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# ENDOMETRİYUM, SERVİKS VE OVER KANSERLİ HASTALARINDA PREOPERATİF NÖTROFİL-LENFOSİT ORANININ TANISAL DEĞERİ

# THE DIAGNOSTIC VALUE OF PREOPERATIVE NEUTROPHIL-TO-LYMPHOCYTE RATIO IN PATIENTS WITH ENDOMETRIAL, CERVICAL AND OVARIAN CANCERS

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## ÖZET

**Amaç:** Bu çalışmanın amacı, endometrium, over ve servikal kanser tanısı almış olan hastaların kanser evrelerinin tahminini için biomarkır olarak ortalama platelet volümü ve nötrofil/lenfosit oranının preoperatif olarak kullanılmasıdır.

**Hastalar ve Yöntem:** 2008 ile 2014 tarihleri arasında Cumhuriyet Üniversitesi Tıp Fakültesi Kadın Hastalıkları Ve Doğum bölümünde servikal kanser, overian ve endemetrium kanseri tanısı alan hastaların verileri toplandı. Endometrium kanseri tanısı almış 69 hasta, epitelyal over kanseri tanısı alan 48 hasta ve skuamöz hücreli servikal kanseri tanısı alan 23 hastaların, sosyademografik ve labaratuvar verileri değerlendirildi. Nötrofil/lenfosit oranları, her hastalık grubu için ayrı ayrı hesaplandı.

**Bulgular:** Over ve endometrium kanseri tanısı alan ileri evre hastalarda, nötrofil/lenfosit oranı, erken evre over ve endometrium kanseri tanısı alan hastalara göre daha yüksek saptandı ($p<0.05$). Servikal kanseri tanısı konmuş olan, erken ve ileri evre hastalarda, nötrofil/lenfosit oranını açısından istatistiksel olarak fark yoktu ($p>0.05$). Tüm kanser hastalarında, platelet volümü benzer olarak saptandı ($p>0.05$).

**Sonuç:** Over ve endometrium kanseri tanısı konmuş olan hastalarda, nötrofil/lenfosit oranını ile tümörün ileri evresi arasında ilişki saptanmasına rağmen, jinekolojik kanserler arasında, ortalama platelet volüme ile tümör evresi arasında ilişki saptanmadı. Nötrofil/lenfosit oranını, ileri evre over ve endometrium kanseri tanısısında biomarkır olarak kullanılabilir.

**Anahtar Kelimeler:** Servikal Kanser; Endometrial Kanser; Ortalama Trombosit Volume; Nötrofil-Lenfosit Oranı; Over Kanseri.

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## ABSTRACT

**Objective:** The aim of this study was to evaluate the usage of preoperative neutrophil-to-lymphocyte ratio and mean platelet volume as biomarkers for the prediction of cancer stage in patients with endometrial, ovarian, and cervical cancer.

**Materials and Methods:** In the study, the file data of patients diagnosed with endometrial, ovarian and cervical cancer between 2008 and 2014 in Obstetrics and Gynecology department of Cumhuriyet University Faculty of Medicine were used. Sixty-nine cases with endometrial adenocancer, 48 cases with epithelial ovarian cancer, and 23 cases with squamous cell cervical cancer were included. Demographic and laboratory data were evaluated. Neutrophil-to-lymphocyte ratio was calculated as the absolute neutrophil count divided by the absolute lymphocyte count.

**Results:** In patients with advanced endometrial and ovarian carcinoma, neutrophil-to-lymphocyte ratios were found higher than those with early stages of such ($p<0.05$). Neutrophil-to-lymphocyte ratios of the cervical cancer patients with early- and advanced-stage tumor were not significantly different ($p>0.05$). The mean platelet volume values of patients with early- and advanced-stage tumors were found similar ($p>0.05$).

**Conclusion:** There is an association between advanced stage of tumor and neutrophil-to-lymphocyte ratio in cases with endometrial and ovarian cancers. However, no relationship was found between the mean platelet volume and tumoral stage in gynecological cancers. Neutrophil-to-lymphocyte ratio may be used in diagnostic work-up of endometrial and ovarian cancers to assess the advanced tumoral stage.

**Key Words:** Cervical Cancer; Endometrial Cancer; Mean Platelet Volume; Neutrophil-to-lymphocyte Ratio; Ovarian Cancer.

## INTRODUCTION

Current tests used to obtain information before the cancer treatment about the stages of the disease might be costly and time-consuming. Thus, development of new biomarkers which will be able to provide information about the stage of cancer prior to cancer treatment has recently become a field of intensive research. The desired features are obtaining test results in a short time and inexpensive way.

