Original Investigation

The Percentage of Peripheral Eosinophils as a Sensitive Marker for Differentiating FIGO Grade in Endometrial Adenocarcinomas

Akış et al. The Role of Eosinophils in Endometrial Carcinoma

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Abstract

Objective: Studies on eosinophils have mostly been directed to parasitic infections and allergic diseases, but the role of eosinophils in oncology has been largely ignored. Eosinophils are an important modulator of the immune response and components of the inflammatory process against the tumor. This study has been done to reveal the relationship between the data of 318 patients whose final pathology result was reported as a pure endometrioid type endometrial carcinoma (EC) and pre-operative peripheral blood eosinophil percentages.

Material and Methods: The data were analyzed in two groups as present/absent according to whether there are tumor metastases in the adnexes, lymph nodes, cervical stroma, and whether there is lymphovascular space invasion. FIGO grade was taken as basis in the evaluation of the tumor grade; Low-grade defines grade 1 or 2, and high-grade defines grade 3. The requirement for lymph node dissection was designed according to Mayo criteria. SPSS software program was used for statistical analysis.

Results: The mean percentage of eosinophils in high-grade patients was 2.75 ± 0.35, and it was statistically significantly higher than the mean percentage of eosinophils of 1.79 ± 0.09 found in low-grade patients (p= 0.013). In the ROC analysis, when the cut-off eosinophil percentage was taken as 1.95%, the sensitivity was calculated as 62% and specificity as 67% (p= 0.004).

Conclusion: Eosinophil percentages which are a simple, easily accessible, and inexpensive method can be an important pre-operative predictive tool. Eosinophil percentages can be used in determining the need for surgical staging in EC.

Keywords: Endometrial adenocarcinoma; eosinophil counts; fertility-sparing; tumor grade; peripheral blood eosinophils

Introduction

Studies on eosinophils derivating from the myeloid series have mostly been directed to parasitic infections and allergic (asthma, etc.) diseases, and the role of eosinophils in oncology has been largely ignored. Whereas, eosinophils are also the basic cells of the immune system like neutrophils and lymphocytes. Studies report that eosinophils are an important modulator of the immune response and components of the inflammatory process against the tumor (1,2). In particular, it has been shown that they can infiltrate the tumor in response to therapeutic agents. In addition, eosinophils have been shown that as one of the main elements of the tumor microenvironment, it can recognize various stimuli coming from the tumor, synthesize various substances, and direct tumor biogenesis. In this context, eosinophils may contribute to the development of new treatment strategies (3).

The increase in the growth rate and aggression of the tumor directly affects the tumor microenvironment and regulates the immune response through various cytokines. Moreover, this immune response may be regulated by eosinophils. The importance of eosinophils, which can work easily and cheaply in peripheral blood analysis, has been reported for different types of cancer such as colon cancer, nasopharyngeal cancer (4,5). And, the importance of eosinophils has been discussed in recent studies in patients with melanoma and lung cancer treated with immunotherapy (6-8). Also, the role of peripheral blood eosinophils in low and high-grade gliomas has been analyzed very recently (9). Although the role of eosinophils in gynecological tumors has been discussed in cancer of the ovary (10) and cervix (2), there is a limited number of studies in endometrial carcinoma (EC) (11).

In the present study, our objective is to evaluate pre-operative peripheral blood eosinophils counts and post-operative prognostic factors in patients with endometrioid type EC.

Material and Methods

This retrospective study has been done to reveal the relationship between the data of 318 patients whose final pathology result was reported as a pure endometrioid type EC and pre-operative peripheral blood eosinophil percentages, between 2014 and 2020. Written and oral informed consents were obtained from all patients before surgery. The study was approved by the local ethics committee of the hospital. (Approval No: 2021/86)

