ARAŞTIRMA YAZISI / RESEARCH ARTICLE

REKÜRRENT VE/VEYA METASTATIK JINEKOLOJIK TÜMÖRLERDE TEDAVİ ÖNCESİ NÖTROFİL-LENFOSİT ORANI VE TROMBOSİT-LENFOSİT ORANI TERAPÖTİK ETKİYE SAHİP MİDİR?

DOES PRETREATMENT NEUTROPHIL-LYMPHOCYTE RATIO AND PLATELET-LYMPHOCYTE RATIO HAVE A THERAPEUTIC EFFECTS IN RECURRENT AND/OR METASTATIC GYNECOLOGICAL MALIGNANCIES?

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ÖZ

AMAÇ: Bu çalışmada radyoterapive/veya radyokemoterapi uygulanan jinekolojik malignitelerde tedavi öncesi nötrofil-lenfosit (NLR) ve trombosit-lenfosit (PLR) oranlarının sağkalım üzerine etkisi incelenmiştir.dıkları ve yan etkilerini incelemek amacıyla planlanmıştır.

GEREÇ VE YÖNTEM: 2009 - 2014 yılları arasında kliniğimize tüm tedavileri yapılmış ve rutin takipleri sırasında nüks ve/veya metastaz gelişmiş 82 hasta retrospektif olarak incelenmiştir. Tüm hastaların tedavi öncesi tam kan parametreleri incelenip, sağkalım üzerindeki etkileri Kaplan Meier ve ROC eğrisi ile analiz edildi.

BULGULAR: Hastaların ortanca yaşı 57,5 (30-82) ve ortanca takip süresi 26 aydı. Kan değerlerine göre medyan WBC: 7.34, RBC: 4.33, hb: 11.7, hct: 36.4, MCV: 85.8, MCH: 27.6, MCHC: 32.1, plt: 270050, lenfosit: 1,66, nötrofil: 4.79, monosit: 0.56, eozinofiller: 0.11, bazofiller: 0.1. idi. ROC analizine göre, istatistiksel olarak PLR değeri 174 ve NLR değeri 2.06 idi. Genel sağkalım oranları 2 ve 3 yılda % 78 ve % 57 idi. Tek değişkenli analizde tedavi öncesi kan tablosunda WBC > 7.34 (p = 0.01), trombosit sayısı> 270050 (p = 0.021) ve mutlak nötrofil sayısı> 4.79 (p = 0.04) olması sağkalım üzerine olumsuz etkisi görüldü. ROC analizinin sonucunda bulunan, NLR oranının>2.06 sağkalımı olumsuz etkilediği (p = 0.005) ancak PLR oranı sağkalımı etkilemediği tespit edildi.

SONUÇ: Gelecekte, jinekolojik kanser teşhisi alan hastaların çok basit ve ucuz bir kan testi ile tedavi şekli belirlenebilir. Yüksek NLR, hastalara daha agresif bir tedavi yapılması gerektiğini gösteren bir parametre olarak kullanılabilir.

ANAHTAR KELİMELER: Radyoterapi, Jinekolojik kanserler, Nötrojil lenfosit oranı, Platelet lenfosit oranı

ABSTRACT

OBJECTIVE: In this study, the effect of pre-treatment neutrophil-to lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) on gynecological malignancies that applied radiotherapy and /or radiochemotherapy was investigated.

MATERIAL AND METHODS: The data obtained from 82 patients who applied to our clinic between 2009- 2014 and developed recurrence and/or metastasis during their routine follow-up were retrospectively evaluated. Pre-treatment whole blood parameters of all patients were examined, and their effects on survival were analyzed by Kaplan Meier and the ROC curve.

