

Original Article

Predictive Value of Complete Blood Count Inflammatory Parameters for Epithelial Ovarian Cancers in Women During Reproductive Period

Reprodüktif Dönemdeki Kadınlarda Epitelial Over Kanserleri İçin Tam Kan Sayımı İnflamatuar Parametrelerin Prediktif Değeri

Hilal Korkmaz¹, Mustafa Akşar², Halis Doğukan Özkan², Vakkas Korkmaz², Nurettin Boran²

¹Gazi University Faculty of Medicine Department of Physiology, Ankara

²Department of Gynecologic Oncology, University of Health Sciences, Etlik Zubeyde Hanım Women's Health Training and Research Hospital

ABSTRACT

Background: Comparison of predictive values of complete blood count inflammatory parameters and serum CA-125 levels in the differential diagnosis of patients with epithelial ovarian tumor (EOTs) diagnosed in the reproductive period.

Materials: In this study, 105 women patients in the reproductive period were retrospectively analyzed. The patients included were examined in terms of clinical, laboratory and pathological features.

Results: The mean age of the patients was 41.5 ± 8.6 years and BMI was 28.6 ± 5.8 kg/m². Of the whole study population, 54 (51.5%) were benign EOTs, 18 (17.1%) were borderline EOTs and 33 (31.4%) were malignant EOTs. When comparing these three tumor groups, a significant difference was found in terms of serum CA-125 [14.7 U/mL (2.7-238.6) vs 60.2 U/mL (7.8 – 557) vs 416.5 U/mL (2.4-7695), $p < 0.001$, respectively], platelet count [294 x10³/ μ L (133-744) vs 303, x10³/ μ L (160-468) vs 383 x10³/ μ L (128-725), $p = 0.018$, respectively], neutrophil count [4.2, x10³/ μ L (1.9 -8.9) vs 4.9 x10³/ μ L (2.6-10.9) vs 5.1 x10³/ μ L (2.2 – 10.7), $p = 0.012$], neutrophil-to-lymphocyte ratio (NLR) [2.1 (0.1-8.2) vs 2.6 (1.2 – 5.9) vs 3.1 (1-6.8), $p = 0.021$, respectively] and platelet-to-lymphocyte ratio (PLR) [154.4 (82.1-658.4) vs 168.1 (91.1-377.8) vs 201.5 (29.6-499.2), $p = 0.008$, respectively] values. In the ROC analyses, serum CA-125 levels (AUC= 0.818, $p < 0.001$), platelet count (AUC= 0.673, $p = 0.005$) and PLR (AUC= 0.690, $p = 0.002$) values significantly predicted malignant EOTs.

Conclusion: Preoperative platelet count, neutrophil count and PLR predict epithelial ovarian cancers significantly. However, diagnostic predictive values of all three parameters are lower than CA-125. Therefore, CA-125 is still the most valuable serum biochemical marker that can be used in the preoperative differential diagnosis of EOTs.

Keywords: Epithelial ovarian cancer, whole blood count, Inflammatory Parameters

ÖZET

Giriş ve amaç: Reprodüktif dönemde tanı alan epitelyal over tümörlerinin (EOTs) ayırıcı tanısında tam kan sayımı inflamatuar parametreleri ile serum CA-125 seviyelerinin prediktif değerlerinin karşılaştırılması.

Yöntem ve gereçler: Bu çalışmada reprodüktif dönemde olan 105 kadın sırasıyla retrospektif olarak incelenmiştir. Dahil edilen kadınlar klinik, laboratuvar ve patolojik özellikleri açısından incelenmiştir.

