

ORIGINAL RESEARCH

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The value of the neutrophil to lymphocyte ratio, platelet to lymphocyte ratio and ca-125 in differential diagnosis of ovarian endometriosis**Mustafa Tas***Acibadem Mehmet Ali Aydinlar University, Department of Obstetrics and Gynecology, Istanbul, Turkey*

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Abstract

The definitive diagnosis of the endometriosis relies on direct visualization at the surgery and the histopathological verification of the endometrial glands and stroma in biopsies of suspected lesions. Non-invasive tests to diagnose the endometrioma are required to avoid the complications of the laparoscopy. The present study was carried out to compare the neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and CA-125 level in patients with endometrioma and in women with other benign ovarian cysts. Retrospective medical data of 73 women who underwent open or laparoscopic surgery for ovarian cysts and 40 healthy controls were analyzed. Patients with endometriomas, other benign ovarian cysts and controls were compared with respect to age, CBC parameters, and Ca-125 measurements to identify the factors associated with the presence of the endometrium. There were no significant differences among the three groups with respect to leukocyte count, neutrophil, lymphocyte, plateletcrit, reticulocyte distribution width, hemoglobin level, platelet count, and mean platelet volume. The neutrophil to lymphocyte ratio and platelet to lymphocyte ratio were also similar in all groups. However, Ca-125 level was significantly higher in patients with endometrioma [86 (36-130) U/ml] compared to that of the benign ovarian cyst group [21.5 (6-62) U/ml] and the healthy controls [26.5 (9-51) U/ml]. ROC curve analysis provided that a cut-off value of 44.5 U/ml could predict the presence of endometrioma with a sensitivity of 97 % and with a specificity of 96 %. Our findings clearly demonstrate that neither neutrophil to lymphocyte ratio nor platelet to lymphocyte ratio has any value in distinguishing women with endometrioma from those with other benign ovarian cysts or healthy controls. However, Ca-125 levels might be used to identify patients with endometrioma, with high sensitivity and specificity.

Keywords: Endometrioma, ovarian cyst, Ca-125, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio**Introduction**

Endometrioma is a type of benign ovarian cyst and characterized by the presence of functional endometrial glands in the ovaries. Endometrioma remains one of the most common benign gynecological conditions among women of reproductive age with an estimated prevalence of 10-15% [1]. The prevalence of this disorder increases up to 30% in women with chronic pelvic pain and infertility. Estrogen dependency, progressive and invasive nature, frequent recurrence, and propensity to metastasize are some of the basic features of the endometrioma [2].

The definitive diagnosis of the endometriosis relies on direct visualization at the surgery and the histopathological verification of the endometrial glands and stroma in biopsies of suspected lesions compared to a minimally invasive or non-invasive diagnostic method. Organ injury, bleeding, infection, and formation of

[3]. However, the surgical diagnosis has multiple disadvantages adhesions are some of these drawbacks [4]. Preoperative diagnosis and differentiation of endometriomas from other benign ovarian cysts by using several certain biomarkers in the peripheral blood has, therefore, attracted attention in recent studies. Several inflammatory markers, including cytokines and antibodies, have been studied for this purpose [5, 6]. The neutrophil to lymphocyte ratio (NLR) and the platelet to lymphocyte ratio (PLR) have been shown to increase in conjunction with the cancer antigen-125(Ca-125) in patients with endometrioma [3]. Nevertheless, whether the increase in NLR and PLR are intrinsic to endometriosis or the consequence of endometriosis-related alterations in the immunologic response is a matter of debate.

The present study was carried out to compare the NLR, PLR, and CA-125 in patients with endometrioma and in women with other benign ovarian cysts.

Material and Methods

The present retrospective study analyzed medical data of 73 women aged 18 to 49 years who underwent open or laparoscopic