Inflammation has a significant role in cancer development and progress (1). The availability of systemic inflammation markers for use in diagnostic and prognostic purposes in several benign and malign diseases is still being investigated (2-5). Neutrophil-to-lymphocyte ratio (NLR) appears to be one of the prominent systemic inflammation markers (6). It was demonstrated that preoperative high NLR is an independent prognostic factor in patients with gastric cancer and breast cancer (7,8).

Cancerous cells might produce cytokines such as interleukin, interferon gamma and tumor necrosis factor. It was demonstrated that cytokines like interleukin-3 and interleukin-6 lead to the production of more reactive and wider platelets by affecting megakaryocytes (9). Overall, the most significant factor which might be indicated as common to all poor prognosis markers for gynecologic cancers is the stage of the disease (10-12). Bellone et al. found that patients with endometrial cancer had increased interleukin-6 levels (13). As mentioned earlier, the possible contribution of MPV in prediction of cancer stage as a marker in endometrial, ovarian and cervical cancer cases might be an important research based on the relevant information. Therefore, it is likely that MPV is increased in advanced-stage endometrial cancer.

It is an important advantage that NLR and MPV biomarkers can be obtained from full blood count analysis which is an easily accessible, inexpensive and routine laboratory analysis. In the relevant literature, there is not sufficient number of research which includes diagnostic value of NLR and MPV biomarkers in prediction of cancer stage in gynecologic cancer cases. The aim of this study was to assess the utility of preoperative NLR and MPV as biomarkers for the prediction of tumoral stage in patients with endometrial, ovarian, and cervical cancer.

## MATERIALS AND METHODS

After obtaining the study approval from the University's Human Ethics Committee, we used, in a retrospective and cross-sectional method, the file data of patients diagnosed with endometrial, ovarian and cervical cancer between 2008 and 2014 in Obstetrics and Gynecology department of Cumhuriyet University Faculty of Medicine. 140 cases in total comprised of 69 cases involving endometrial adenocancer, and 48 cases involving epithelial ovarian cancer, and 23 cases involving squamous cell cervical cancer were included in the study.

Patients with smoking habits, obesity, hypertension, diabetes mellitus, hematologic disease, coronary artery disease, metabolic syndrome, renal and hepatic disease, steroid hormone use for any reason, stroke, rheumatic and inflammatory disease history, and those receiving neoadjuvant chemotherapy and radiotherapy were excluded from the study. Demographic data such as

age, gravidity, parity and menopausal status were gathered along with preoperative hemoglobin, hematocrit, WBC, platelet count, neutrophil count, lymphocyte count and MPV values. NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count.

Staging in patients with ovarian cancer was conducted according to International Federation of Gynecology and Obstetrics (FIGO) 2014 guideline (14). Staging in patients with endometrial and cervical cancer was conducted according to International Federation of Gynecology and Obstetrics (FIGO) 2009 guideline (15).

Data were presented as median (min-max or interquartile range) or percentage. For the statistical analysis of data, Kruskal-Wallis ANOVA with Mann-Whitney test was used for post hoc pairwise comparisons. Statistical analysis was performed with SPSS software (IBM SPSS Statistics, IBM Corporation, Chicago, IL).

## RESULTS

In the study population of cases with endometrial (n=69), ovarian (n=48) and cervical (n=23) cancers, 15 patients had advanced-stage endometrial cancer, and 37 patients had advanced-stage ovarian cancer, and 7 patients had advanced-stage cervical cancer. Of patients with endometrial, ovarian and cervical cancers, the ages of the cases were 56 (36-86), 55 (19-81), and 53 (38-82), respectively. The gravidity of the cases was 4 (0-18), 5 (0-16), and 6 (0-10), respectively. The parity of the cases was 3 (0-13), 4 (0-16), and 5 (0-9), respectively. The number of menopausal cases was 51, 34, and 14, respectively. Hemoglobin levels (g/dL) of the cases were 13.2 (8.5-17), 12.4 (8.9-14.4), and 13 (7.5-16), respectively. Hematocrit levels (%) of the cases were 40.3 (26.8-52.7), 37.5 (28.9-43.1), and 38.5 (24.4-47.2), respectively. WBC count (103/mcL) of the cases was 8.9 (3.9-20), 7.9 (2.5-17.7), and 7.8 (4.9-21.8), respectively. Platelet count (103/mcL) of the cases was 295 (135-590), 327 (193-670), and 261 (183-466). Overall, the study groups were found to be comparable with regard to these parameters.