Bulgular: Hastaların ortalama yaşı 41.5 ± 8.6 ve BMI 28.6 ± 5.8 idi. Tüm çalışma popülasyonunun 54 (51.5%) tanesi benign EOTs, 18 (17.1) tanesi borderline EOTs ve 33 (31.4%) tanesi malign EOTs idi. Bu üç tümör grubunun karşılaştırılmasında serum CA-125 [14.7 U/mL (2.7-238.6) vs 60.2 U/mL (7.8 – 557) vs 416.5 U/mL (2.4-7695), $p < 0.001$, sırasıyla], platelet count [294, x10³/ μ L (133-744) vs 303, x10³/ μ L (160-468) vs 383, x10³/ μ L (128-725), $p = 0.018$, sırasıyla], neutrophil count [4.2, x10³/ μ L (1.9 -8.9) vs 4.9, x10³/ μ L (2.6-10.9) vs 5.1, x10³/ μ L (2.2 – 10.7), $p = 0.012$], neutrophil-to-lymphocyte ratio (NLR) [2.1 (0.1-8.2) vs 2.6 (1.2 – 5.9) vs 3.1 (1-6.8), $p = 0.021$, sırasıyla] ve platelet-to-lymphocyte ratio (PLR) [154.4 (82.1-658.4) vs 168.1 (91.1-377.8) vs 201.5 (29.6-499.2), $p = 0.008$, sırasıyla]

değerleri açısından anlamlı fark saptandı. ROC analizinde, serum CA-125 seviyesi (AUC= 0.818, $p<0.001$), platelets (AUC= 0.673, $p= 0.005$) ve PLR (AUC= 0.690, $p= 0.002$) değerleri malign EOTs'lerini anlamlı olarak öngörmekte idi.

Tartışma ve sonuç: Preopratif platelet sayısı, nötrofil sayısı ve PLR epitelyal over kanserlerini anlamlı olarak öngörmektedir. Ancak her üç parametrenin de tanısal öngörü değerleri CA-125'den daha düşüktür. Bu nedenle CA-125 hala EOTs'lerinin preoperative ayırıcı tanısında kullanılabilecek en değerli serum biyokimyasal belirteçtir.

Anahtar Kelimeler: Epitelial over kanseri, Tam kan sayımı, İnflamatuvar parametreler

Introduction

Ovarian tumors are the second most common gynecological tumors. Epithelial ovarian tumors (EOTs) account for 95% of these tumors [1]. EOTs are divided into three histopathological subgroups: benign, borderline and malignant. Although these tumors are frequently seen in the postmenopausal period, preoperative differential diagnosis of these three subgroups is vital for women at all ages [2, 3]. In the differential diagnosis, many methods such as clinical, laboratory and imaging have been described to date. For this purpose, one of the most used biochemical markers in clinical practice is to measure the serum CA-125 level [4-6].

CA-125 has a glycoprotein structure. It rises in 80% of advanced malignant EOTs. However, in addition to genital malignancies, it also increases in many other system malignancies and benign diseases. Therefore, sensitivity and specificity values are low for routine clinical use. Since endometriosis, tubo-ovarian abscess, and functional ovarian cysts are frequently seen in women's life, especially in the reproductive period, the diagnostic value of CA-125 in these diseases is even lower. This leads to researchers look for different diagnostic tests [1, 7].

Recently, in many articles have been emphasized the importance of complete blood count inflammatory parameters. Complete blood count is a simple, easily accessible, inexpensive, automated and standardized method [8]. Also, complete blood count is measured routinely in the preoperative period in patients to be operated on. For all these reasons, the idea of being able to be used in the differentiation of benign and malignant ovarian tumors has caused wide repercussions [9]. The basis of this idea is the inflammatory

response associated with cancer [10]. The most emphasized hematological parameters are leukocyte count, platelet count, neutrophil count, neutrophil leukocyte ratio (NLR) and platelet lymphocyte ratio (PLR) [6, 11].

The aim of this study is to compare the predictive values of preoperative serum CA-125 levels and complete blood count inflammatory parameters for the diagnosis of malignant EOTs in reproductive women diagnosed with EOTs.

