The percentage of peripheral eosinophils as a sensitive marker for differentiating FIGO grade in endometrial adenocarcinomas

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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 was performed to investigate the pre-operative peripheral blood eosinophil percentages in patients with a histopathologically diagnosed pure endometrioid type endometrial carcinoma.

Material and Methods: Patients' 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 was lymphovascular space invasion. FIGO grade was taken as the basis of the tumor grade: Low-grade equated to grade 1 or 2, and high-grade equated to grade 3. The requirement for lymph node dissection was based on the Mayo criteria.

Results: The data of a total of 268 patients were included. The mean percentage of eosinophils in high-grade patients (n=29) was 2.75±0.35, and was significantly higher than the mean percentage of eosinophils of found in low-grade patients (n=239), which was 1.79±0.09 (p=0.013). Receiver operator curve analysis showed that a cut-off eosinophil percentage of 1.95% resulted in a sensitivity of 62% and specificity of 67% (p=0.004).

Conclusion: Eosinophil percentages, which are a simple, easily accessible, and inexpensive can be an important pre-operative predictive tool. Eosinophil percentages can be used in determining the need for surgical staging in endometrial cancer. (J Turk Ger Gynecol Assoc 2022; 23: 99-105)

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

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Introduction

Studies on eosinophils, derived from the myeloid series, have mostly concentrated on this cell type's role in parasitic infections and allergic diseases, and the role of eosinophils in oncology has been largely ignored. However, eosinophils are one of the basic cells types 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 tumors (1,2). In particular, it has been shown that eosinophils 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, they 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, some of which will be produced by the intratumoral eosinophil population. The

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importance of eosinophils, which can be easily and cheaply evaluated using modern laboratory automated hematology analyzers in peripheral blood analysis, has been reported for different types of cancer, including colon and nasopharyngeal cancer (4,5). Furthermore, the importance of eosinophils has been discussed in recent studies in patients with melanoma and lung cancer treated with immunotherapy (6-8), while 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 relation to cancer of the ovary (10) and cervix (2), there is a limited number of studies in endometrial carcinoma (EC) (11). The aim of the present study was to evaluate pre-operative peripheral blood eosinophil counts and post-operative prognostic factors in patients with endometrioid type EC.

Material and Methods

This retrospective study examined the data, including pre-operative peripheral eosinophil percentages, of patients whose final pathology result was reported as a pure endometrioid type EC. Patients attended between 2014 and 2020. Written and oral informed consent was obtained from all patients before surgery. The study was approved by the University of Health Sciences Turkey, Zeynep Kamil Women and Children Diseases Training and Research Hospital Local Ethics Committee (approval number: 2021/86).

The patients were divided into two groups, based on percentage of the myometrium infiltrated by the tumor (<50% and ≥50%), the presence or absence of tumor metastases in the adnexes, lymph nodes, and cervical stroma, and whether there was lymphovascular area invasion (LVSI) and the data of the two groups was compared. Tumor size (mm) was based on the largest diameter stated in the final pathology report. FIGO grade was used as the basis for evaluation of the tumor grade: low-grade equated to grade 1 or 2, and high-grade equated to grade 3. The requirement for lymph node dissection was based on the Mayo criteria. These were: lymph node dissection was 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 adequate lymph dissection was defined as the removal of at least 15 pelvic and/or paraaortic lymph nodes (13,14). All patients were re-evaluated in the gynecologic oncology multidisciplinary team meeting before anesthesia examination. As a clinic practice, the maximum acceptable period of approval obtained by consultation is 4 weeks. The percentage of eosinophils in 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 into potassium EDTA tubes on a Mindray BC-6800 hematology analyzer. Eosinophil percentages were derived by dividing the eosinophil count by white blood cells (WBC) and multiplying by 100 [(eosinophil/WBC) x100)]. Twenty-seven patients who required lymph dissection but were not staged, 19 patients who were insufficiently staged, and four 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

The Statistical Package for the Social Sciences (SPSS) software, version 20 (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. 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. A $p<0.05$ was interpreted as significant. Receiver operating characteristic (ROC) analysis was used to determine the threshold value and diagnostic utility of the variables.

