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Araştırma

The Effect of Neutrophil Lymphocyte Ratio on Prognosis of Ovarian Cancer

Nötrofil Lenfosit Oranının Over Kanserinin Prognozuna Etkisi

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ABSTRACT

Objective: In this study, we planned to investigate the association between neutrophil lymphocyte ratio (NLR) and prognosis in ovarian cancer.

Materials and Methods: IThe data of 84 patients who were followed up at Manisa Celal Bayar University Medical Oncology Clinic between May 2011 and November 2018 were analyzed retrospectively. NLR was calculated by dividing absolute neutrophil count by absolute lymphocyte count. The cut-off value of NLR was 4.2 according to the result of ROC analysis and the patients were divided into two groups as <4.2 and ≥4.2. These groups were compared with regard to overall survival (OS) and progression free survival (PFS) rates.

Results: Preoperative neutrophil and lymphocyte values were examined from 71 of 84 patients. PFS in all study population was 20 months (95% CI: 8,3-31,6, std: 5,9). PFS of 47 (66%) patients with an NLR of less than 4.2 was found to be 31 months and PFS was 12 months in 24 (33%) patients with a value higher than 4.2, and was statistically significant (p ; 0,010). There was no significant difference between two groups in OS rates (p: 0.279).

Conclusion: The results of our study indicate that pre-treatment high NLR is associated with poor prognosis in ovarian cancer patients.

Keywords: Ovarian Cancer, Neutrophil Lymphocyte Ratio, Prognosis

ÖZET

Amaç: Bu çalışmada over kanserinde nötrofil lenfosit oranı (NLR) ile prognoz arasındaki ilişkiyi araştırmayı planladık.

Gereç ve Yöntemler: Mayıs 2011-Kasım 2018 tarihleri arasında Manisa Celal Bayar Üniversitesi Tıbbi Onkoloji Kliniğinde takip edilen 84 hastanın verileri retrospektif olarak incelendi. NLR, mutlak nötrofil sayısının mutlak lenfosit sayısına bölünmesiyle hesaplanmıştır. ROC analizi sonucuna göre NLR'nin cut-off değeri 4.2 idi ve hastalar 4.2 olarak iki gruba ayrıldı. Bu gruplar genel sağkalım (OS) ve progresyonsuz sağkalım (PFS) oranları açısından karşılaştırıldı.

Bulgular: 84 hastanın 71'inde preoperatif nötrofil ve lenfosit değerleri incelendi. Tüm çalışma popülasyonunda OS (% 95 GA: 8,3-31,6, std: 5,9) oranları arasında anlamlı fark yoktu (p: 0.279). NLR'si 4.2'den az olan 47 hastanın (% 66) PFS'si 31 ay, NLR değeri 4.2'den yüksek olan 24 (% 29.2) hastada 12 aydı ve istatistiksel olarak anlamlıydı (p; 0,010).

Sonuç: Çalışmamızın sonuçları yüksek tedavi öncesi yüksek NLR'nin over kanseri hastalarında kötü prognoz ile ilişkili olduğunu göstermektedir.

Anahtar Kelimeler: Over kanseri, nötrofil lenfosit oranı, prognoz

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Introduction

Ovarian carcinoma is the most difficult malignancy of all gynecological malignancies to detect at an early stage because of its insidious onset. The vast majority of patients are diagnosed in the advanced phase. Prognostic parameters in ovarian cancer include age, tumor stage, tumor grade, histological type, and residual disease after surgery (1).

Due to high mortality and high recurrence rates, additional parameters are needed to determine the prognosis of ovarian cancer.

There is growing evidence that inflammation markers play an important role in cancer progression (2). Additionally, blood-based tests are simple and low cost to determine inflammatory state. Therefore immune cells such as neutrophil and lymphocytes have been studied as prognostic markers (3). Neutrophil lymphocyte ratio (NLR) is commonly searched for the assesment of inflammation in cancer patients (4).

The aim of this study (considering the number of patients) is the local evaluation and correlation of the neutrophil lymphocyte ratio in ovarian cancer with the literature data.