Material Methods

105 reproductive women (15-49 years) who underwent an adnexial mass indication and laparotomy between 2015 and 2020 at the Etlik Zübeyde Hanım Women's Health Training and Research Hospital and who had EOTs as a result of pathology were examined in the study. The study protocol has been approved by a suitably constituted Local Ethics Committee. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Postmenopausal patients, patients having any other systemic disease such as cardiovascular disease, diabetes, acute inflammation, blood disease, kidney disease or other cancers, patients receiving chemotherapy and / or radiotherapy and recent blood transfusion within the previous 3 months and incomplete medical records patients were excluded from the study. In addition, despite the premenopausal period, patients with other ovarian diseases such as endometriosis, tubo-ovarian abscess, hydrosalpinx or other ovarian tumors such as germ cell ovarian tumors, sex cord stromal tumors and patients with tumors belonging to other systems such as the gastrointestinal system was excluded from the study. Preoperative age, gravity, parity, body

mass index (BMI), serum CA-125 level, white blood cell count (WBC), platelet count, neutrophil count, lymphocyte count, monocyte count, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio results and post-operative final pathology results were evaluated.

Statistical analysis

Statistical analysis was performed using the Statistics Package for Social Sciences software (ver. 21.0, SPSS Inc., Chicago, IL, USA). The distribution of data was calculated using the normality test. In the comparison of three groups, the oneway ANOVA test was used for parametric variables and the Kruskal-Wallis test was used for nonparametric data. When statistical differences were found between three groups, each was compared separately. Continuous variables with normal distributions were compared using independent sample t-test and non-normal distributions were compared with the Mann-Whitney U test. To define relationship between numeric parameters, Pearson's correlation analysis was used for variables with normal distributions and Spearman's correlation analysis for variables with non-normal distributions. Receiver operating characteristic (ROC) analysis was used to calculate cutoff values. $p < 0.05$ values were accepted as statistically significant.

Results

The mean age of the patients included was 41.5 ± 8.6 (years), BMI 28.6 ± 5.8 (kg/m²) and the median CA-125 value was 34.5 U / mL (range 2.4-7695). Of the whole study population, 54 (51.5%) were benign EOTs, 18 (17.1%) were borderline EOTs and 33 (31.4%) were malignant EOTs. 35 (64.8%) of benign EOTs were serous cystadenoma, 18 (33.3%) were mucinous cystadenoma and 1 (1.9%) were benign Brenner tumor. 8 (44.4%) of the Borderline EOTs were serous and 10 (55.6%) were of mucinous histological type. Of the malignant EOTs, 22 (66.7%) were serous cystadenocarcinoma, 7 (21.2%) were endometrioid carcinoma, 3 (9.1%) were mucinous carcinoma and 1 (3%) were mixed

(serous + mucinous) carcinoma. Clinical, laboratory and pathological features of the whole study group are summarized in Table 1.

Comparing Groups

In the comparison of benign, borderline and malign EOTs; no significant difference was found in terms of age, gravida, parity, BMI, WBC, lymphocyte count and monocyte count ($p > 0.05$). In the comparison of the three groups were found to differ significantly in terms of serum CA-125 level ($p < 0.001$), platelet count ($p = 0.018$), neutrophil count ($p = 0.012$), NLR ($p = 0.021$) and PLR ($p = 0.008$). In the pairwise comparisons between these groups, which were found to be statistically significant between the three groups, using Bonferonni correction (Adjusted); serum CA-125 value was found to be highest in the malign EOTs groups (Adj $p < 0.001$), but similar between borderline EOTs group and malign EOTs groups (Adjusted $p = 0.247$). Platelet count, Neutrophil count, NLR and PLR values were different only between benign EOTs group and malign EOTs group (Adjusted $p = 0.014$, Adjusted $p = 0.041$, Adjusted $p = 0.038$, Adjusted $p = 0.006$, respectively). Comparison of the three groups is summarized in Table 2.