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surgery for ovarian cysts in Acibadem Kayseri Hospital between March 2017 and May 2019. The study population was divided into two groups according to the histopathological findings as women with endometriomas and women with other non-malignant ovarian cysts. Endometrioma was classified according to the revised American Society for Reproductive Medicine classification, which is based on localization and size of implants and extent of adhesions, as follows: Minimal (Stage 1), mild (Stage 2), moderate (Stage 3), and severe endometriosis (Stage 4) [7]. Exclusion criteria were as follows: Aged < 18 years or > 49 years, > stage 1-2 endometrioma, smoking, patients with autoimmune disorders, previous ovarian surgery, presence of hematological disease, malignancy, cardiovascular disease including hypertension, diabetes, advanced liver or kidney disease, chronic obstructive pulmonary disease, acute infectious disease within the last 3 months, and acute or chronic inflammatory diseases. In addition, a group of age-matched healthy volunteers who underwent gynecologic examination in our institute and were diagnosed as negative for any gynecologic disease was selected as the control group. Written informed consent was obtained from all subjects included in the study. The study was approved by the Institutional Ethical Committee of Acibadem Mehmet Ali Aydınlar University (2019-1/34) and was performed in accordance with the recent version of the Helsinki Declaration. Data regarding the participants' age, complete blood count (CBC) results, and Ca-125 measurements were obtained were retrieved from the institutional digital database. CBC parameters were measured using the Coulter LH-500 hematology blood analyzer (Beckman Coulter Inc, Brea, California) and Ca-125 was measured using the electrochemiluminescence immunoassay method (Elecsys CA 125 II, Roche Diagnostics, Mannheim, Germany).

Patients with endometriomas, other benign ovarian cysts and controls were compared with respect to age, CBC parameters, and Ca-125 measurements to identify the factors associated with the presence of the endometrioma.

Statistical analysis

All analyses were performed on SPSS v21. Shapiro-Wilk test was

used for the normality check. Data are presented as mean $\pm$ standard deviation or median (minimum-maximum) for continuous variables regarding normality. Normally distributed variables (age, mean platelet volume) were analyzed with one way ANOVA test. Non-normally distributed variables were analyzed with the Kruskal-Wallis test. In case of statistical significance, posthoc comparisons were performed with the Tamhane's T2 test. Logistic regression analysis was performed to find out the blood parameters associated with the presence of the endometrioma. The variables for which the P value was < 0.1 in group comparisons were included in the logistic regression model. Diagnostic performance of the variables to identify the presence of the endometrioma was assessed by the Receiver Operating Characteristic (ROC) curve analysis. A two-sided $p < 0.05$ was accepted as statistically significant.

Results

Thirty-seven (37) women with endometrioma [median age 25 (18-48) years], 36 women with benign ovarian cysts [median age 26 (18-49) years] and 40 healthy controls [median age 28 (18-48) years] were enrolled in this retrospective study. The groups were similar with respect to age ($p = 0.338$). CBC parameters of the study groups are presented in Table 1. There were no significant differences among the three groups with respect to Leukocyte count, neutrophil, lymphocyte, plateletcrit, reticulocyte distribution width, hemoglobin level, platelet count, and mean platelet volume. The NLR and PLR were also similar in all groups. Nevertheless, Ca-125 level was significantly higher in endometrioma patients [86 (36-130)U/ml] compared to that of the benign ovarian cyst group [21.5 (6-62)U/ml] and the healthy controls [26.5 (9-51)U/ml, $p < 0.001$].

Logistic regression analysis showed that the Ca-125 level was a significant predictor of the presence of the endometrioma (Odds ratio: 1.235, 95 % confidence interval: 1.106-1.380, $p < 0.001$, Table 2). ROC curve analysis provided that a cut-off value of 44.5U/ml could predict the presence of endometrioma with a sensitivity of 97 % and with a specificity of 96 % (Area under the curve: 0.994, 95 % confidence interval: 0.985-1.000, $p < 0.001$, Figure 1).

Table 1. Comparison of the laboratory measurements in all groups

	Endometrioma n=37	Other benign ovarian cysts n=36	Control n=40	p value
Age, years	25 (18-48)	26 (18-49)	28 (18-48)	0.338
Leukocyte, /mm ³	8.6 (5.1-13.5)	9.0 (4.1-15.5)	8.2 (4.4-12.3)	0.199
Neutrophil, /mm ³	5.3 (2.4-9.2)	5.4 (1.9-18.2)	4.7 (2.1-8.5)	0.225
Lymphocyte, /mm ³	2.2 (1.2-4.7)	2.5 (1.1-5.2)	2.5 (1.7-3.7)	0.562
Hemoglobin, gr/dl	13.3 (10.1-13.6)	12.7 (8.5-14.7)	12.5 (6.6-15.2)	0.241
Platelet, /mm ³	263 (193-410)	293 (204-427)	268 (136-513)	0.068
MPV, fl	8.5 $\pm$ 1.2	9.3 $\pm$ 1.9	8.7 $\pm$ 1.7	0.071
Plateletcrit, %	0.23 (0.16-0.31)	0.26 (0.11-0.35)	0.24 (0.13-0.47)	0.187
RDW, %	12.6 (11.1-18.6)	12.8 (9.0-18.1)	12.9 (9.8-19.9)	0.808
NLR	1.9 (0.9-5.2)	1.9 (0.7-16.3)	1.8 (0.9-3.7)	0.589
PLR	109 (42-238)	122 (62-260)	102 (67-280)	0.158
Ca-125, U/ml	86 (36-130) ^a	21.5 (6-62) ^b	26.5 (9-51) ^b	<0.001