The data were analyzed in two groups as what percentage of the myometrium is infiltrated with the tumor (<50% and 50%) and present/absent according to whether there are tumor metastases in the adnexes, lymph nodes, cervical stroma, and whether there is lymphovascular area invasion (LVSI). Tumor size (mm) was based on the largest diameter stated in the final pathology report. FIGO grade was taken as basis in the evaluation of the tumor grade; Low-grade defines grade 1 or 2, and high-grade defines grade 3. The requirement for lymph node dissection was designed according to Mayo criteria; It has been determined that lymph node dissection is not required in cases of ≤ 2 cm tumor size (TD), <1/2 myometrial invasion (MI), and low-grade tumors (12). Otherwise, patients with adequate lymph dissection were included in the study, and it was decided to remove at least 15 pelvic and/or paraaortic lymph nodes for adequate lymph dissection (13,14). All patients were re-evaluated in the gynecologic oncology council before anesthesia examination. All patients had blood test results during the anesthesia consultation (except 4 patients). As a clinic practice, the maximum acceptable period of approval obtained by consultation is 4 weeks. The percentage of eosinophils in the peripheral blood analysis performed during the pre-operative anesthesia consultation was used for analysis to standardize and reduce the tendency for variability. Complete blood count analyzes were performed within 4 hours after collection of blood samples K2EDTA on a Mindray BC-6800 hematology analyzer. Eosinophil percentages; It was found by dividing the eosinophil count by white blood cells and multiplying by 100 [(Eosinophil / Wbc) x 100)]. Twenty-seven patients who required lymph dissection but were not staged, 19 patients who were insufficiently staged, and 4 patients without pre-operative peripheral blood analysis were

excluded from the study. All inclusion and exclusion criteria are presented in *Figure 1*. A further analysis was performed to evaluate the aging factor in EC in terms of tumor grade and eosinophil percentages.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) software 20 (SPSS, Inc. Chicago, IL, USA) program was used for statistical analysis. The histogram and normality plots and Shapiro–Wilk normality test were used for data distribution analysis. Parametric tests were used to analyze continuous variables with normal distribution. P values less than 0.05 were interpreted as significant. Receiver Operating Characteristic (ROC) analysis was used to determine the threshold value and diagnostic qualifications of the variables.

Results

A total of 268 patients with the lowest age of 26 and the oldest age of 82, were included in the study. Among these patients, 239 patients with FIGO grade 1 or 2 were defined as Low Grade and 29 patients with FIGO grade 3 as High Grade. The mean percentage of eosinophils in high-grade patients was 2.75 ± 0.35, and it was statistically significantly higher than the mean percentage of eosinophils of 1.79 ± 0.09 found in low-grade patients (*p= 0.013*).

The mean percentage of eosinophils in patients with lymph node metastasis was 2.43 ± 0.34, and the mean percentage of eosinophils in the group without lymph node metastasis was 1.84 ± 0.1. Although there was no statistically significant difference between the two groups, it was noteworthy that the p-value was close to 0.05 (p= 0.066). The mean eosinophil percentage of 102 (38.1%) patients with tumor size ≤ 2 cm was 1.89 ± 0.16, and 166 (61.9%) patients with > 2 cm had an mean eosinophil percentage 1.90 ± 0.12 (p= 0.940). The mean percentage of eosinophils of 184 (68.7%) patients with MI ≤ 1/2 was 1.94 ± 0.11, and the mean percentage of eosinophils of 84 (31.3%) patients with > 1/2 was 1.79 ± 0.17 (p= 0.464). When the patient groups were compared according to the LVSI, cervical stromal invasion, and adnexal involvement, there was no statistically significant difference in terms of the mean percentage of eosinophils. When the patients were separated according to FIGO stages, there was no statistically significant difference in the mean percentage of eosinophils. All detailed statistical analysis results were given in Table.

The percentage of eosinophils predicting high-grade tumors with the highest sensitivity and specificity was analyzed. In the ROC analysis, when the cut-off eosinophil percentage was taken as 1.95%, the sensitivity was calculated as 62% and specificity as 67%. ROC Curve analysis was statistically significant (p= 0.004) and the area under the curve (AUC) was calculated as 0.66 (Figure 2A). When the patients were divided into two groups with eosinophil percentages <1.95% and ≥ 1.95%, the percentages of high-grade in these groups were 6.5% (11/170) and 18.4% (18/98), respectively. Also, a subgroup analysis was performed in FIGO stage 1A; when the ROC Curve cut-off eosinophil percentage was taken as 1.95%, the sensitivity was calculated as 80% and the specificity as 65%. This statistical analysis was significant (p= 0.006) and the area under the curve (AUC) was calculated as 0.76 (Figure 2B).