Results

A total of 268 patients, with ages ranging from 26 to 82 years, were included. 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, which was

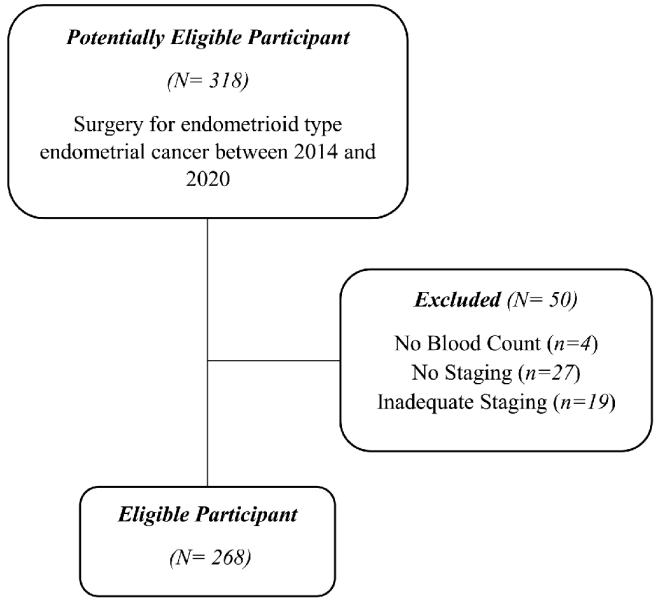

Figure 1. Flow diagram of the study

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 tended to be greater than the mean percentage of eosinophils in the group without lymph node metastasis (1.84±0.1). Although this was not significant it was approaching significance (p=0.066). There was no difference in the mean eosinophil percentage of 102 (38.1%) patients with tumor size ≤2 cm (1.89±0.16) and 166 (61.9%) patients with >2 cm diameter tumors (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 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 are given in Table 1.

The percentage of eosinophils predicting high-grade tumors with the highest sensitivity and specificity was investigated. In the ROC analysis, when the eosinophil percentage cut-off was taken as 1.95%, the sensitivity was 62% and specificity as 67%. ROC curve analysis was significant (p=0.004) and the area under the curve (AUC) was 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. Using the ROC curve cut-off eosinophil percentage cut-off of 1.95% in ROC curve analysis yielded an improved sensitivity of 80% and specificity of 65%, which was again significant (p=0.006) with an AUC of 0.76 (Figure 2B).

In further analysis, 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 was 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, which did not differ (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 that a higher percentage of eosinophils were associated with high-grade tumors in patients with pure endometrioid type EC, which may have promise 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 malignant disease, which is reported in approximately 10% of cases, excluding

Table 1. Mean percentages of peripheral blood eosinophils according to pathology-related characteristics (n=268)

	n (%)	Mean eosinophils (% ± S.E)	p
Tumor size	-	-	0.940
≤2 cm	102 (38.1)	1.89±0.16	-
>2 cm	166 (61.9)	1.90±0.12	-
MI	-	-	0.464
≤½	184 (68.7)	1.94±0.11	-
>½	84 (31.3)	1.79±0.17	-
FIGO grade	-	-	**0.013**
Low	239 (89.2)	1.79±0.09	-
High	29 (10.8)	2.75±0.35	-
LVSI	-	-	0.413
No	179 (66.8)	1.87±0.11	-
Yes	89 (33.2)	1.95±0.17	-
Cervical stromal invasion	-	-	0.921
No	250 (93.3)	1.90±0.10	-
Yes	18 (6.7)	1.86±0.32	-
Adnexal involvement	-	-	0.721
No	261 (97.4)	1.90±0.09	-
Yes	7 (2.6)	1.69±0.50	-
Lymph node metastasis	-	-	0.066
No	243 (90.7)	1.84±0.10	-
Yes	25 (9.3)	2.43±0.34	-
FIGO stage	-	-	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 were obtained by Independent samples t-test (*: Obtained by One-Way ANOVA).