Figure 1 shows NLRs of the study population according to tumor type and stage. In the patients with advanced endometrial and ovarian carcinoma, NLRs were higher than those with early stages of these (4.57±2.69 advanced stage End vs. 3.43±2.71 early stage End and 4.53±1.85 advanced stage EOC vs. 3.60±3.54 early stage EOC, respectively) (p<0.05). However, NLRs of the cervical cancer patients with early- and advanced-stage tumor were found to be comparable (p>0.05). Among the patients with early stages of endometrial, ovarian and cervical cancers, patients with endometrial, ovarian and cervical cancers had similar NLRs (p>0.05). Among the patients with advanced stages of endometrial, ovarian and cervical cancers, NLRs of patients with endometrial and ovarian cancers were significantly higher than those of the patients with cervical cancer (4.57±2.69 advanced stage End, 4.53±1.85 advanced stage EOC, and 2.46±1.74 advanced stage cervical cancer, respectively) (p<0.05).

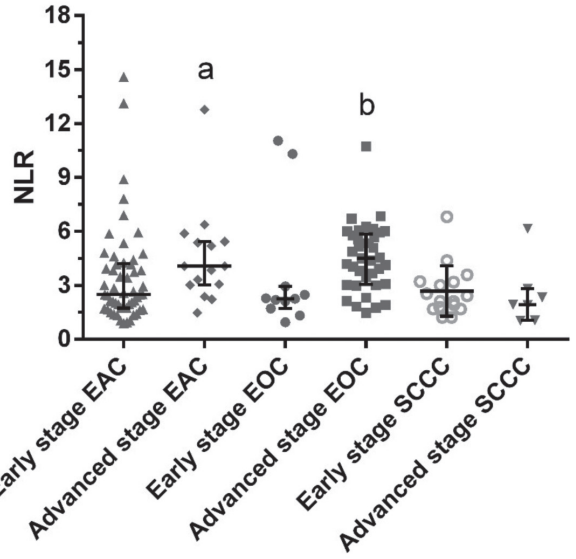


**Figure 1** • Neutrophil-to-lymphocyte ratio (NLR) of study population. EAC, endometrial adenocarcinoma (n=69); EOC, epithelial ovarian cancer (n=48); SCCC, squamous cell carcinoma of the cervix (n=23). Data were presented as median with interquartile range. aP<0.05, advanced stage EAC vs. early stage EAC. bP<0.05, advanced stage EOC vs. early stage EOC.

Figure 2 shows MPV ratio of study population according to tumor type and stage. Among the patients with endometrial, ovarian and cervical cancers, MPV ratios of patients with early- and advanced-stage tumors were comparable (8.84±1.04 advanced stage End vs. 9.1 early stage End, 8.45±1.18 advanced stage EOC vs. 9.02±1.71 early stage EOC, and 8.08±1.17 advanced stage cervical cancer vs. 9.1±1.0 early stage cervical cancer, respectively) (p>0.05). Among the patients with early- and advanced-stages of endometrial, ovarian and cervical cancers, the MPVs of patients with endometrial, ovarian and cervical cancers were found to be similar (p>0.05).

## DISCUSSION

In this study which evaluated the utility of NLR and MPV as biomarkers for the prediction of tumoral stage

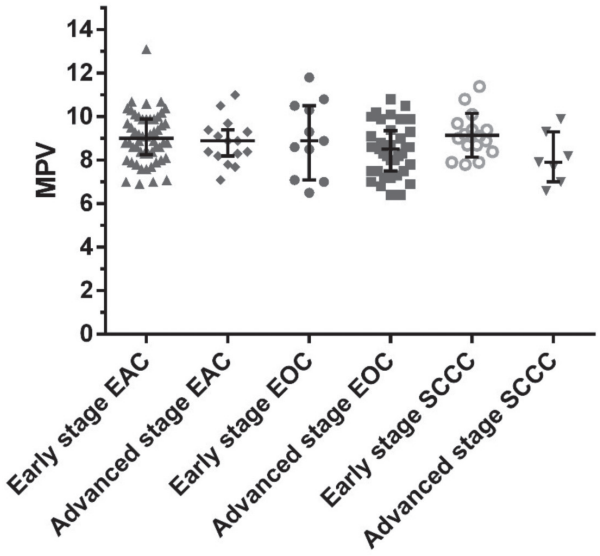


**Figure 2** • Mean platelet volumes (MPV) of study population. EAC, endometrial adenocarcinoma (n=48); EOC, epithelial ovarian cancer (n=69); SCCC, squamous cell carcinoma of the cervix (n=23). Data were presented as median with interquartile range.

of endometrial, ovarian and cervical cancers, the study groups had comparable demographic and basic hematological characteristics overall. While NLR was found higher in patients with advanced-stage endometrial and ovarian cancer compared to early stages of these cancer types, NLRs of the patients with early- and advanced-stage cervical cancer were found comparable. In cases with early-stage cancer, there is no significant difference in NLR of patients with endometrial, ovarian and cervical cancers. However, in cases with advanced-stage cancer, NLRs were higher in patients with ovarian and endometrial cancers but not in those with cervical cancer. Considering the tumoral type and tumoral stage, MPV did not provide a significant difference. Among studied gynecological cancers, increased NLR provided a correlation with the advanced stage of endometrial and ovarian cancers. However, it had no correlation with advanced stage of cervical cancer. MPV provided no clinical value as a biomarker for determination of advanced stages of endometrial, ovarian and cervical cancers.