In further analysis, we found that the mean eosinophil percentages in patients < 65 (*n= 217*) and > 65 (*n= 51*) years old, were 2.15 ± 0.26 and 1.83 ± 0.09, respectively. There was no significant difference (p= 0.273). In addition, age status were evaluated in low-grade (*n= 239*) and high-grade (*n= 29*) patients, and the mean age were 56.2 ± 0.59 and 57.86 ± 1.78, respectively (p= 0.375) (*Figure 3*).

The power analysis of the study was calculated using OpenEpi- Power For Comparing Two Means Calculator at www.openepi.com. The mean percentage of eosinophils of the Low grade and High-grade groups was calculated as 74.4% at a 95% confidence interval with ± standard deviation values.

Discussion

Although EC generally appears to have a favorable prognosis, studies have begun to investigate risk factors that may have an impact on survival besides conventional risk factors (15). Systemic inflammatory biomarkers play an important role in both tumor biogenesis and tumor response, however, the role of eosinophils has long been overlooked in this field. The most striking observation to emerge from our data was high percentages of eosinophils were associated with high-grade tumors in patients with pure endometrioid type EC which have been promising in terms of predicting pre-operative tumor grade.

Tumor-associated leukocytosis (TRL) is defined as the increase in the number of circulating leukocytes without the presence of any infectious condition during the disease, which is reported in approximately 10% of cases, excluding hematopoietic malignancies (16). However, studies on cervical cancer have reported higher rates of TRL in patients with larger tumor size, advanced stage, a greater number of lymph node metastases, and poorer response to radiotherapy (17). These results are interpreted as leukocytosis, which is evidence of advanced disease, has a negative impact on the prognosis (18). It has been shown that the response to chemotherapy in breast cancer is associated with immune cells in the peripheral blood (19). Lower eosinophil count is associated with worse survival outcomes in hepatobiliary cancer (20). Similarly, low eosinophil counts were found to be associated with worse survival in melanoma recently (21). Conversely, blood eosinophilia may be the result of tumor necrosis, it may indicate advanced disease. Inflammation caused by necrosis leads to eosinophilia related to poor prognosis (22,23). In addition, prostaglandins (PG), which are important lipid building blocks of the body, play an important role in tumor immunology (24). Particularly, PG-E2 is secreted by eosinophils and weakens antigen presentation by creating an immunosuppressive microenvironment resulting in inhibition of T-cell activation (25). Apart from this, eosinophils can accelerate the disruption of the extracellular matrix structure. Briefly, the role of blood eosinophils in gynecological tumors has not yet been clarified. So, we examined the role of eosinophils in EC whose importance was evaluated in many cancer types.

In the presented study, patients with pure endometrioid histopathology were enrolled to evaluate the analysis in a histopathologically homogeneous structure. Although the percentages of the eosinophils according to MI (≤1/2, >1/2), TD (≤2cm, >2 cm), LVSI (yes/no), cervical stromal invasion (yes/no), adnexal involvement (yes/no), lymph node metastasis (yes/no) and FIGO stages did not show a significant difference, higher eosinophil percentages showed statistically significant in the high-grade tumors which are promising in terms of predicting pre-operative grade. Since the possibility of lymph node involvement is significantly increased in high-grade tumors, staging is required regardless of other factors (12). While informing the patient whether to perform staging, it can be made more comprehensive information by examining the percentage of eosinophils from the complete blood count and more confident steps can be taken in the pre-operative period.

In a subgroups analysis, we evaluated whether the aging factor would have a relationship with tumor grade and eosinophil percentages. There were no significant differences, so it was indicating that the age variability did not affect the main results of this study. Maybe, these results were due to analyzing only endometrioid-type EC. Multi factors and lifestyles can unintentionally change the white blood cells and thus the eosinophil count. Even non-steroidal anti-inflammatory drugs can affect this value more (26,27). The percentage of eosinophils was calculated to be higher in male participants (compared to female) and <18 years of age (compared to ≥ 18 years old) in a study conducted with 11,000 patients (28). Because of our study is based on oncology patients older than 18 years old, possible confounding factors can be ignored. Immune functions may change with aging. Aging does not change eosinophils' chemotaxis and adhesion but may cause a decrease in degranulation (29). However, current

information does not contain aging among the factors that can increase eosinophil count, consistent with this study (30).