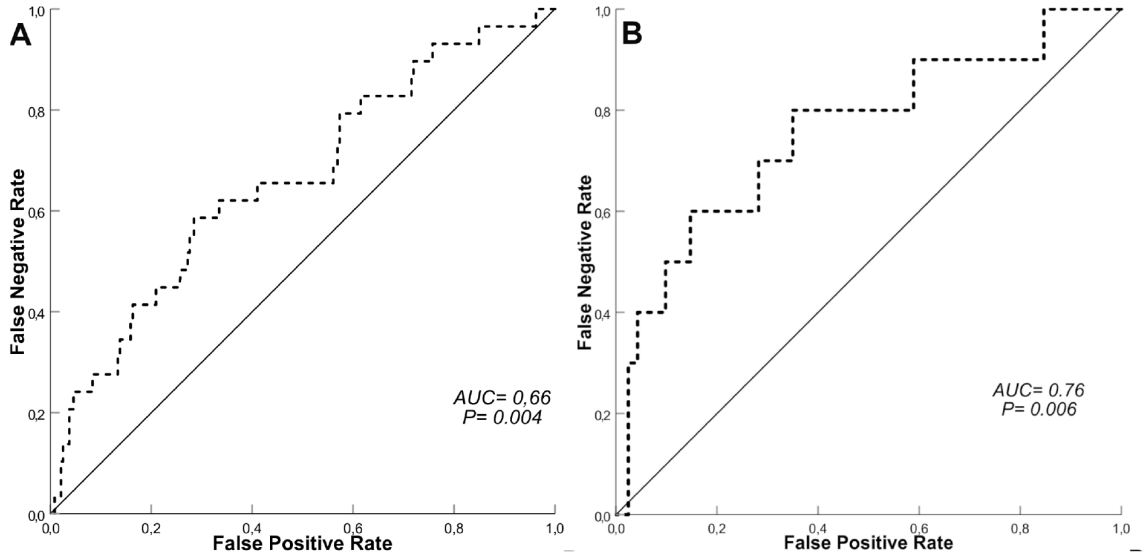

Figure 2. A) Receiver operating characteristic (ROC) curve analysis of mean eosinophils percentages regarding high-grade tumors (cut-off: 1.95%, sensitivity: 62%, specificity: 67%). B) ROC analysis of mean eosinophils percentages regarding high-grade tumors in FIGO-stage-1A (cut-foff: 1.95%, sensitivity: 80%, specificity: 65%)

AUC: Area under the curve

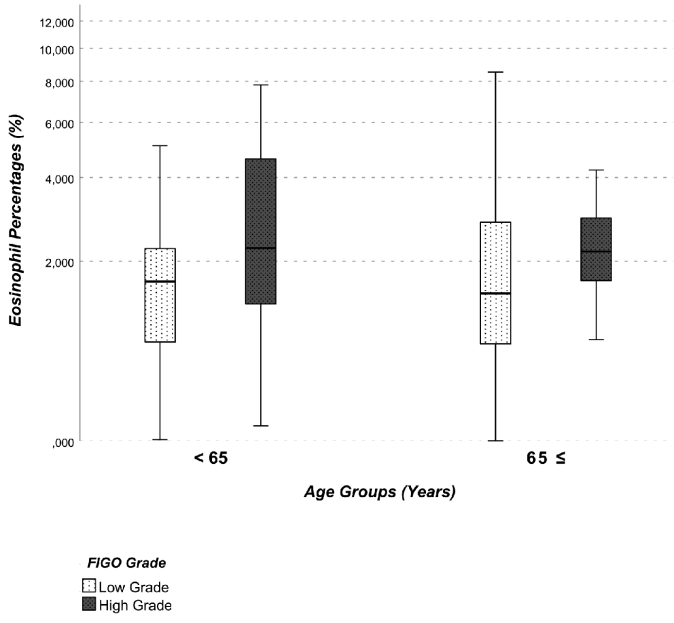

Figure 3. The mean percentages of eosinophils in low-grade and high-grade patients according to age groups (<65 and ≥65) (p=0.273)

FIGO: International Federation of Gynecology and Obstetrics

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, and 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). A lower eosinophil count is associated with worse survival outcomes in hepatobiliary cancer (20). Similarly, low eosinophil counts were recently found to be associated with worse survival in melanoma (21). Conversely, blood eosinophilia may be the result of tumor necrosis and 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 and important mediators of systemic responses, play an important role in tumor immunology (24). Particularly, PG-E2 which is secreted by eosinophils, 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. Briefly, the role of blood eosinophils in gynecological tumors has not yet been clarified. Thus the aim of this study was to examine the role of eosinophils in EC.