RESULTS: The median age was 57.5 (30-82), follow-up was 26 months. According to the blood values median WBC: 7.34, RBC: 4.33, hb: 11.7, hct: 36.4, MCV: 85.8, MCH: 27.6, MCHC: 32.1, plt: 270050, lymphocyte: 1,66, neutrophils: 4.79, monocytes: 0.56, eosinophils: 0.11, basophils: 0.1.Statistically; according to the ROC analysis, the boundary PLR value was 174 and the NLR value was 2.06. Overall survival rates were 2 and 3 years 78% , 57% . In univariate analysis the pre-treatment blood values; WBC > 7.34 (p = 0.01), the platelet value > 270050 (p = 0.021) and the absolute neutrophil value > 4.79 (p = 0.04) found to have a negative effect on survival. At the end of the ROC analysis, the NLR ratio was found to be above 2.06, adversely affecting survival (p = 0.005), but the PLR rate did not affect survival.

CONCLUSIONS: In the future, the treatment method of patients diagnosed with gynecological cancer can be determined with a very simple and inexpensive blood test. High NLR before treatment can be used as a parameter indicating a more aggressive treatment approach may be required in patients.

KEYWORDS: Radiotherapy, Gynecological cancer, Neutrophil-lymphocyte ratio, Platelet-lymphocyte ratio

INTRODUCTION

Despite the gradual decline in the incidence, gynecological malignancies remain to be the second leading type of cancer in women globally and the leading cause of death by cancer in women in developing countries (1). The neutrophil-to-lymphocyte ratio (NLR) is a cost-effective and simple parameter to investigate systemic inflammation, as well as predicting cancer prognosis and survival (2). Its role in the prediction of prognosis has been promoted in gastrointestinal tract malignancies (3), hepatocellular cancer (4), pancreatic cancer (5), non-small cell lung cancer (6), and urinary tract cancers (7). Furthermore, pretreatment levels of NLR have been reported as a predictor of survival in epithelial ovarian cancer (8) and uterine cervical cancer (9, 10). The inflammatory response in cancer may induce irreversible DNA damage.

Consequently, malignant cell apoptosis is inhibited, and angiogenesis is induced, leading to incessant tumor growth, surrounding tissue invasion, and metastases (11- 13). Contributing to the tumor growth further, platelets secret growth factors such as platelet-derived growth factor, transforming growth factor-β, and vascular endothelial growth factor (14, 15). Therefore, thrombocytosis is also associated with poor prog-nosis since more platelets will indicate elevated levels of platelet-related growth factors (16).

Neutrophil to lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been investigated by numerous studies as pretreatment inflammatory markers in cancer (17 - 20). The significantly elevated blood levels of inflammatory markers in different types of cancer (21, 22) formed the grounds for the hypothesis that these pretreatment inflammatory markers can serve as cost-effective parameters in predicting survival outcomes before and/or pre-radiotherapy.

The present study aimed to investigate blood cell count parameters, survival factors, and blood cell count-derived PLR and NLR values in recurrent and/or metastatic gynecologic malignancies to identify associations among them.

MATERIAL AND METHODS

Between 2009 - 2014, a total of eighty-two patients who were admitted to our clinic, diagnosed with a gynecological tumor and underwent all treatment in our hospital, and who had a recurrence and/or metastasis in their subsequent routine follow-up were evaluated retrospectively. The data were collected from the hospital database and patient files. The treatment failure in gynecological cancers was 54 patients with inoperable cervix cancer, 19 patients operable endometrial cancer, five patients with inoperable endometrial cancer, two patients with recurrent cervical cancer, one patient with endometrial sarcoma and one patient with vulvar cancer. All were evaluated according to the complete blood count (CBC) results. The white blood cells (WBC), red cell distributing width (RDW), absolute neutrophil count, absolute lymphocyte count, and absolute platelet count were used as parameters of interest. The neutrophil-lymphocyte ratio (NLR) was defined as the absolute neutrophil count divided by the absolute lymphocyte count; similarly, the platelet-lymphocyte ratio (PLR) was defined as the absolute platelet count divided by the absolute lymphocyte count. After reviewing the medical history, we collected information on clinical-pathological variables for patient analysis.

The final cytological and pathological diagnosis of the lesions followed the FIGO (International Federation of Gynecology and Obstetrics) classification based on the 2001 Bethesda System, and the classification of histological types was examined for consistency by a single specialist pathologist.