Materials And Methods

The data of 84 patients who were followed up at Manisa Celal Bayar University Medical Oncology Clinic between May 2011 and November 2018 were analyzed retrospectively. Age, smoking, additional diseases, diagnostic stage, metastasis sites, preoperative neutrophil and lymphocyte levels were recorded. NLR was calculated by dividing absolute neutrophil count by absolute lymphocyte count.

The cut-off value of NLR was 4.2 according to the result of ROC analysis and the patients were divided into two groups as <4.2 and ≥4.2. These groups were compared with regard to overall survival (OS) and progression free survival (PFS) rates.

Consent from the ethics committee was not required because of the retrospective nature of this study.

Statistical Analysis

SPSS 18.0 program was used for statistical evaluations. Comparisons between the two groups were performed using t-test, Chi-square and Fisher's exact tests. ROC analysis was performed in order to determine threshold values in patients with NLR. Kaplan-Meier was used to determine the disease-specific survival. p <0.05 was considered statistically significant.

Statistical

A total of 84 patients were included in the study. The mean age of the 84 patients was 57.51 (min: 34, max: 86). 16 (19%) of the patients were stage 1, and 42 (50%) were stage 4 at the time of diagnosis. Patients were queried about their smoking habit; 9 (10,7%) patients were current smokers, 66 (78,6%) were ever smokers and 9 (10,7%) were former smokers. 58 (69%) patients had no comorbid disease, however the remaining others had comorbid diseases like hypertension, diabetes mellitus, coronary artery disease. 58 (69%) patients were metastatic at the time of diagnosis. (see table 1 for patient characteristics).

Preoperative neutrophil and lymphocyte values were examined from 71 of 84 patients. PFS in all study population was 20 months (95% CI: 8,3-31,6, std: 5,9). PFS of 47 (66%) patients with an NLR of less than 4.2 was found to be 31 months and PFS was 12 months in 24 (33%) patients with a value higher than 4.2, and was statistically significant (p ; 0,010) (figure 1). There was no significant difference between two groups in OS rates (p: 0.279) (figure 2).

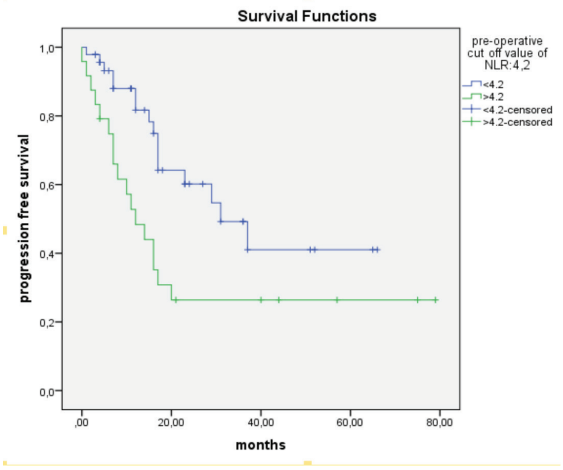

Figure 1. The relationship between progression free survival and NLR.

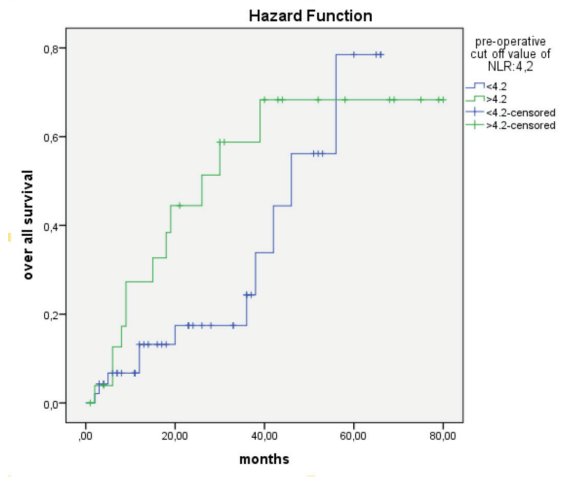

Figure 2. The relationship between overall survival and NLR.

Table 1 • Patient characteristics.

