ORIGINAL RESEARCH

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Evaluation of Preoperative Hematological Parameters in Patients with Endometrial Adenocarcinoma

Endometrium Adenokanserli Hastalarda Preoperatif Hematolojik Parametrelerin Değerlendirilmesi

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Abstract

Objective: The aim of the study was to compare mean platelet volume (MPV), platelet distribution width (PDW), neutrophil/lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), eosinophil-lymphocyte ratio (ELR), platelet/lymphocyte ratio (PLR) between the patients diagnosed as low-risk or intermediate-advanced risk endometrial cancer and those with benign endometrial pathology.

Method: The study included patients who underwent hysteroscopy, dilatation curettage, or endometrial biopsy with endometrial sampling due to abnormal uterine bleeding between March 2014 and April 2022. The groups were formed according to the pathology report of endometrial sampling. In addition, subgroup analysis was made based on intraoperative frozen evaluation and final pathology results. Group 1 included benign endometrial pathology; group 2 included low-risk endometrial adeno cancer cases; and group 3 were those with endometrial adeno cancer other than low-risk endometrial cancer.

Results: No statistically significant difference was found between the groups in terms of neutrophil count, lymphocyte count, platelet count, eosinophil count, MPV, PDW, NLR, MLR, ELR, PLR (p>0.05). Endometrial thickness, body mass index, advanced age were found to be statistically significant in the endometrial adeno cancer groups.

Conclusion: MPV, NLR, ELR, MLR, and PLR values did not show any difference between groups may be because systemic inflammation was not triggered in low-risk or medium-high-risk endometrial cancer.

Keywords: ELR, endometrium adeno ca, MLR, MPV, NLR, PLR

Öz

Amaç: Çalışmamızın amacı düşük riskli ve orta ileri riskli endometrium kanseri tanısı konan hastalar ile benign endometriyal patoloji tanısı konan hastaların ortalama trombosit hacmi (MPV), platelet dağılım genişliği (PDW), nötrofil/lenfosit oranı (NLO), monosit lenfosit oranı (MLO), eozinofil lenfosit oranı (ELO), trombosit/lenfosit oranı (PLO) değerlerini karşılaştırmaktır.

Yöntem: Çalışmamıza Mart 2014-Nisan 2022 tarihlerinde hastanemizde anormal uterin kanama ön tanısıyla histeroskopi, dilatasyon küretaj ya da endometriyal biyopsi ile endometriyal örnekleme yapılan hastalar dahil edilmiştir. Endometriyal örnekleme sonuçlarına göre gruplar; benign grup, malign grup olarak isimlendirildi. Ek olarak; malign grup kendi arasında intraoperatif frozen değerlendirme ve postoperatif kesin patoloji sonucuna göre iki gruba ayrılarak alt grup analizi yapıldı. Endometriyal patolojisi olmayanla grup 1, düşük riskli endomeriyal adenokanserli olgular grup 2, düşük riskili endometrun Ca dışındaki endometrum adenokanserli (orta ve daha ileri riskli endometrum adenokanserli) olgular grup 3 olarak tanımlandı.

Bulgular: Gruplar arasında nötrofil sayısı, lenfosit sayısı, trombosit sayısı, eozinofil sayısı, MPV, PDW, NLO, MLO, ELO, PLO (p>0,05) açısından istatistiksel olarak anlamlı fark bulunmadı. Endometriyal kalınlık değeri, vücut kitle indeksi, ileri yaş endometriyal kanser grubunda anlamlı bulundu.

Sonuç: Gruplar arasında MPV, NLO, ELO, MLO ve PLO değerleri istatistiksel açısından farklılık izlenmedi. Bunun sebebi düşük riskli ve de orta-yüksek riskli endometrium adenokanserinin sistemik enflamasyonu tetiklemediğinden kaynaklanmış olabilir.