Pre-recurrence and/or metastasis treatment schedule for all patients were: 54 inoperable cervix cancer; 50 of them had pelvic radiotherapy (45Gy/1,8Gy daily with 25 fractions) with concurrent cisplatinum weekly 40mg/m2 5 weeks after pelvic radiotherapy, 5 of them couldn't get concurrent chemotherapy only had pelvic radiotherapy (45 Gy/1,8 Gy daily with 25 fractions), all inoperable cervical cancer patients had intracavitary radiotherapy (30 Gy; 6Gy/5 fraction); 19 operable endometrial cancer had a total abdominal hysterectomy and pelvic bilateral

salpingo- oophorectomy with pelvic-para-aortic lymphadenectomy was administered then pelvic radiotherapy was done (45 Gy/1,8 Gy with fraction 25) after pelvic radiotherapy intracavitary radiotherapy was done (18 Gy; 6Gy/3 fraction), 5 inoperable endometrium cancer patients had pelvic radiotherapy (45 Gy ;1,8 Gy /25 fraction) then intracavitary radiotherapy(30Gy; 6Gy/5 fraction) was done . Others had only pelvic radiotherapy (45 Gy;1,8 Gy/25 fraction) was done. After recurrence and /or metastasis 67 of 82 patients had 6 cycle carboplatinum with paclitaxel chemotherapy regimen was administered.

In addition, we evaluated the effect of pretreatment median WBC, RBC, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet, lymphocyte, neutrophils, monocytes, eosinophils, basophils counts for overall survival (OSS). Overall survival was defined as the time of pathological diagnosis of the tumor from the last follow-up.

All events were measured from the time of recurrent disease diagnosis to loco-regional or distant failure, death or last follow-up. The endpoints were analyzed using the Kaplan-Meier method and the median values were reported.

The Log-rank analysis was used to compare prognostic factors, and factors found to influence prognosis on univariate analysis were subjected to multivariate analysis using Cox's proportional hazard regression model. All calculations were performing SPSS, version 17.0 statistical software package (SPSS, Chicago, IL) and p values < 0.05 were considered significant.

ETHICS COMMITTEE

This study approved by SBÜ Kartal Dr. Lütfi Kırdar Training and Research Hospital (2019/514/156/1).

RESULTS

The median age of recurrent and/or metastatic gynecological cancer patients was 57.5 (30-82) and the median follow-up was 26 months.

Overall survival rates 2 and 3 years for recurrent and/or metastatic gynecological cancer patients were 79 % and 54 %, respectively. According to the blood values; median WBC: 7.34,

RBC: 4.33, hb: 11.7, hct: 36.4, MCV: 85.8, MCH: 27.6, MCHC: 32.1, plt: 270050, lymphocyte: 1,66, neutrophils: 4.79, monocytes: 0.56, eosinophils: 0.11, basophils: 0.1. The median pre-treatment NLR and PLR were 2,9 and 164,5, respectively. Patient characteristics and pre-treatment blood accounts were shown in **(Table 1)**.

Table 1: Clinico-pathologic and laboratory parameters in patients with recurrent and/or metastatic gynecological malignancies

Characteristics	N(%)	Median
Age	82	57,5(range 30-82)
Histology		
İnopere Servix ca.	54	
Opere Endometrium ca.	19	
İnopere Endometrium ca.	5	
Recurrent Servix ca.	2	
Sarcoma.	1	
Vulvar Ca.	1	
Treatment		
Pelvik RT+ICRT	74	
Pelvik+Paraaortik RT	8	
Blood Values		
WBC		7,34
RBC		4,33
Hb		11,7
Hct		36,4
Plt		270050
Lymphocyte		1,66
Neutrophils		4,79
Monocytes		0,56
Eosinophiles		0,11
Basophiles		0,1
MCV		85,8
MCH		27,6
MCHC		32,1
NLR		2,9
PLR		164,5