Number of patients (n)		84
Average age of the patients (min-max)		57,51 (34-84)
Smoking (n-%)	Yes	9 (10,7)
	No	66 (78,6)
	Ex smoker	9 (10,7)
Stage (n-%)	Stage 1	16 (19)
	Stage 2	4 (4,8)
	Stage 3	22 (26,7)
	Stage 4	42 (50)
Comorbidity (n-%)	No	58 (69)
	HT	13 (15)
	DM	4 (4,7)
	ASCH	2 (2,3)
	AF	3 (3,5)
	SVD	1 (1,1)
	COPD	3 (3,5)
Overall survival (months)	20	Comorbidity (n-%)
NLR	< 4,2 PFS (n-month)	47 (31)
	> 4,2 PFS (n- month)	24 (12)

HT: Hypertension DM: Diabetes mellitus, ASCAH: Atherosclerotic Coronary Artery Disease, AF: Atrial Fibrillation, SVD: Cerebrovascular Disease. COPD: Chronic Obstructive Pulmonary Disease, NLR: Neutrophil Lymphocyte Ratio PFS: Progression Free Survival

Discussion

Inflammatory cells and cytokines stimulate tumor growth by facilitating the inhibition of apoptosis while increasing the angiogenesis of cancer cells (5). Therefore, the inflammatory response may play a role in the formation and growth of various tumors. Since neutrophils can increase the production of inflammatory cytokines, they can provide a favorable environment for tumor proliferation and survival (6). Lymphocytes play a critical role in cancer-specific immune response and increased infiltration of lymphocytes in tumor tissue has been found to be associated with better prognosis (7).

An elevated level of NLR may predict increased pro-tumor inflammation and reduced anti-tumor immune power. The response of leukocytes to stress causes an increase in neutrophil count and a decrease in lymphocyte count, so the ratio of these two subgroups to each other in clinical practice is used as an indicator of inflammation (8). A study of 192 patients diagnosed with ovarian cancer by HanByoul et al. reported that OS and PFS rates for NLR positive patients (>2.60) were significantly lower than the survival rates of NLR negative patients (P = 0.034, 0.014, respectively) (9). A recent published meta-analysis of Huang et al. showed that an increased NLR is associated with a poor overall survival and shorter PFS in ovarian cancer patients, and this is in line with the results of studies with many other types of cancer (10). In 2018, Gaowen et al. published a comprehensive meta-analysis of 4046 patients on the prognostic role of the neutrophil / lymphocyte ratio in ovarian cancer patients. Their results revealed that patients with depressed NLR were expected to have higher OS after treatment (HR ¼ 1.409, 95% CI ¼ 1.112-1.786, P ¼ .005) (11). Again in 2018, a meta-analysis of Zhao et al. (3467 patients with ovarian cancer), including thirteen studies, was published. They found that the high NLR had a poor prognostic impact on OS and PFS in ovarian cancer, with a pooled HR 1.70, and HR 1.77, respectively (12). As we mentioned above several retrospective studies have been conducted to determine the effect of NLR on the prognosis of ovarian cancer. As shown in the meta-analysis of Shubo et al., it was reported that high NLR, which is consistent with our findings, is significantly associated with worse PFS compared to low NLR (13). However, in our study, there was no significant difference between the two groups in terms of OS (p: 0.279). It is thought that the possible reason for the absence of OS difference is due to the use of multiple chemotherapy regimens and types of surgery.

The mechanism between the high level of NLR and poor prognosis of various cancer is unclear. Several possible explanations have been made for the association between elevated NLR and poor prognosis in breast cancer (14). This can be explained by an inflammatory response due to tumor cells. Lymphocytes may help reducing malignant progression as tumor infiltration through a series of lymphocytes, CD3 + T cells, CD8

+ T cells, Th1 CD4 + T cells, and natural killer cells, which has been shown to improve patients' survival (15).

In conclusion, the results of our study indicate that pre-treatment high NLR is associated with poor prognosis in ovarian cancer patients. NLR can be used in daily clinical practice as a promising prognostic marker that can be obtained with simple, low cost and easily repeatable parameters. Limitations of our study are being retrospective and that tumour infiltrating neutrophils and lymphocytes have not been evaluated. Finding new prognostic markers is important for the development of treatment options in ovarian cancer. More aggressive treatment modalities would be considered in patients with negative prognostic indicators before treatment. Markers such as NLR may be helpful in determining the treatment plan. However further prospective studies with large populations are required to investigate the role of NLR on the prognosis of cancer patients.

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