Anahtar kelimeler: Endometrium adenokanser, ELO, MNO, MPV, NLO, PLO

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Introduction

The inflammation process has a critical role in tumor development and progression (1). Neutrophils, lymphocytes, and platelets are thought to have a major role in tumor inflammation and immunology (2). Platelets, neutrophils, lymphocytes, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), eosinophil-lymphocyte ratio (ELR) monocyte/lymphocyte ratio (MLR) and mean platelet volume (MPV), and platelet distribution width (PDW) were evaluated for prediction of systemic inflammatory response in various solid tumors (3). Studies have shown that hematopoietic cytokines secreted by tumor cells cause an increase in neutrophil count (4). Nitric oxide secreted from increased circulating neutrophils, and reactive oxygen radicals suppress the T-cell response and reduce lymphocytes (5). Relative lymphopenia accompanies neutrophilia and NLR increases (6). Lymphocytes have an important role in tumor defense by preventing tumor cell proliferation and migration leading to inducing cytotoxic cell death (7). Lymphopenia has been found to associated with poor prognosis in some cancers (8). An excess of neutrophils contributes to tumor growth by affecting the cytolytic activity of lymphocytes or NK cells (9). Since the physiological reaction of leukocytes to stress causes an increase in the number of neutrophils and a decrease in the number of lymphocytes, practically the ratio of neutrophil to lymphocytes has been used as an inflammation marker (10). NLR seems to be a cost-effective inflammatory marker with prognostic and predictive value in cancer and inflammatory diseases. NLR has now been shown to be a prognostic factor for lung cancer, colorectal and ovarian cancer (11,12). On the other hand, platelets have a role in cancer progression. For example, platelets can increase angiogenesis and stimulate tumor growth with cytokines and vascular endothelial growth factor (13). In conclusion, NLR and PLR in preoperative peripheral blood are increased in many cancers including colon, esophagus, stomach, ovarian and breast cancers and are thought to be associated with poor prognosis (14-17).

Endometrial cancer is the most common cancer among gynecological malignancy in developing countries, and the most common type is endometrioid endometrial cancer (18).

Patients with early diagnosis and low-risk factors have good survival rates (95%) (19). However, adjuvant therapy (radiotherapy and/or chemotherapy) is needed in the high-risk patients. The management of the disease is carried out by determining risk groups as a result of surgical staging and evaluation of risk factors (19). Low-risk, medium, medium-high and high-risk groups are defined (19). The risk group of the patient is decided by evaluating age, stage, grade of tumor, histopathological type, degree of myometrial invasion (MI), and lymphovascular space invasion (LVSI) (19). But it is thought that the above-mentioned parameters do not determine survival with sufficient accuracy (20). Therefore, new prognostic factors are needed to predict survival in patients who have endometrial cancer.

Inflammation is the most important cause in the pathophysiology of carcinogenesis. Endometrial tumor cells first develop the ability to spread locally, and then spread to the lymphatic and vascular area from the inter-endothelial cell connections. Then they metastasize to other sites. There are no well-defined risk factors and markers to predict intermediate/advanced risk for endometrial cancer preoperatively. Tumor cells cause inflammation in the uterus. Low-cost markers that can be useful in predicting this inflammation can be useful in guiding patients' treatment. NLR, NLR, PLR, ELR, MLR, MPV in blood are simple markers of systemic inflammatory response that can be easily obtained by complete blood count. The aim of this study is to determine whether the inflammation in uterus stimulates the systemic generalized inflammatory response which can be detected by the markers of the immune response.

In a study conducted on precancerous and cancerous lesions of the endometrium, white blood cell (WBC) count has been suggested in the differentiation of endometrial hyperplasia/carcinoma. Additionally, it was emphasized that patients with abnormal uterine bleeding (AUB) without pathological findings could be identified with the help of many inflammatory parameters (21).

In this study we aim to explore the values of WBC, NLR, MLR, ELR, PLR, MPV, PDW in discrimination of the benign endometrial findings and endometrioid endometrial adeno cancer also in diffentiation of the low-risk and high-risk endometrial cancer. To the best of knowledge, this is the first study evaluating the effect of WBC, NLR, MLR, ELR, PLR, MPV, PDW among low-risk and high-risk endometrial cancer patients and benign endometrial findings individually.