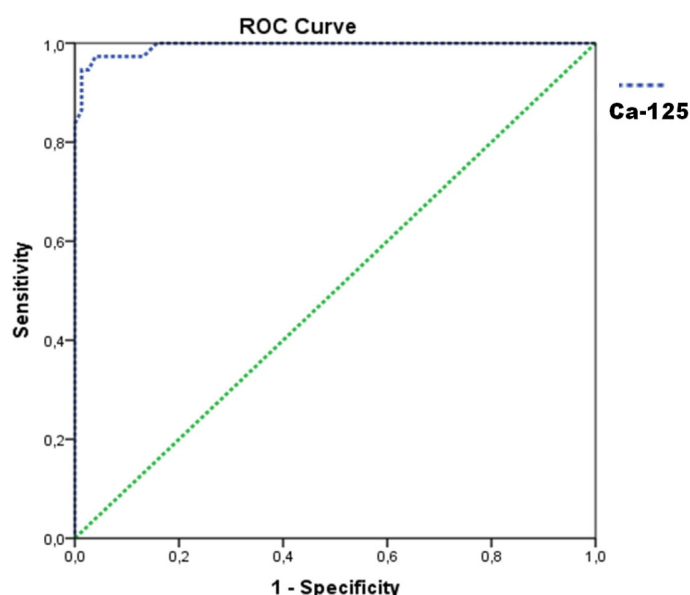
Data are presented as mean $\pm$ standard deviation or median (minimum - maximum) for continuous variables regarding normality

^{ab} = Presence of the same letter denotes the lack of the statistical significance.

MPV = Mean platelet volume, NLR = Neutrophil to lymphocyte ratio, PLR = Platelet to lymphocyte ratio, RDW = Red cell distribution width

Table 2. Variables included in the logistic regression model to predict the presence of endometrioma

	Odds ratio	95 % CI	P value
Platelet count	0.992	0.973-1.011	0.413
Mean platelet volume	0.755	0.340-1.677	0.491
Ca-125	1.235	1.106-1.380	<0.001

**Figure 1.** ROC curve analysis demonstrating the performance of Ca-125 in identifying subjects with endometrioma

Discussion

Except for the Ca-125 level, the three groups were similar with respect to the NLR and PLR. Our findings clearly demonstrate that neither NLR nor PLR has any value in distinguishing women with endometrioma from those with other benign ovarian cysts or healthy controls. However, Ca-125 levels might be used to identify patients with endometrioma, with high sensitivity and specificity.

Despite the physical, social, psychological, and economic burden caused by the endometriosis, the gold standard diagnostic tool is limited to direct visualization during laparoscopy combined with the histopathological confirmation. Thus, additional non-invasive diagnostic tools are required to assist the diagnostic accuracy and to overcome the potential complications of the laparoscopy.

The need for a reliable non-invasive marker of the endometriosis led to the conduction of much research in this area. Several non-invasive markers for diagnosis of the endometriosis have undergone investigation for this purpose. Ca-125, a well-established marker

for epithelial cell ovarian cancer, has attracted the most attention among these markers. Ca-125 is derived from the coelomic epithelia, including the peritoneum, ovary, fallopian tube, and the endometrium [8]. However, the amount of the randomized and controlled trials are limited, and the individual studies have methodological drawbacks in patient selection and conduction of the index test [9,10]. As shown in the meta-analysis conducted by Mol et al., which reviewed earlier studies of the utilization of the Ca-125 in the detection of endometriosis, the sensitivity

of Ca-125 for stage I-IV was found 50 % and the specificity was noted 72 % [11]. A recent meta-analysis of 22 studies and 3626 participants, reported that CA-125 does well as a rule-in test when the blood level of ≥ 30 units/ml is determined the cutoff-value. However, Ca-125 level < 30 units/ml, for which 49 % of the women with endometriosis were negative, was unable to rule out endometriosis [12]. Contemporary data from the study of Oliveira et al. confirmed the evidence indicating the diagnostic role of the Ca-125 supported the evidence derived from the previous studies [13]. Despite the extensive evidence concerning the role of the Ca-125 in diagnosing endometriosis, there is currently no validated, accurate test available with satisfactory sensitivity and specificity exceeding 75%.