The 5-year survival rate in endometrioid type EC has been reported as 90.3% in stage IA (31). It is also quite reasonable for stage 1A patients who died in 5 years to be FIGO grade 3 endometrioid EC. This situation is more important in young patients with fertility desire. Since EC is seen even at a very young age, such as 13, this is of concern in young patients with a desire to have children (32). The main treatment of EC is hysterectomy, but grade becomes the most important parameter in patients who desire fertility preservation and are considered to be stage 1A in imaging methods (33). Unfortunately, the probe curettage (PC) to predict FIGO grade has low power, which also often depends on experience (34,35). In this context, pre-operative blood eosinophils percentages can be guide to patient selection and risk determination. The combined use of PC FIGO grade and pre-operative eosinophil percentages in grade determination may show higher accuracy values. Models created with a parameter containing both can be planned. Because fertility-sparing surgery is not recommended for high-grade tumors. For this reason, a subgroup analysis was also performed in our patients who were reported as stage 1A. We found that the percentages of eosinophils in stage 1A patients were extraordinarily high in predicting high grades. Patients with cervical stromal involvement, deep myometrial invasion, lymph node involvement, or distant metastasis may be exposed to confounding immunological factors that we cannot explain in the peripheral blood eosinophil analysis. However; the present study, which was completed with a pure and large number of patients, may be reassuring for the grade confirmation of patients who desired fertility.

Socio-demographic characteristics of the population were not taken into account because eosinophils can be affected by multi factors. Since even having possible an under-diagnosed diabetic and rheumatological state or any allergic disease, etc. could lead to misleading results. In addition, the role of combining chronic diseases (allergic asthma or not), the dietary habits remain unclear. As a conclusion, sociodemographic data may provide commonalities of the population studied, but we did not willingly detail the sociodemographic characteristics of the population. In addition to being a retrospective single-center study, there were several limiting factors. A high-grade tumor was present in 10.8% of the patients. Also, there is a tendency between lymph node involvement and the percentage of eosinophils, but not reaching the statistical differences. Further large-scale studies may help to determine this possible association. As well, this study only contains endometrioid type EC that have a better prognosis than other histological subtypes. So, the absence of possible confounding factors allowed us to give a clearer result. But, the role of blood eosinophils can show less stature in EC than the other cancers. In this regard, the percent of high-risk patients in the study population, can change this significance and prognostic factors status. In addition, progression-free survival and overall survival could not be added in the analysis of the prognostic significance of eosinophils. However, almost all studies involving biomarkers of systemic inflammation are retrospective study designs (6,16,21). The results of this study need to be supported by further larger studies on this issue.

In conclusion, a statistically significant correlation was found between pre-operative percentages of peripheral blood eosinophils and tumor grade. Eosinophil percentages, which are a simple, easily accessible, and inexpensive method, can be used as an important predictive tool in determining the need for pre-operative and intra-operative surgical staging in EC.

Disclosure Statement
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Data Availability Statement
Data available on request due to privacy/ethical restrictions.

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Table= Mean percentages of peripheral blood eosinophils according to pathology-related characteristics (N=268)

	N (%)	**Mean Eosinophils (% ± S.E)**	**P Value**
Tumor Size			p= 0,940
≤ 2 cm	102 (38.1)	1,89 ± 0,16	
> 2 cm	166 (61.9)	1,90 ± 0,12	
MI			p= 0,464
≤ ½	184 (68.7)	1,94 ± 0,11	
> ½	84 (31.3)	1,79 ± 0,17	
FIGO Grade			**p= 0,013**
Low	239 (89.2)	1,79 ± 0,09	
High	29 (10.8)	2,75 ± 0,35	
LVSI			p= 0,413
No	179 (66.8)	1,87 ± 0,11	
Yes	89 (33.2)	1,95 ± 0,17	
Cervical Stromal Invasion			p= 0,921
No	250 (93.3)	1,90 ± 0,10	
Yes	18 (6.7)	1,86 ± 0,32	
Adnexial Involvement			p= 0,721
No	261 (97.4)	1,90 ± 0,09	
Yes	7 (2.6)	1,69 ± 0,50	
Lymph Node Metastasis			p= 0,066
No	243 (90.7)	1,84 ± 0,10	
Yes	25 (9.3)	2,43 ± 0,34	
FIGO Stage			p= 0,566*
1	226 (84.3)	1,85 ± 0,10	
2	9 (3.4)	1,82 ± 0,27	
3	25 (9.3)	2,30 ± 0,34	
4	8 (3.0)	2,07 ± 0,64	