Materials and Methods

Ethical approval for this retrospective study was obtained from the University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital Clinical Research Ethics Committee and the study was approved

on 03.04.2018 with the decision number 08/03. Patients over the age of 40 who admitted to outpatient clinics suffering from AUB or post menapousal bleeding (PMB) in the University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital, Clinic of Obstetrics and Gynecology between March 2014 and April 2022, and underwent endometrial sampling for histopathological evaluation with three basic diagnostic methods such as hysteroscopy, dilatation and curettage or endometrial biopsy, were included in the study. Histopathologicaly confirmed 115 cases with endometrial cancer and 75 cases with benign findings were included in the study. The data of the cases were evaluated retrospectively. The cases were divided into 3 groups according to the pathological results. The first group is consisted of 75 cases that were found to have benign endometrial findings. In cases with endometrial cancer, operation and pathological staging were performed in accordance with the 2009 recommendations of International Federation of Gynecology and Obstetrics (22). The patients with pathologic diagnose of endometrial cancer were divided into two groups by risk stratification according to preoperative histological type, intraoperative frozen, and postoperative final pathological results. Seventy-three patients with histological type of endometrial adenocancer grade 1-2, MI less than 50%, and those with negative LVSI were considered as low-risk patients consisting group 2 (stage 1a grade 1-2, lymphovascular area invasion negative). Fourty-two cases with intermediate and high-risk endometrial adenocancer greater than stage 1a grade 1-2 were evaluated in group 3 (Figure 1).

Patients with AUB, PMB, endometrial cells in cervical cytology, and postmenopausal endometrial thickness greater than 4 mm in routine gynecologycal examination were included in the study. Exclusion criteria were as follows: Having endometrial polyp(s), endometritis, acute infection, diabetes mellitus, hypertension, autoimmune diseases, chronic inflammatory disease, liver disease, malignancy hematological disease, using some medications (recombinant granulocyte colony stimulating factor, corticosteroid, tamoxifen, anticoagulant therapy and chemotherapeutic agents, hormonal therapy in the last 12 months), history of pelvic radiation and history of blood product administration in the last 12 months. In addition, patients who underwent operations such as endometrial ablation, bilateral oophorectomy, and hysterectomy were also excluded from the study.

Demographic data such as gravida, parity, age, height, weight, endometrial sampling results, transvaginal ultrasonography findings (endometrial thickness), hematological parameters were obtained from medical records retrospectively and compared. Body mass index (BMI) was calculated by dividing the weight to the square of height. A sample of 5-7 cc peripheral venous blood taken