The role of the inflammation in endometriosis and the diagnostic values of the inflammatory markers in the detection of endometriosis have also undergone comprehensive research.

Recent studies focused on the diagnostic performance of more simple and readily available blood markers of inflammation in detecting endometriosis. The NLR and PLR, as simple systemic inflammatory response (SIR) markers which are derivatives of the complete blood cell count parameters, have been found to be increased in several systemic conditions associated with low-grade inflammation [14-16]. The study of Cho et al. was one of the earliest studies addressing the role of the NLR in endometriosis. The authors found out in their study that NLR was appropriate for use in discriminating patients with endometriosis from those with benign ovarian tumors and from healthy controls [17]. In contrast to the findings of the Cho and colleagues, the results reported by Yavuzcan et al. which compared the NLR, PLR, mean platelet volume and the Ca-125 in patients with endometrioma, non-endometrioma benign ovary cysts and in healthy controls found that mean platelet volume, NLR and PLR values were not suitable for identifying patients with endometrioma and discriminating them from those with other ovarian pathologies. The study of Tokmak et al., which included 807 women who underwent surgery due to benign ovarian cysts, reported that the combination of NLR and Ca-125 could differentiate endometriomas from other benign ovarian cysts with favorable diagnostic accuracy [18]. Recently, Surya et al. evaluated the NLR and PLR in infected and non-infected endometrioma and demonstrated that blood levels of leukocytes, neutrophils, and the NLR were higher in patients with an infected endometrioma than that of the patients with non-infected endometriomas [19]. The association between the severity of the endometriosis and the level of the PLR and NLR has also been investigated. In a retrospective analysis of 419 patients, Kim et al. found no correlation between the severity of endometriosis and the serum level of CA 125 or the NLR [20]. The most recent study investigating the NLR and PLR in patients with endometrioma enrolled 128 patients with endometriomas and 85 subjects with other benign ovarian cysts. That study revealed that the NLR, PLR, and Ca-125 were increased in patients with endometriomas, and were predictive for the presence of the endometrioma although increases in NLR and PLR have not contributed to the diagnostic value of Ca-125 [3].

The present study demonstrates that the NLR, PLR, and mean platelet volume are similar among patients with endometriomas, other benign ovarian cysts and healthy controls. However, Ca-125

is significantly higher in patients with endometriomas compared to that of the patients with other non-endometrioma ovarian cysts and to the healthy controls. While NLR and PLR have had no value in discriminating patients with endometriomas from those with other benign ovarian cysts, Ca-125 level of >44.5 unit/ml was able to discriminate patients with endometriomas from other pathologies with a sensitivity of 97% and specificity of 96 %. Our results support the findings of Yavuzcan et al. in which the authors were failed to demonstrate any significant difference for NLR and PLR among patients with stage endometrioma and non-endometrioma ovarian cysts. Given the high NLR observed in infected endometriomas rather than the non-infected endometriomas as shown by Surya et al. we suppose that the increase in NLR and PLR are not intrinsic to endometriosis, but the consequence of endometriosis-related alterations in the immunologic response. We also consider that Ca-125 level > 44.5 unit/ml may be used to identify subjects with endometrioma in preoperative evaluation of patients with ovarian cysts. With this in mind, we believe that these findings raise intriguing questions regarding the involvement of the inflammation in the pathogenesis of the endometrioma. A further study with more focus on the role of inflammatory markers in endometriosis is therefore suggested.

The present study has some limitations to be mentioned. Retrospective design is the main disadvantage of this study, as some of the demographic data are lacking in the digital database, including body mass index, size of the adnexal mass, and the hormone tests. In addition, the phase of the menstrual cycle in which the blood measurements were obtained has not been recorded in our study, although some evidence recommends blood sampling during the menstruation and in midcycle. These results, therefore, need to be interpreted with caution. Further studies, which take these variables into account, will need to be undertaken.

Conclusions

The NLR, PLR and mean platelet volume, which are simple and readily available markers of the systemic inflammation, are not increased in patients with endometrioma compared to that of the patients with other benign ovarian cysts or the healthy controls. These CBC parameters have no value in identifying patients with endometrioma. However, Ca-125 exerts favorable performance in discriminating patients with endometrioma from those with other benign ovarian cysts.

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Ethical approval

The study was approved by the Institutional Ethical Committee of Acıbadem Mehmet Ali Aydınlar University (2019-1/34)

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