In the presented study, patients with pure endometrioid histopathology were enrolled to evaluate the analysis in a histopathologically homogeneous cohort. Although the percentages of the eosinophils according to MI (≤1/2, >1/2), TD (≤2 cm, >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, in the high-grade tumors there was a significantly higher percentage of peripheral eosiniphils which may be 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). The addition of information about peripheral eosinophil percentages may provide more supporting evidence when informing the patient about whether to perform staging, should the findings of this study be supported by more evidence.

In a subgroups analysis, we evaluated whether patient age would have an effect on tumor grade and, in particular, on eosinophil percentages. There were no significant differences, so it was accepted that age variability did not affect the main results of this study. A further confounder may have been the fact that we only analyzed endometrioid-type EC. Multiple factors can unintentionally change the WBCs and thus the eosinophil count. Even non-steroidal anti-inflammatory drugs can affect this (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). As our study is based in female oncology patients, all older than 18 years, these possible confounding factors can be ignored. Immune function changes with aging. Aging does not change the chemotaxis or adhesion of eosinophils but may cause a decrease in degranulation (29). However, there is no current evidence to suggest an increase in eosinophil count as an individual ages, consistent with this study (30).

The 5-year survival rate in endometrioid type EC has been reported to be 90.3% in stage 1A (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 who wish to remain fertile. Since EC is seen even at a very young age, even as young as as 13 years, this is of concern in young patients with a desire to have children (32). The main treatment for EC is hysterectomy, but grade becomes the most important parameter in patients who desire fertility preservation and are considered to be stage 1A by 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 eosinophil percentages may be a 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 as fertility-sparing surgery is not recommended for high-grade tumors, even in younger patients. For this reason, a subgroup analysis was also performed in our patients who were reported to be stage 1A. We found that the sensitivity and specificity of percentages of eosinophils in stage 1A patients were even better in predicting high-grades. Patients with cervical stromal involvement, deep MI, lymph node involvement, or distant metastasis may be exposed to confounding immunological factors that we cannot explain, simply in terms of peripheral blood eosinophil analysis. However, the present study, which was completed with a homogeneous cohort 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 and eosinophils can be affected by multiple factors, including lifestyle. Undiagnosed comorbidities, such as diabetes, allergy or inflammatory diseases, would affect the peripheral eosinophil percentage either by affecting the eosinophil count directly or by changing the ratio of eosinophils to other leukocytes. In addition, the role of coexistant chronic diseases and dietary habits remain unclear. Thus, adjustment for, sociodemographic variability may provide an even more homogenous study population, but this was not taken into account in the present study. There were several other limiting factors. A high-grade tumor was present in 10.8% of the patients. Also, there is an association between lymph node involvement and the percentage of eosinophils, but this did not reach statistical significance. Further large-scale studies may help to determine this possible association. Moreover, this study only contained endometrioid type EC, which is known to 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 assessed in this study 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.

Conclusion

A statistically significant correlation was found between pre-operative percentages of peripheral blood eosinophils and tumor grade. Eosinophil percentages, which are simple, easily accessible, and inexpensive, may have use as a predictive tool in determining the need for pre-operative and intra-operative surgical staging in EC.

Ethics Committee Approval: *The study was approved by the University of Health Sciences Turkey, Zeynep Kamil Women*

and Children Diseases Training and Research Hospital Local Ethics Committee (approval number: 2021/86).

Informed Consent: *Written and oral informed consent was obtained from all patients before surgery.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Surgical and Medical Practices: S.A., M.A., C.K.; Concept: S.A., U.K.Ö., M.A.; Design: S.A., U.K.Ö., E.K., M.A., C.K.; Data Collection or Processing: S.A., U.K.Ö., E.K., C.M.A.; Analysis or Interpretation: S.A., U.K.Ö., C.M.A.; Literature Search: S.A., U.K.Ö., E.K., C.M.A.; Writing: S.A., U.K.Ö., E.K., C.M.A., M.A., C.K.*

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