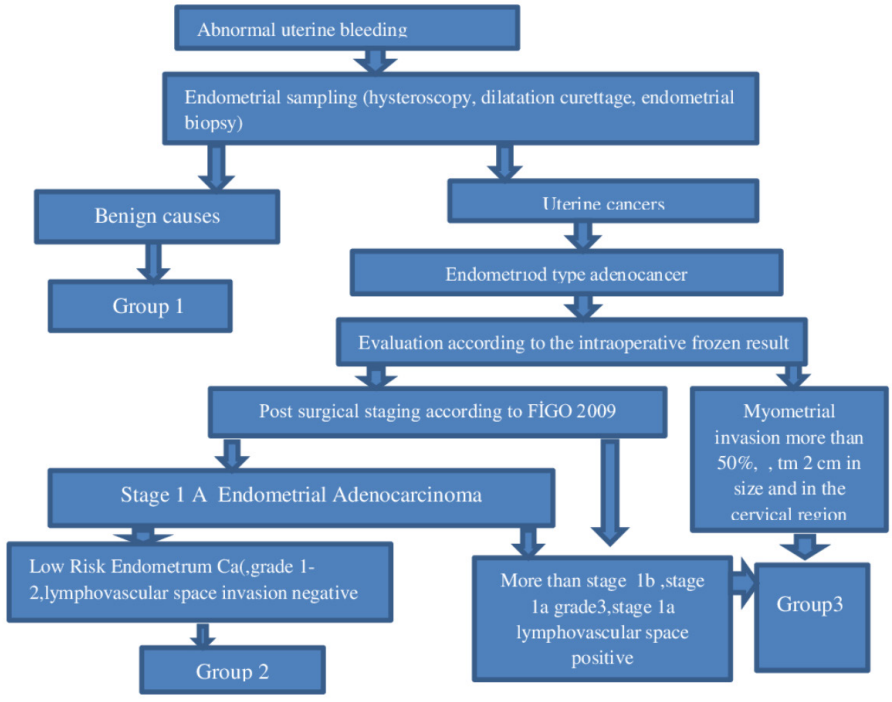

Figure 1. Shows the patients' selection flow chart

from antecybital vein and placed in a sterile EDTA tube to prevent coagulation. Hematological parameters were calculated automatically with Abbott cell dyn 3,700 blood count device within thirty minutes. MPV, PDW, eosinophil (10^3/uL), neutrophil (10^3/uL), monocyte, lymphocyte (10^3/uL) and thrombocyte (10^3/uL) counts were recorded. The ratio of ELR, MLR, NLR and PLR was calculated using these parameters. The values of MPW, PDW, NLR, PLR, MLR, ELR which are considered systemic inflammatory markers in patients diagnosed with low-risk endometrial ca, moderate-high-risk endometrial ca, and patients with benign endometrial findings were compared with each other.

Statistical Analysis

The IBM SPSS Statistics 22 (IBM SPSS, Turkey) program was used for statistical analysis. Shapiro-Wilk normality tests were used to check whether the variables follow a normal distribution. In addition to descriptive statistical methods (mean, standard deviation, frequency), One-Way ANOVA test was used for the comparison of the normally distributed quantitative variables, and the Tamhane's T2 test was used to determine the group that show difference. The Kruskal-Wallis test was used for the comparison of the parameters that did not show normal distribution, and the Dunn's test was used to determine the group showing difference. Statistical significance was evaluated at the level of $p<0.05$.

Results

The study was conducted with 190 patients. Seventy-five patients with benign endometrial biopsy results, 73 cases diagnosed aslow-risk endometrium cancer, and 42 cases diagnosed as medium-high-risk endometrium cancer were named as group 1, group 2, and group 3 respectively. The mean age, endometrial thickness, and BMI were significantly lower in group 1 compared to group 2 and group 3 ($p<0.05$). Parity was similar among groups ($p>0.05$). When groups 2 and group 3 were compared within themselves, there was no significant difference in demographic characteristics ($p>0.05$). Comparison of demographic data and endometrial thicknesses between 3 groups is given in Table 1.

When the groups were evaluated in terms of hematological parameters before treatment, it was determined that there was no statistically important difference among the groups in terms of any inflammatory parameters measured ($p>0.05$) (Table 2).

Discussion

Transvaginal sonography and endometrial biopsy are suggested to diagnose any endometrial pathology in patients with perimenopausal and postmenopausal bleeding at high-risk for endometrial cancer. Dilatation and curettage is the most common gynecological procedure for sampling endometrial tissue for histopathological evaluation (23). The use of tumor markers in the diagnosis of endometrial cancer is limited. Although there are conventional prognostic parameters used to predict the survival or to plan treatment modality for patients with endometrial cancer, these parameters seem to be insufficient especially for predicting survival. Therefore, new prognostic factors are needed (20). Many recent studies have tried to reveal the relationship between inflammation and cancer pathogenesis. Currently, there is no clear consensus on the specificity of hematological parameters in the diagnosis of endometrial cancer (24).