Correlations

In the correlation analysis between variables; serum CA-125 with WBC ($r = 0.290$, $p = 0.003$), platelets ($r = 0.290$, $p = 0.003$), neutrophils ($r = 0.330$, $p = 0.001$), monocytes ($r = 0.273$, $p = 0.005$) NLR ($r = 0.307$, $p = 0.002$) and PLR ($r = 0.292$, $p = 0.003$) values were statistically significant.

ROC analysis

Serum CA-125 level (AUC = 0.818, $p < 0.001$), platelet count (AUC = 0.673, $p = 0.005$) and PLR (AUC = 0.690, $p = 0.002$) predicted that malignant EOTs were statistically significant, while neutrophil count (AUC = 0.621, $p = 0.050$) and NLR (AUC: 0.620, $p = 0.053$) could not achieve this. Optimal cutoff value for serum CA-125 level 51.2 U / mL with 69% sensitivity and 70% specificity, for platelet count $325 \times 10^3 / \mu\text{L}$ with 62% sensitivity and 63% and for PLR 172.2 with 62% sensitivity and 63%

Table 1. Clinic, laboratory and pathological characteristics of whole study group

Characteristics	n= 105
Age, years, mean \pm SD	41.5 \pm 8.6
Gravidity, median (range)	3 (0-8)
Parity, median (range)	2 (0-6)
BMI, kg/m ² , mean \pm SD	28.6 \pm 5.8
CA-125, U/mL, median (range)	34.5 (2.4-7695)
WBC, x10 ³ / μ L, mean \pm SD	7.4 \pm 1.9
Platelets, x10 ³ / μ L, median (range)	308 (128-744)
Neutrophils, x10 ³ / μ L, median (range)	4.5 (1.9 -10.9)
Lymphocytes, x10 ³ / μ L, median (range)	1.8 (0.7-4.3)
Monocytes, x10 ³ / μ L, median (range)	0.37 (0.15-1.21)
NLR, median (range)	2.4 (0.1-8.2)
PLR, median (range)	166.3 (29.6-658.4)
Histological type, n (%)	
Benign EOTs	
Serous cystadenoma	35 (64.8)
Mucinous cystadenoma	18 (33.3)
Benign Brenner Tumor	1 (1.9)
Borderline EOTs	
Serous BOTs	8 (44.4)
Mucinous BOTs	10 (55.6)
Malign EOTs	
Serous cystadenocarcinoma	22 (66.7)
Endometrioid carcinoma	7 (21.2)
Mucinous carcinoma	3 (9.1)
Mixed (serous + mucinous) ovarian carcinoma	1 (3)

Abbreviations: BMI, body mass index; CA125, cancer antigen 125; Hb, Hemoglobin; Hct, hematocrit; WBC, white blood cell count; NLR, neutrophil-to- lymphocyte ratio; PLR, platelet-to- lymphocyte ratio; EOTs, Epithelial Ovarian Tumors; BOTs, Borderline Ovarian Tumor

