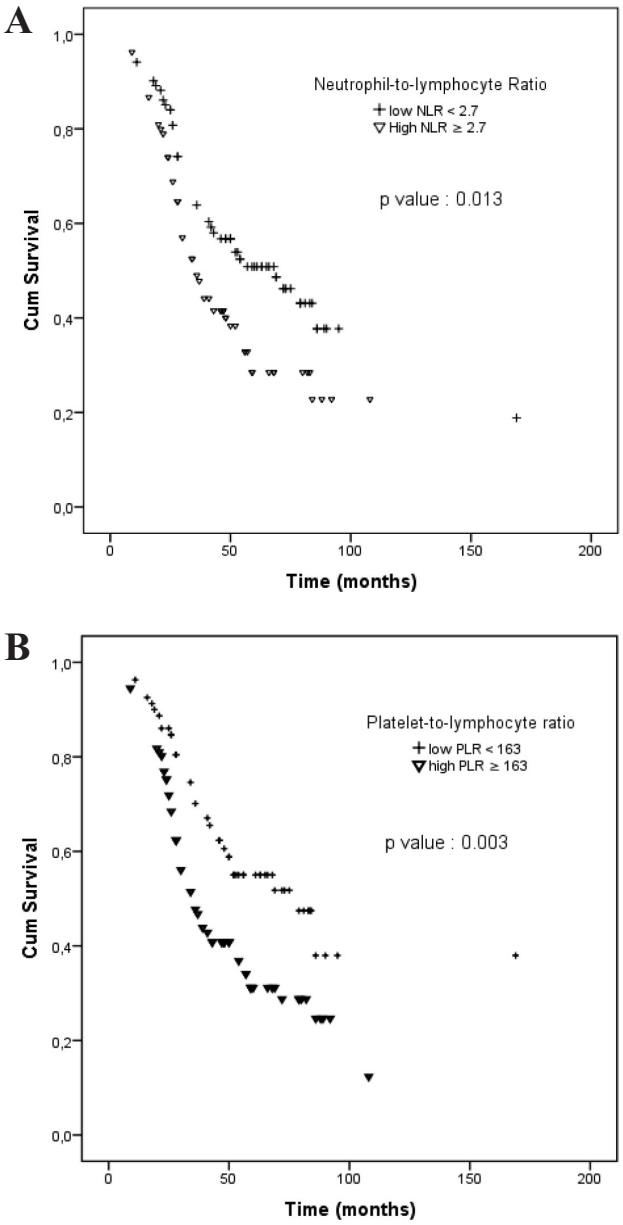

Figure 2. — A). OS curve for all patients in terms of NLR (Kaplan-Meier OS). B). OS curve for all patients in terms of PLR (Kaplan-Meier OS).