The data from the entire cohort were used to select the optimal cutoff point of NLR and PLD to predict recurrence based on the analysis of the receiver operating characteristic (ROC) curve and determined that the optimal cutoff point of NLR and PLD were 2.06 and 174 **(Fig. 1A, B)**.
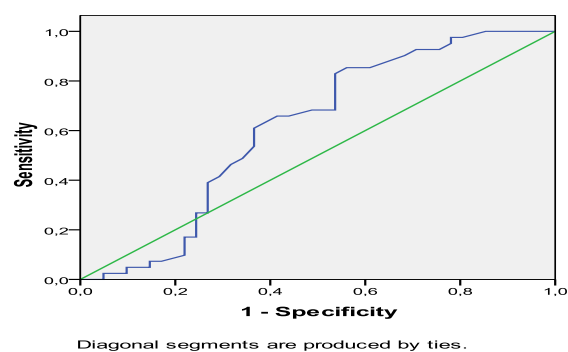

Diagonal segments are produced by ties.

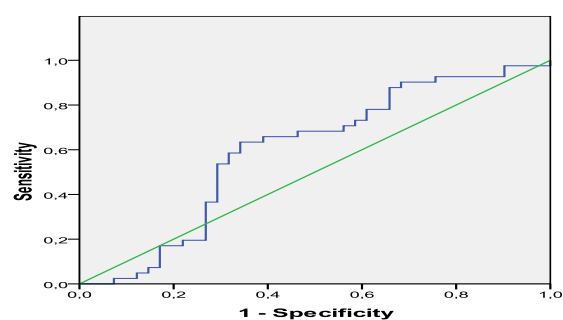**Figure 1A:** ROC Curve for Neutrophil Lymphocyte Ratio (NLR)

Figure 1B: ROC Curve for Platelet Lymphocyte Ratio (PLR)

We divided all patients into two groups depending on the cutoff value of NLR and PLR as follows: NLR-low (NLR≤ 2.06) and NLR-high (NLR>2.06), PLR-low (PLR<174) and PLR-high (PLR>174). When univariate analysis was performed, the WBC value of pre-treatment blood table was >7.34 (p = 0.008; 2 years OSS; >7.34 67.7% & < 7.34 86.2%); the platelet count was >270050 (p = 0.004; 2 years OSS ; > 270050 69.5 % & < 270050 86%) and the absolute neutrophil count was >4.79 (p = 0.003;2 years OSS ; >4.79, 70.9% & < 4.79, 88.7%) found to have a negative effect on survival. At the end of the ROC analysis, the NLR that ratio was found to be above 2.06, adversely affecting survival (p = 0.005; 2 years OSS ;>2.06 74.2% & < 91.5%), but the PLR rate did not affect survival(p=0.123), **(Fig 2A, B, C, D)**.
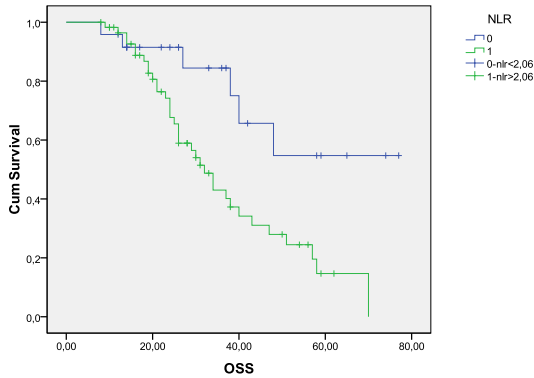

Figure 2A: Cumulative overall survival according to Neutrophil-Lymphocyte Ratio (NLR)*
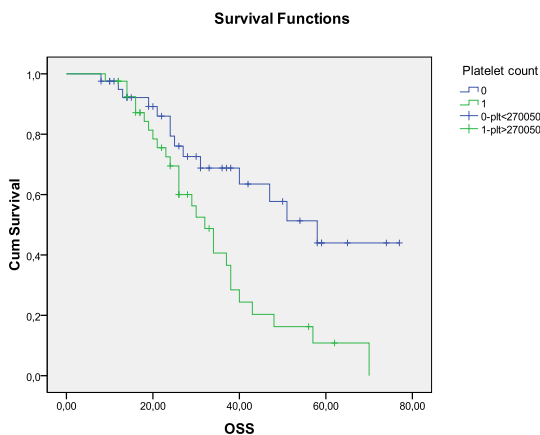*(2 years OSS; NLR >2.06 74,2% & NLR< 2.06 91.5%:p=0.005)