In a study investigating the relationship between endometrial pathologies and NLR, Mete Ural et al. (25) found NLR obviously higher in patients who have endometrial cancer than in patients who have not. Haruma et al.'s (26) study conducted with 320 endometrial cancer patients revealed that patients with high NLR had a shorter disease-free and overall survival rate than patients with low NLR. Yayla Abide et al. (27) found no significant relationship

Table 1. Comparison of demographic data between groups

	Group 1: Benign endometrial pathology (n=75)	Group 2: Low-risk endometrial adeno cancer cases (n=73)	Group 3: Medium-high-risk endometrial cancer cases (n=42)	p
	Mean ± SD	Mean ± SD	Mean ± SD	
Age	48.67±6.78	60.36±10.8	63.6±8.36	[1]**0.000***
Parity	3.31±1.28	3.25±0.78	3.07±1.7	[2]**0.428**
BMI	26.29±5.46	30.78±4.35	31.14±3.65	[1]**0.000***
Endometrial thickness (mm)$_{(median)}$	7.73±3.85	15.45±7.2	17.81±8.39	[2]**0.000***

[1]One-Way ANOVA test, [2]Kruskal-Wallis test,*p<0.05, SD: Standard deviation, BMI: Body mass index

between endometrial hyperplasia, endometrial cancer and control groups in terms of NLR and PLR. Likewise with Yayla Abide et al. (27), in our study, no significant relationship was found among groups in terms of NLR.

The presence of thrombocytosis in patients with malignant tumors was shown in some previous studies (28). Gücer et al. (29) showed that thrombocytosis negatively affects the prognosis in endometrial cancer and significantly reduces the 5-year survival rat. Conversely, Oge et al. (30) reported that hemoglobin value and platelet count did not change between endometrial cancer patients and healthy women in their study. In another study, Acmaz et al. (21) showed that PLR was lower in patients with benign endometrial findings and suggested that this ratio could be used to differentiate these patients from endometrial cancer and hyperplasia. On the other hand, Mete Ural et al. (25) suggested that unlike NLR, PLR was not useful in distinguishing these three groups from each other in a study of 472 cases including benign endometrial findings, endometrial hyperplasia, and endometrial cancer cases. In our study, no significant relationship was found between groups in terms of PLR.

There are many studies showing that MPV is increased in gastrointestinal and urinary system malignancies independent of the number of platelets (31,32). In the study by Oge et al. (30), conducted with 310 patients diagnosed with endometrial cancer, MPV values were statistically significantly higher in patients diagnosed with advanced endometrial cancer compared to control group (30). In a study by Karateke et al. (33), the highest MPV and N/L rates were found in endometrial cancer group compared to hyperplasia, and benign pathologies. There are also studies that have opposing results. Temur et al. (34) reported that MPV values were not associated with prognostic factors or survival rate in endometrial cancer. They found no difference between the benign group and cancer group regarding endometrium in terms of the MPV value (35). In our study, no significant relationship was found between groups in terms of MPV.

Monocytes/macrophages also have a very important role in tumor progression. There is increasing proof that tumor-associated macrophages originating from circulating monocytes depress the host immune system and induce tumor angiogenesis, proliferation, migration, and metastasis (36,37). In the study of Cummings et al. (38), no relationship was found between MLR and survival, and it was emphasized that NLR and PLR are superior markers than MLR in endometrial cancer. There was no evidence of an effect of absolute lymphocyte count, MLR, NLR on overall, cancer-specific or recurrence-free survival (39). In our study, no important relationship was found among groups in terms of MLR value.

There is only one study in the literature addressing the prognostic potential of ELR in endometrial cancer (40). Increased ELR portend worse overall survival in endometrial cancer, especially in patients characterized as a high-risk group (40). In this study, no important relationship was found between groups in terms of ELR.