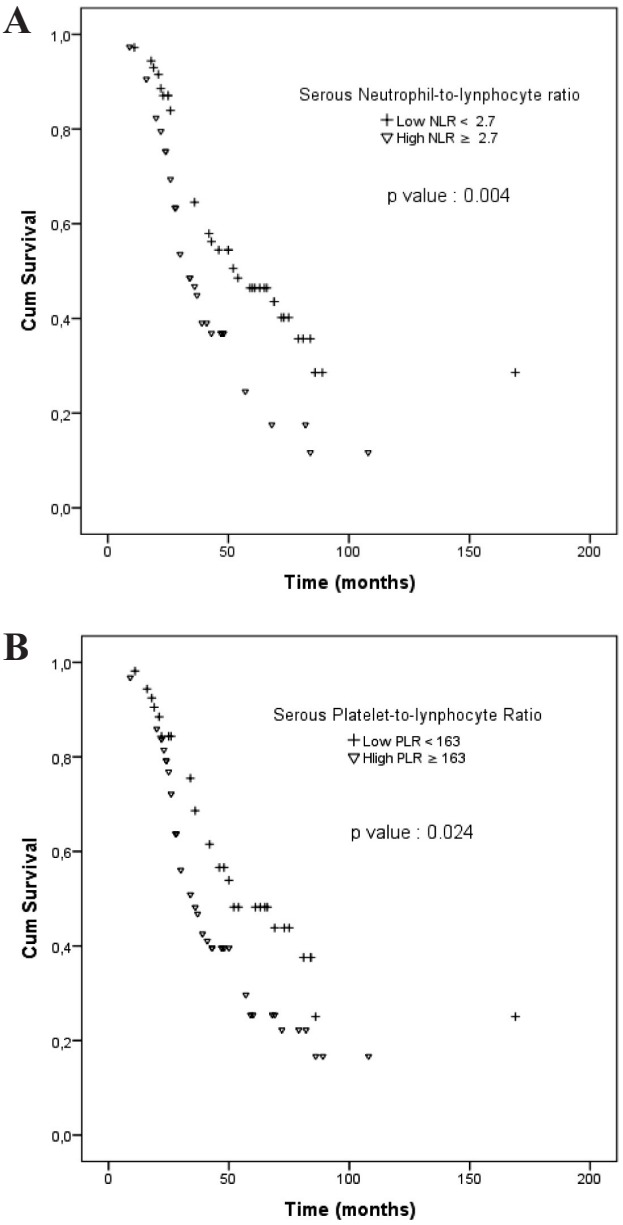

Figure 3. — A). OS curve for the serous subgroup of patients in terms of NLR (Kaplan-Meier OS). B). OS curve for the serous subgroup of patients in terms of PLR (Kaplan-Meier OS).

349×10^9/L, respectively. To categorize patients as NLR and PLR, high or low, an optimal cut-off value that maximized the sum of sensitivity and specificity in the ROC curve was used. According to ROC curve analysis of the NLR (Figure 1A) and PLR (Figure 1B), cut off values were 2.7 and 163, respectively. In all ovarian cancers, NLR yielded a sensitivity of 60% and a specificity of 50% (95% CI, 0.513−0.668). PLR yielded a sensitivity of 70% and a specificity of 50% (95% CI, 0.538−0.690).

Prognostic implications of NLR and PLR

When OS was used as an endpoint, the numbers of low NLR and high NLR patients were 102 and 106, while the numbers of low PLR and high PLR patients were 81 and 127, respectively. The median duration of OS for patients with low NLR was 69 months (95% CI, 43.0−94.9 and high NLR was 36 months (95% CI, 29.1−42.8). OS was significantly longer with low NLR than with high NLR patients (p = 0.013) (Figure 2A). For patients with low PLR, the median

Table 2. — *Outcomes of EOC patients in terms of NLR and PLR.*

	n (%)	OS (months)	*p*
All patients NLR < 2.7	102 (52.0%)	69	0.013
All patients NLR ≥ 2.7	106 (39.6%)	36	
Serous NLR < 2.7	72 (48.6%)	54	0.004
Serous NLR ≥ 2.7	75 (36.0%)	34	
All patients PLR < 2.7	81 (58%)	35	0.003
All patients PLR ≥ 2.7	127 (37.8%)	76	
Serous PLR <163	54 (51.9%)	51	0.024
Serous PLR ≥163	93 (36.6%)	35	

NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio.

duration of OS was 76 months (95% CI, 46.4−105.5) and with high PLR it was 35 months (95% CI, 28.5−41.4). OS was significantly longer with low PLR than with high PLR patients ($p = 0.003$) (Figure 2B).

When the authors analysed the values only in serous subgroup, the median duration of OS for low NLR and high NLR was 54 months (95% CI, 27.9−80.0) and 34 months (95% CI, 28.2−39.7), respectively. OS was significantly longer with low NLR than with high NLR ($p = 0.004$) (Figure 3A). In serous tumors, the median duration of OS for low PLR was 51 months (95% CI, 21.2−80.7) and high PLR it was 35 months (95% CI, 27.8−42.1). Overall survival was significantly longer with low PLR than with high PLR ($p = 0.024$) (Figure 3B, Table 2).