Figure 2B: Cumulative overall survival according to platelet count (PLT)*
*(2 years OSS; PLT>270050 69.5% & PLT< 270050 86%: p=0.004)

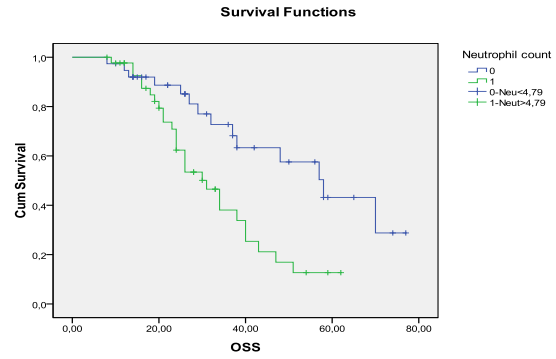**Figure 2C:** Cumulative overall survival according to Neutrophil count (NEU)*
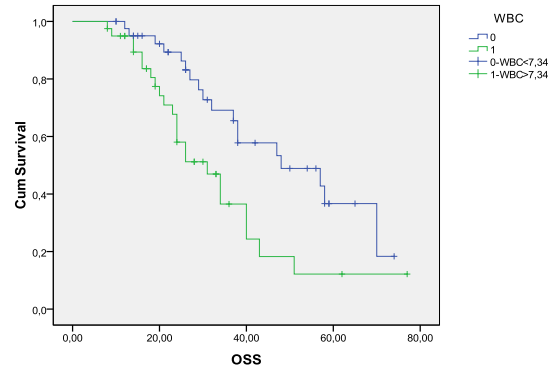*(2 years OSS; NEU>4.79 70.9% & PLT< 4.79 88.7%: p=0.003)

Figure 2D: Cumulative overall survival according to WBC count*
*(2 years OSS; WBC>7.34 67.7% & WBC< 7.34 86.2%: p=0.008)

In multivariate analysis the platelet count (HR, 1,93; 95% CI,0,99-3,76;p=0,05), NLR (HR, 2,59; 95% CI,1,06-6,32);p=0,035) and WBC (HR, 1,99; 95% CI,1,05-3,76;p=0,034) count was prognostic factor for recurrent and/or metastatic gynecologic cancers (p=0,046). It was observed that, in the univariate and multivariate analysis none of the treatment modalities which was administered (chemotherapy and/ or radiotherapy) did not effect survival **(Table 2)**.

Table 2: Relationships between laboratory parameters and overall survival in patients with recurrent and /or metastatic gynecological cancers

Variable	Univariate P-value	Multivariate P-value
NLR		
>2.06 & ≤ 2.06	0,005	0,035
WBC		
>7.34 & ≤ 7,34	0,008	0,034
PLT		
>270050 & ≤ 270050	0,004	0,05
NEUTROPHIL		
>4.79 & ≤ 4.79	0,003	0,56

DISCUSSION

The role of NLR as a potential marker for determining inflammation in systemic diseases has been demonstrated in the literature (23, 24). The majority of the studies in the literature agree that neutrophils are the primary source of circulating VEGF, which is a major player in tumor-associated angiogenesis. Furthermore, neutrophils synthesize different inflammatory cytokines including the tumor necrosis factor and interleukin-1 (IL-1), which build a favorable microenvironment for tumor growth consistently (25).

Lymphocytes, on the other hand, are major players in the cancer-specific immune response (26). The lymphocytic infiltration into tumor tissues predicts a favorable prognosis in cancer (27). In the present study, we found that elevated NLR values were associated with poor OS in recurrent and/or metastatic gynecological cancers, parallel to the results reported by studies about several other cancer types. In the figure 2A demonstrated that NLR>2.06 2 years OSS was 74.2 % & 91.5 %. Leukocyte migration is the mobilization of white blood cells to the inflammation site. It has been demonstrated that leukocyte migration also occurs in response to cancer. A study which examined the role of leukocytosis in lung cancers and colorectal cancer showed that leukocytosis is both a risk factor and a predictor of prognosis in both cancers (28). Another study in the literature demonstrated that leukocytosis and cervical cancer were associated with each other (29).