Inflammation plays a significant role in cancer development in all stages from the inception to the metastasis stage (16). It is believed that inflammatory leucocytes and lymphocytes such as neutrophils, monocytes, macrophages and eosinophils are important in the link between inflammation and cancer development. Although it is thought that hematopoietic and proinflammatory cytokines cause the cancerous tissue, the complex mechanism of hematologic changes in cancer patients has not been fully clarified (17). NLR is a marker intensively studied recently in connection with cancer diagnosis and prognosis (18-20). In a study conducted among patients with colorectal cancer, NLR was reported as a significant parameter that can be used in tumor staging (21). MPV which works as a parameter providing information about the size and activity of platelets was studied in several research, and it was reported that increased MPV was associated with diseases such as hepatocellular carcinoma, colon cancer, gastric carcinoma, and non-small-cell lung cancer (22-25).

In a study conducted by Kokcu et al., it was demonstrated that in patients with early- and advanced-stage epithelial ovarian cancer, NLRs, platelet counts and platelet/lymphocyte ratio increased as the stage of the cancer progressed (26). In a study where Williams et al. studied the relationship of NLR with tumor characteristics, risk factors, CA125 levels and survival rates among patients with ovarian cancer, it was concluded that CA 125 level and risk factors correlated, and that it was also significant in predicting aggressive disease and low survival rates (27).

Overall, in those studies related to the use of NLR in cancer cases, the increased NLR was found to be related to the malignancy and its stage. These findings show that increased NLR provided an association with the malignancy and its advanced stage in patients with endometrial and ovarian cancers. In accordance with the relevant literature, the current study supported the value of NLR in patients with endometrial and ovarian cancer during the diagnostic work-up of patients preoperatively.

Karateke et al. reported in their study on 194 patients including those with endometrial hyperplasia, and endometrial cancer, and the control group that high levels of MPV was associated with advanced level of endometrial pathology, and that the patients with endometrial cancer had higher values (28).

Kemal et al. demonstrated in their study where they retrospectively studied 113 patients with epithelial ovarian cancer that MPV was significantly higher in patients with epithelial ovarian cancer than the healthy subjects, and that MPV was significantly low in patients with EOC postoperatively (29).

Kurtoglu et al. reported in their study that there was no significant correlation between NLR and MPV, and the stages of endometrial cancer cases, but MPV could be used while distinguishing between benign and malign endometrial diseases (4).

Overall, in previously mentioned studies, MPVs were found to be increased in patients with endometrial and ovarian cancers. However in our study, MPVs

were not higher in patients with these types of cancer and with advanced stages of such. We believe that our finding may result from the lower number of cases in our study groups, especially in the number of cases with the early stage of ovarian cancer and advanced stage of endometrial cancer.

Oge et al. conducted a study assessing the use of MPV as a biomarker in patients with endometrial adenocarcinoma. They found that the MPV value was slightly higher compared to the healthy controls. They suggested that MPV could be a biomarker for predicting advanced stage of endometrial cancers (30).

Retrospective design and single-institution experience, decreasing the number of included cases, are the main limitations of this present study. To the best of our knowledge, in endometrial, ovarian, and cervical cancer cases together, this was the first study investigating the clinical utility of preoperative NLR and MPV biomarkers among the laboratory tests used to determine whether tumoral stage is advanced or not. Further studies performed as multicenter investigation including appropriate number of cases can provide the predictive and cut-off values of NLR for detection of advanced stages of the disease in patients with endometrial and ovarian cancers.

As stated in a recent meta-analysis related to the clinical value of NLR in gastrointestinal cancers, NLR, as an easy and inexpensive laboratory test, features the important advantage of being used widely. Another advantage of NLR could be its relationship with advanced stage of disease in cancer cases (23).

In summary, there is a relationship between advanced stage of tumor and NLR in cases with endometrial and ovarian cancers. MPV has no diagnostic value for the determination of advanced stage of tumor in patients with endometrial, ovarian and cervical cancers. NLR may contribute to the diagnostic work-up of endometrial and ovarian cancers to detect the advanced tumoral stage.

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## Disclosure

The authors declare no conflicts of interest.

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