N= Number, %= Percent, S.E= Standart Error, FIGO=The International Federation of Gynecology and Obstetrics, Low-Grade= defines FIGO grade 1 and 2, High-Grade= defines Figo Grade 3, MI= Myometrial Invasion, LVSI= Lymphovascular Space Invasion. Statistical analyses was obtained by Independent Samples T-Test (*= obtained by One Way Anova).

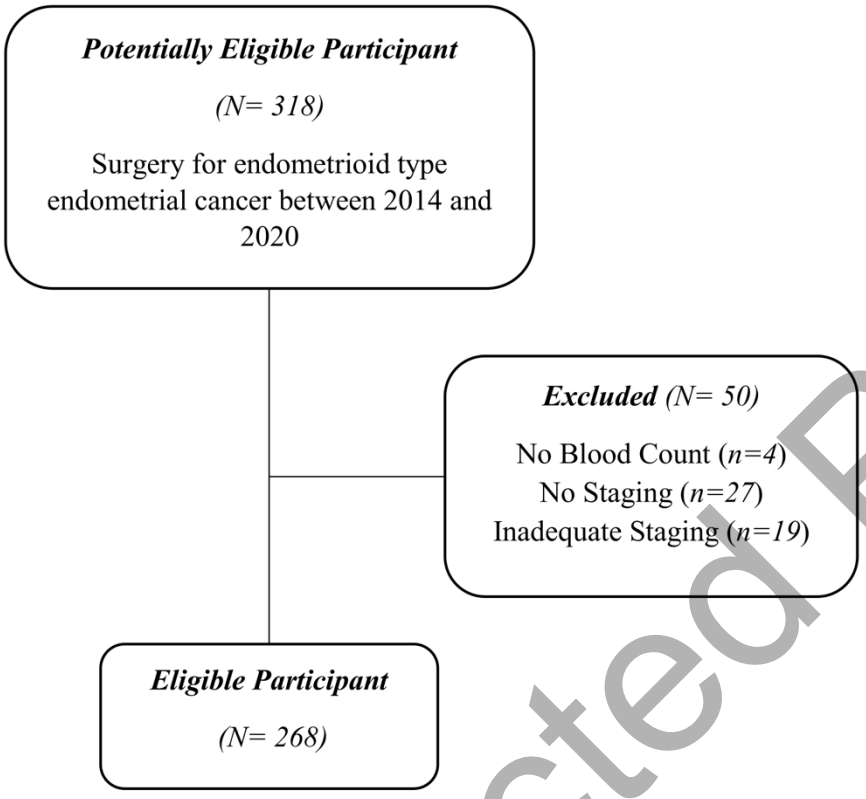

Figure 1. Flow diagram of the study

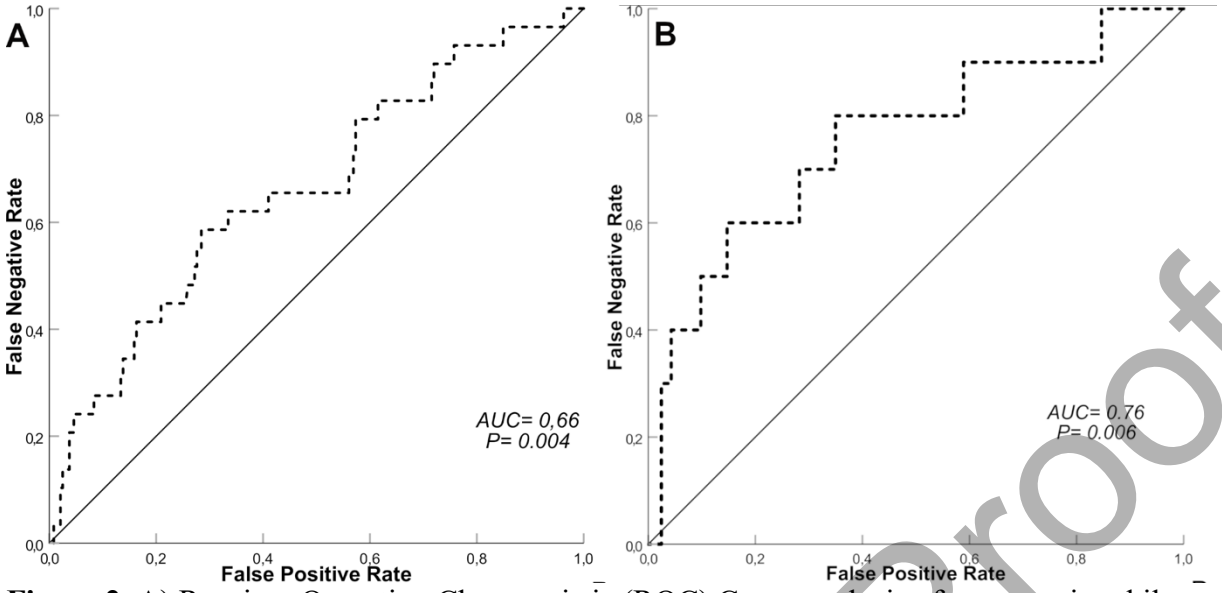