The authors concluded that leukocytosis closely relates to the tumor stage, too. Similarly, our study identified significantly high leukocyte counts in patients treated for recurrent or metastatic gynecological cancers. The present study showed that pre-treatment leukocyte counts >7.34 had poorer survival than <7.34 and 2 years survival was 67.7 % & 86.2 (Figure 2D).

Also, pre-treatment neutrophil count was the prognostic factor for recurrent or/and metastatic gynecological cancers. The patients, who had pre-treatment neutrophil count >4.79, had low survival rates than <4.79 neutrophil count (Figure 2C). These results show that inflammation was one of the prognostic factors for recurrent or/and metastatic gynecological cancers.

The platelet count is another marker involved in systemic inflammation and cancer. The platelet count is found elevated in inflammatory conditions caused by the tumor. Megakaryocytic proliferation is induced by proinflammatory cytokines, including IL-1 and IL-6, resulting in thrombocytosis (30). A recent study has reported that proinflammatory cytokines are markers of thrombocytosis and lymphocytopenia occurring due to systemic inflammatory conditions and that platelet counts of more than 270050 are negative predictive factors for OS in recurrent and/or metastatic gynecological cancers. figure 2B found that >270050 platelet count had poor OSS, and two years OSS was 69.5% & 86 %.

Smith et al. have argued that PLR is a new marker for inflammation, and it comprises two hematological parameters studied in the literature for their significance in inflammatory conditions (31). Specifically, a study in the literature reported an association between PLR values and malignant lesions of the uterus (24). However, we did not find an association between PLR and recurrent and/or metastatic gynecological malignancies in this current study; most probably due to the primary limitation of our study, which was its retrospective design and small sample size.

Our current study demonstrated that the pretreatment NLR is a good marker to monitor recurrent or metastatic gynecological cancers.

However, no correlations were found between the PLR and other parameters used in our study. Subgroups of peripheral white blood cells (WBC) are well known for undergoing alterations in systemic inflammation; particularly manifesting as relative neutrophilia and lymphocytopenia (32). Pretreatment neutrophil counts and platelet counts are suggested as potential prognostic factors independent of OS. Gwak et al. (33) reported higher values of NLR and higher leukocyte subgroup counts in women compared to males after gastrectomy for gastric cancer. That finding suggests that

women might be vulnerable to immune system alterations in female malignant diseases and surgical stress, too. Therefore, the significance of inflammatory markers in gynecologic malignancies may be higher in diagnosis and estimating prognosis. Dhammapoj et al. (34) demonstrated that there are potential independent predictive factors for resistance to treatment with cisplatin in high NLR and PLR epithelial ovaries, fallopian tube and primary peritoneal cancer. Hyun Jung Lee et al. (35) evaluated the clinical results of hematological parameters before and after treatment as prognostic factors in patients with locally advanced cervical cancer who received concomitant chemo-radiotherapy and found that post-treatment NLR was significant for overall survival.

The value of NLR in predicting the treatment response has not been established extensively for all types of diseases. Furthermore; and more specifically, there is a need to study the significance of NLR in predicting response to targeted and immune-oriented treatment modalities.

As a readily available prognostic marker in the pre-treatment setting, NLR needs to be further investigated for its potential and impact in predicting treatment response particularly to immune-focused and targeted therapies.

CONCLUSION

This study demonstrated that the neutrophil-to-lymphocyte ratio could be found high along with the elevated counts of leukocytes, platelets, and neutrophils in patients with recurrent or metastatic gynecological cancers.

The WBC count and NLR derived from a complete blood count are inexpensive and readily available parameters; which can provide useful information to evaluate treatment aggressiveness. Particularly NLR can be utilized as a predicting factor in recurrent and/or metastatic gynecological malignancies.

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