Discussion

This study investigated the prognostic significance of NLR and PLR in EOC patients. PLR had more influence on survival; high NLR and PLR at diagnosis were associated with poor OS in EOC patients. The low NLR and PLR group had better OS than high NLR and PLR group. In addition, subgroup analysis according to serous tumor pathology showed that OS in low NLR and PLR group was significantly longer than OS in high NLR and PLR group. Due to these reasons, the present authors suggest that NLR and PLR are independent prognostic factors for survival in EOC patients.

The role of NLR and PLR present immune response in cancer are very inconsistent. A total of 166 EOC patients were included in a study conducted by Raungkaewmanee *et al*. The patients with high PLR (> 200) had significantly shorter OS than the patients with low PLR (< 200). However, NLR (≥ 2.6) was not found to be remarkable [12]. In contrast, the present authors found both NLR and PLR correlated significantly with OS. Another study by Asher *et al*. investigated the importance of PLR in terms of survival in EOC patients. In this study, PLR (> 300) was determined as a novel independent prognostic marker [13].

In another study of 519 ovarian cancer women with an elevated NLR before treatment showed more aggressive disease course and correlation with risk factors [14]. Yildirim *et al.* evaluated 306 patients with adnexal masses who underwent surgical resection and whose diagnosis was based on pathological examination. Patients with malign ovarian tumor showed significantly higher NLR ($p < 0.05$) and PLR ($p < 0.001$) values. Consequently, they concluded that preoperative NLR and PLR values may help to identify ovarian cancer diagnosis in patients with adnexal masses [15].

The NLR and PLR values have been investigated in many other types of cancer. In triple negative breast cancer, Pistelli *et al.* showed that patients with NLR higher than 3 had significantly lower DFS ($p = 0.002$) and OS ($p = 0.009$) than patients with NLR equal or lower than 3 [16]. In head and neck squamous cell carcinoma, higher NLR was found to be a poor prognostic marker which was shown in a similar study; for each one unit increase in the NLR, the risk of death particularly increased by 4% [17]. In a study of 187 patients with small cell lung cancer, median OS was inferior in the high NLR group (NLR > 4) than low NLR group (NLR < 4). In contrast, PLR was not significantly correlated with OS at diagnosis [18].

The cytokines including chemokines, lymphokines, interferons, interleukins, and TNF are a number of group small proteins. Cytokines affect the tissue and cells by means of paracrine or autocrine effects. The chemokines play an important role in cancer-related inflammation [19]. NF-kB activates neutrophils and persists neutrophil survival by inhibiting neutrophil apoptosis [20]. Systemic inflammation is linked to the release of several proinflammatory mediators such as interleukin (IL)-1, IL-6, and TNF-α to stimulate megakaryocyte proliferation leading to neutrophilia and thrombocytosis [21]. On the other hand, cytokines, particularly IL-1β and TNF –α, lessen lymphocytes as an inverse effect and adaptive immune system is subverted [22], because the lymphocyte response is a major factor in the suppression of cancer progression [23-24]. Eventually, inflammation as a host response leads to thrombocytosis, neutrophilia, and lymphopenia [25]. Chronic or tumor-related inflammation and inflammation-related stimuli within the tumor microenvironment are responsible for cell proliferation, angiogenesis, invasion, migration, and metastasis [6,26]. The importance of inflammation in carcinogenesis was prominent and the incidence of most cancers can be diminished by controlling inflammation.

In conclusion, evaluating NLR and PLR is a method of inflammation assessment which may be easier and more cost-effective in clinical practice. The present results clearly emphasized that high NLR and PLR values predicted poorer survival and there was an OS benefit with low NLR and PLR in patients with EOC. In relation to this study, all the studies summarized previously also showed that NLR and PLR is closely associated with prognosis in cancer patients.

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