Table 2. Comparison of hematological parameters among the three groups

	Group 1: Benign endometrial pathology (n=75)	Group 2: Low-risk endometrial adeno cancer cases (n=73)	Group 3: Medium-high-risk endometrial cancer cases (n=42)	p
	Mean ± SD	Mean ± SD	Mean ± SD	
$NLR_{(median)}$	2.21±0.88 (2)	2.31±0.88 (2.1)	2.47±0.95 (2.5)	[1]**0.309**
$MLR_{(median)}$	0.2±0.07 (0.2)	0.23±0.1 (0.2)	0.22±0.11 (0.2)	[1]**0.263**
$ELR_{(median)}$	0.07±0.05 (0.1)	0.08±0.1 (0.1)	0.11±0.15 (0.1)	[1]**0.303**
$PLR_{(median)}$	132.17±46.09 (129.9)	145.8±59.05 (136.6)	139.71±48.76 (134.5)	[1]**0.592**
$Neutrophil_{(median)}$	4.76±1.53 (4.8)	4.64±1.72 (4.5)	5.05±1.38 (4.9)	[1]**0.222**
$Lymphocyte_{(median)}$	2.36±0.93 (2.1)	2.13±0.82 (2)	2.24±0.82 (2.3)	[1]**0.256**
Monocyte	0.45±0.13	0.45±0.14	0.46±0.16	[1]**0.912**
Platelet	281.67±61.71	280.63±74.06	292.17±76.96	[1]**0.666**
$Eisonophile_{(median)}$	0.17±0.1 (0.2)	0.15±0.11 (0.1)	0.19±0.15 (0.2)	[1]**0.196**
$MPV_{(median)}$	8.87±1.22 (9.1)	9.09±0.91 (9.1)	9.11±0.88 (9)	[1]**0.653**
$PDW_{(median)}$	16.20±1.310 (16.1)	15.67±2.45 (15.9)	15.59±1.94 (15.8)	[1]**0.062**

[1]Kruskal-Wallis test, *p<0.05, SD: Standard deviation, NLR: Neutrophil/lymphocyte ratio, PDW: Platelet distribution width, MLR: Monocyte-lymphocyte ratio, ELR: Eosinophil-lymphocyte ratio, PLR: Platelet/lymphocyte ratio, MPV: Mean platelet volume

Karateke et al. (33) found a significant relationship between endometrial hyperplasia, endometrial cancer and control groups in terms of PDW in their study. Conversely, Temur et al. (35) found no difference in PDW value between benign endometrial pathology and endometrial cancer. In this study, no meaningful relationship was found among the 3 groups in terms of PDW.

Conclusion

In cancer patients, prognostic parameters provide information about the possible clinical course of the disease and allow patients to be divided into different risk groups. Presence of reliable and valid prognostic markers is very important in planning the treatment modality. It has been indicated in certain studies that MPV, NLR and PLR values are elevated in advanced endometrial malignancies and may be used as a prognostic factor. However, the results of our study revealed that the use of inflammatory parameters before treatment in endometrial cancer does not give an idea about the course of the disease. There is still no clear consensus on the specificity of these hematological parameters in the diagnosis of endometrial cancer.

In our study, we see that MPV, NLR, PLR, ELR, and MLR values did not change regardless of the etiology (benign or endometrial cancer) for AUB or PMB. This may be because the inflammation occurring in endometrium due to cancer did not trigger the release of some cytochemicals known to stimulate a systemic generalized inflammatory response.

Ethics

Ethics Committee Approval: Ethical approval required for this retrospective study was obtained from the University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital Clinical Research Ethics Committee and was approved on 03.04.2018 with the decision number 08/03.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.K., F.K.G., Concept: S.K., D.K., Ö.K., F.K.G., H.Y.N., E.N.D., N.B.C., Design: S.K., D.K., Ö.K., F.K.G., H.Y.N., E.N.D., N.B.C., Data Collection or Processing: S.K., D.K., Ö.K., F.K.G., H.Y.N., E.N.D., N.B.C., Analysis or Interpretation: S.K., D.K., Ö.K., F.K.G., H.Y.N., E.N.D., N.B.C., Literature Search: S.K., D.K., Ö.K., F.K.G., H.Y.N., E.N.D., N.B.C., Writing: S.K., D.K., Ö.K., F.K.G., H.Y.N., E.N.D., N.B.C.

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