Figure 2. A) Receiver Operating Characteristic (ROC) Curve analysis of mean eosinophils percentages regarding high grade tumors (Cut off= 1.95 % , Sensitivite= 62%, Spesifite= 67%). B) ROC analysis of mean eosinophils percentages regarding high-grade tumors in FIGO Stage 1A (Cut off= 1.95 %, Sensitivite= 80%, Spesifite= 65%)

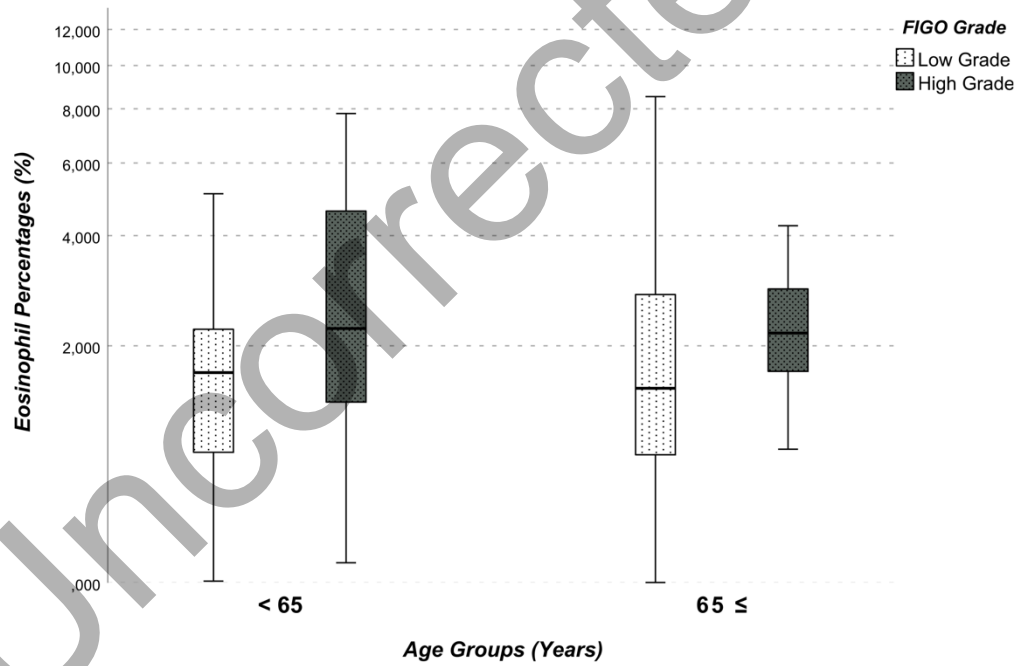

Figure 3. The mean percentages of eosinophils in low-grade and high-grade patients according to age groups (< 65 and ≥ 65) (p= 0.273)