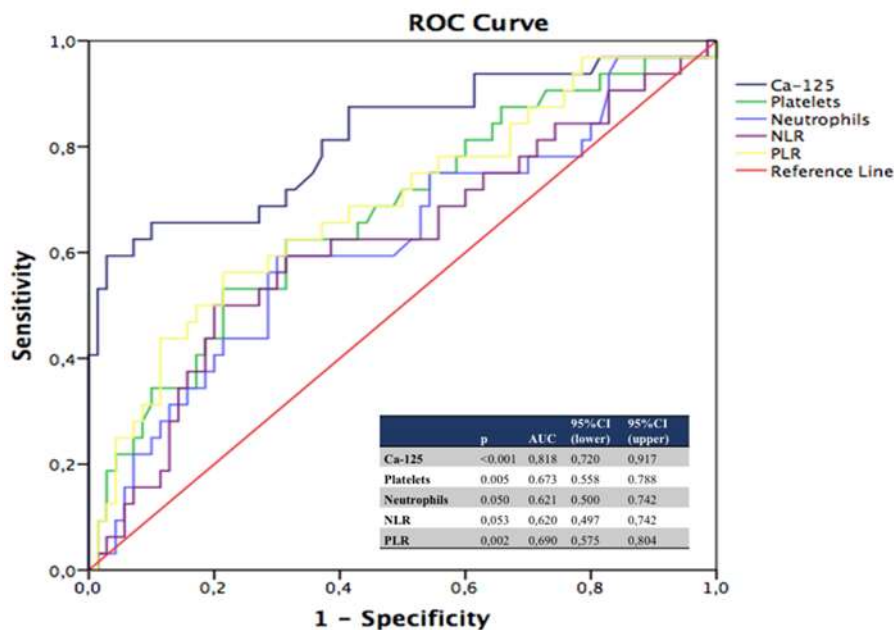


Figure 1. Predictive values of serum CA-125 levels, platelet count, neutrophil count, NLR and PLR for malign EOTs.

Abbreviations: EOTs, Epithelial Ovarian Tumors; AUC: area under the ROC curve; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio

Table 2. Comparisons of the three groups

	Benign EOTs n: 54	Borderline EOTs n: 18	Malign EOTs n: 33	p
Age, years, mean \pm SD	42.5 \pm 9.4	37.1 \pm 8.5	42.5 \pm 6.7	0.052
Gravidity, median (range)	3 (0-8)	3 (0-4)	2 (0-7)	0.393
Parity, median (range)	2 (0-6)	1(0-4)	2 (0-4)	0.493
BMI, kg/m ² , mean \pm SD	29.6 \pm 6.3	27.4 \pm 6.6	27.8 \pm 4.5	0.350
CA-125, U/mL, median (range)	14.7 (2.7-238.6)	60.2 (7.8 – 557) *	416.5 (2.4-7695) *	<0.001
WBC, x10 ³ / μ L, mean \pm SD	6.9 \pm 1.7	7.9 \pm 2.3	7.7 \pm 2.2	0.054
Platelets, x10 ³ / μ L, median (range)	294 (133-744)	303 (160-468)	383 (128-725) *	0.018
Neutrophils, x10 ³ / μ L, median (range)	4.2 (1.9 -8.9)	4.9 (2.6-10.9)	5.1 (2.2 – 10.7) *	0.012
Lymphocytes, x10 ³ / μ L, median (range)	1.8 (1.1-3.7)	1.8 (1.1-3.9)	1.8 (0.7-4.3)	0.917
Monocytes, x10 ³ / μ L, median (range)	0.35 (0.16-1.21)	0.38 (0.15-0.719)	0.38 (0.20-0.91)	0.433
NLR, median (range)	2.1 (0.1-8.2)	2.6 (1.2 – 5.9)	3.1 (1-6.8) *	0.021
PLR, median (range)	154.4 (82.1-658.4)	168.1 (91.1-377.8)	201.5 (29.6-499.2) *	0.008

Table 3. Correlations between CA-125 and Hematologic Inflammatory Parameters.

	WBC, x10 ³ / μ L	Platelets, x10 ³ / μ L	Neutrophils, x10 ³ / μ L	Lymphocytes, x10 ³ / μ L	Monocytes, x10 ³ / μ L	NLR	PLR
Ca -125, U/mL							
r	0.290	0.290	0.330	-0.028	0.273	0.307	0.292
p	0.003	0.003	0.001	0.779	0.005	0.002	0.003

CA125, cancer antigen 125; Hb, Hemoglobin; Hct, hematocrit; WBC, white blood cell count; NLR, neutrophil-to- lymphocyte ratio; PLR, platelet-to- lymphocyte ratio

specificity were calculated. ROC analysis results are shown in figure 1.

Discussion

In this study, we investigated the clinical, laboratory and pathological characteristics of patients with benign, borderline and malignant EOTs managed at our clinic. At the end of the study, we found that serum CA-125 levels, platelet counts, neutrophil counts, NLR and PLR were higher in malignant EOTs group compared to benign EOTs group. In ROC analysis; only CA-125 levels, platelet count and PLR ratios significantly predicted malignant EOTs. We found the highest predictive value in serum CA-125. In the correlation analyses, there was a significant correlation between serum CA-125 value and WBC, platelet count, neutrophil count, monocyte count, NLR and PLR values.

So far, the increased preoperative platelet count was reported in many of gynecological malignancies such as ovarian, endometrial, vulvar and cervical cancer [12-14]. Of these

cancers, ovarian cancer is the most emphasized in the literature. Yilmaz et al. showed that platelet count in the detection of malignant ovarian tumors have been evaluated as useful new marker [15]. In another study by Watrowski et al. found that a total of 44.8 % malignant and 8.6 % benign ovarian cases presented with thrombocytosis (PLT \geq 350/nl) and the sensitivity and specificity of preoperative thrombocytosis and CA-125 were calculated as %45/%91 and 88%/76%, respectively. So, they concluded that platelet count is an ubiquitously available parameter that could be useful in the diagnostic evaluation of pelvic mass [16]. Similarly, in our study, the number of platelets had a significant predictive value for malign EOTs. However, this predictive value was lower than CA-125.

PLR and NLR are both easily to calculate markers. These markers evaluated in many studies on ovarian neoplasms. In a study by Yıldırım at al. showed that patients with ovarian cancer exhibited significantly higher

NLR and PLR values. Also, they found that higher NLR and PLR values predicted ovarian cancer at the cut-off value of 3.35, sensitivity of 55% and specificity of 81% for NLR and at the cut-off value of 572.9, sensitivity of 100% and specificity of 0.38% for PLR. [17]. In a retrospective study, Bakacak et al. Investigated the utility of preoperative NLR, PLR and lymphocyte count as biomarkers to distinguish malignant from benign ovarian masses. They identified NLR (68.8% sensitivity and 54.1% specificity) and PLR (81.8% sensitivity and 50.8% specificity) as markers for distinguish malignant from benign masses [18]. In another study by Yıldırım et al. reported that NLR and PLR were useful methods that could be applied together with CA-125 due to the relatively high sensitivity values for the malign-benign differentiation of ovarian masses [19]. In addition to, Prodromidou et al. and Eo, Wan Kyu, et al. suggested that both PLR and NLR seemed to be promising screening and prognostic factors of epithelial ovarian cancer [20, 21]. In the present study, NLR and PLR rates were higher in malignant EOTs than benign EOTs. However, only PLR significantly predicted malignant EOTs in the ROC analysis.

Our study has two important limitations. The first is that our number of participants is relatively low. The second is that it is a retrospective study. Despite these limitations, retrospective studies reflect real life data and make important contributions to the body of knowledge. Our study also has two important strengths. First, all patients included in the study have histopathological diagnoses. Secondly, histological subtypes of EOTs, benign, malignant and borderline, were compared completely.

In conclusion, complete blood count inflammatory parameters in the reproductive period are associated with CA-125. Among these inflammatory parameters, platelet counts, neutrophil counts, NLR and PLR values are significantly higher in Malign EOTs. Also, platelet count and PLR can be used to distinguish malign EOTs from benign EOTs. However, the area under curve of these parameters is not higher than CA-125. Therefore, CA-125 is still the most valuable diagnostic marker that can be used pre-operatively for the differential diagnosis of EOTs in reproductive aged women. Whereas, platelet count or PLR can be used in combination with CA-125.

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Corresponding author e-mail: hilalkorkmaz@gazi.edu.tr

Orcid ID:

Hilal Korkmaz 0000-0002-9097-1024

Mustafa Akşar 0000-0002-4565-5241

Halis Doğan Özkan 0000-0002-4202-1681

Vakkas Korkmaz 0000-0001-8895-6864

Nurettin Boran 0000-0002-0367-5551

Doi: