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Overyan Endometriomalı Hastalarda Derin İnfiltratif Endometriozis Varlığının Kan Testleri Yardımıyla Ameliyat Öncesi Öngörülebilirliği

Preoperative Predictability of the Presence of Deep Infiltrative Endometriosis in Patients with Ovarian Endometrioma with the Help of Blood Tests

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ÖZ

Giriş: Çalışmanın amacı over endometrioması (OMA) nedeniyle ameliyat edilen hastalarda ek derin infiltran endometriozis (DİE) varlığını öngörebilecek preoperatif kan değerlerini belirlemektir.

Yöntem: Bu retrospektif kohort çalışması OMA nedeniyle ameliyat edilen 149 hastayla gerçekleştirildi. Bu hastaların 43'ünde DIE varken, 106'sında DIE yoktu.

Bulgular: DIE hasta grubunda HB (hemoglobin) değeri daha düşük (p=0,014), PLR (trombosit-lenfosit oranı), CA125, CA19-9, CA15-3 değerleri daha yüksekti (p=0,028, p =0,000, p=0,004, p=0,003, sırasıyla). Gruplar arasında tiroid stimülan hormon (TSH), nötrofil sayısı, lenfosit sayısı, trombosit sayısı, NLR (nötrofil-lenfosit oranı), c-reaktif protein (CRP), protrombin zamanı (PT), aktive parsiyel tromboplastin zamanı (APTT), Uluslararası standardize oran (INR) ve CEA değerleri açısından anlamlı fark yoktu. (tümü için p>0,05). OMA'lı hastalarda DIE tanısında HB, PLR, CA125, CA15-3, CA19-9 değerlerinin ve üç kombinasyon modelinin tanısal etkinliği de değerlendirildi. ROC eğrileri HB, PLR, CA125, CA15-3, CA19-9, Kombinasyon 1 (CA125, CA15-3, CA19-9), Kombinasyon 2 (PLR ve CA125) ve Kombinasyon 3 (PLR, CA125, CA15-3, CA19-9) 'ün sırasıyla 0,629, 0,615, 0,701, 0,650, 0,656, 0,705, 0,698 ve 0,759 AUC (eğrinin altındaki alan) 'ye sahip olduğunu gösterdi.

Sonuç: OMA'lı hastalarda DIE varlığında HB değerleri düşme, PLR, CA125, CA15-3 ve CA19-9 değerleri ise artma eğilimindedir. PLR, CA125, CA15-3 ve CA19-9 değerlerinin kombinasyonu, OMA'lı hastalarda ameliyat öncesi DIE varlığının tespit edilmesine yardımcı olabilir.

Anahtar Kelimeler: derin infiltratif endometriozis, endometrioma, hemoglobin, trombosit-lenfosit oranı, CA125

ABSTRACT

Objective: The aim of the study is to determine the preoperative blood values that can predict the presence of additional deep infiltrating endometriosis (DIE) in patients operated for ovarian endometrioma (OMA).

Method: This retrospective cohort study was conducted with 149 patients who had undergone surgery for OMA. While 43 of these patients had DIE, 106 did not have DIE.

Results: In the group of patients with DIE, HB (hemoglobin) value was lower (p=0.014), PLR (platelet-to-lymphocyte ratio), CA125, CA19-9, CA15-3 values were higher (p=0.028, p=0.000, p=0.004, p=0.003, respectively). There was no significant difference between groups in terms of thyroid stimulating hormone (TSH), neutrophil count, lymphocyte count, platelet count, NLR (neutrophil-to-lymphocyte ratio), c-reactive protein (CRP), prothrombin time, (PT), activated partial thromboplastin time (APTT), International standardized ratio (INR), and CEA values (p> 0.05 for all). The diagnostic efficacy of HB, PLR, CA125, CA15-3, CA19-9 values and the three combination models in the diagnosis of DIE in patients with OMA were also evaluated. ROC curves showed that HB, PLR, CA125, CA15-3, CA19-9, Combination 1 (CA125, CA15-3, CA19-9), Combination 2 (PLR and CA125) and Combination 3 (PLR, CA125, CA15-3, CA19-9) had AUC (area under the curve) of 0.629, 0.615, 0.701, 0.650, 0.656, 0.705, 0.698 and 0.759, respectively.

Conclusion: HB values tend to decrease and PLR, CA125, CA15-3 and CA19-9 values tend to increase in patients with OMA in the presence of DIE. The combination of PLR, CA125, CA15-3, and CA19-9 values may help detect the presence of DIE preoperatively in patients with OMA.

Keywords: deep infiltrating endometriosis, endometrioma, hemoglobin, platelet-to-lymphocyte ratio, CA125

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INTRODUCTION

Endometriosis is the presence of the endometrial gland and stroma outside the uterine cavity (1,2). Endometriosis, one of the most common benign diseases in women of reproductive age, can cause chronic pelvic pain, dysmenorrhea, dyspareunia, bleeding disorders, cyclical voiding or defecation disorders, and reproductive failure (2-5). Endometriosis can be classified into three subtypes according to localization and depth of infiltration: superficial peritoneal endometriosis (SUP), ovarian endometrioma (OMA), and deep infiltrating endometriosis (DIE) (1,5-9).

Intraoperative imaging (with laparoscopy if possible), preferably with histological confirmation, is considered the gold standard for diagnosing endometriosis (5,10). Imaging methods such as magnetic resonance imaging and ultrasonography can also be used in diagnosis (2,4,5,10). Transvaginal ultrasound (TVUS), a widely available economical and minimally invasive method, is the first-line diagnostic imaging procedure for the detection of endometriosis (2,3,5). TVUS has a high diagnostic value for OMA with a sensitivity of approximately 93% and a specificity of approximately 96%. TVUS is also useful for diagnosis in DIE, but the diagnostic value of TVUS in the diagnosis of DIE is slightly lower than the diagnostic value in OMA (approximately 79% sensitivity and 94% specificity) (4,10). As a result, there may be delays and oversight in the diagnosis of DIE (7).

OMAs are probably the most frequently detected type of endometriosis due to the relative ease, accessibility and high diagnostic value of ultrasonographic diagnosis (6). The presence of OMAs is thought to be a marker for DIE, especially in extensive pelvic and intestinal lesions (11). In DIE, which is the most aggressive type of endometriosis, there is penetration more than 5 mm below the peritoneal surface. DIE can affect the uterosacral ligaments, parameter, bladder and bowel, causing very severe pelvic pain and a drastic decrease in pregnancy rate (1,2,4,12). Surgery in DIE is usually more complex and difficult than other types of endometriosis, and morbidity is higher. As a result of not removing all of the endometriotic tissue in DIE, recurrence may occur and the symptoms may become permanent in the patient (1,12).

Incidental intraoperative diagnosis of DIE is common. Unexpected DIE may be detected during planned surgery, especially in patients with OMA (1,12). Simultaneous excision of OMA and DIE lesions, which are often associated with each other, is associated with pain symptom resolution and low recurrence rate (7). Since the presence of DIE can significantly increase the difficulty of the operation, new approaches need to be developed to predict DIE before surgery in patients with OMA.

The aim of this study is to determine the blood values that can predict the presence of deep infiltrating endometriosis in patients who have been operated for ovarian endometrioma. For this purpose, it was planned to compare the preoperative blood tests between the group with ovarian endometrioma (OE) alone and the group with ovarian endometrioma and deep infiltrative endometriosis (OE+DIE).

MATERIALS AND METHODS

Study Design and Participants

This retrospective cohort study was conducted with 149 patients who had undergone laparoscopic or laparotomy surgery for ovarian endometrioma. This study was conducted in line with the principles of the Declaration of Helsinki. The study was approved by the local ethics committee.

Patients who were operated for ovarian endometrioma and whose complete blood count, thyroid stimulating hormone (TSH), c-reactive protein (CRP), prothrombin time, (PT), activated partial thromboplastin time (APTT), International standardized ratio (INR), CA125, CA19-9, CA15-3 and CEA values were controlled by blood test in the preoperative period were included in the study.

Patients with chronic diseases, pregnant women, patients known to be the source of acute infection such as upper respiratory tract infection or urinary tract infection during blood analysis, patients with fibroids or adenomyosis, patients receiving hormone therapy such as oral contraceptive drugs within 3 months, and patients with known malignancies were excluded from the study.

Protocol

Information on women who had ovarian endometrioma surgery were obtained from the hospital information system and data records. In addition to ovarian endometrioma, the presence of deep infiltrative endometriosis was examined from surgical and pathological records. Demographic data, information about whether the operation was laparoscopic or laparotomic, information about the size of the endometrioma, some blood values (hemoglobin, neutrophil count, lymphocyte count, platelet count, TSH, CRP, PT, APTT, INR, CA125, CA19-9, CA15-3 and CEA) performed in the last 3 months before the operation and the ratios calculated from these values (neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio) were recorded. This information was compared between patients with ovarian endometrioma alone and those with deep infiltrative endometriosis together with ovarian endometrioma.

Statistical Analysis

Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) Version 20.0 (IBM Corp., Armonk, NY, USA). Compliance with normal distribution was evaluated with the Kolmogorov-Smirnov test or the Shapiro-Wilk test. Numerical variables with normal distribution were shown as mean ± standard deviation, numerical variables with non-normal distribution were shown as median (25th - 75th percentile), and categorical variables were shown as frequency (percentage). The difference between the groups was determined by student-t test for numerical variables with normal distribution, and by Mann Whitney U test for numerical variables without normal distribution. Relationships between categorical variables were evaluated by Chi-square analysis. Receiver operating characteristic (ROC) analysis was used to evaluate the predictive performance of HB, PLR, CA125, CA19-9, CA15-3 values and three combination models in the diagnosis of DIE in patients with OMA.

RESULTS

149 women with OMA were included in this study. While 43 of these women had DIE, 106 did not have DIE.

The basic patient characteristics of the women participating in the study and the OMA dimensions in ultrasonography were compared in Table 1 according to the presence of DIE. It was observed that the mean age of the group with DIE was higher (p=0.01) and its parity was higher (p= 0.031). There was no significant difference between the groups in terms of smoking status and OMA size.

Table 1. Comparison of Baseline Patient Characteristics and OMA Dimensions of Women with and Without DIE

	DIE negative (n=106)	DIE positive (n=43)	P
Age (years)	35.34 ± 8.28	40.53 ± 8.69	***0.01*** [b] *****
Parity	1 (0–2.5)	2.5 (2-3)	***0.031*** [a] *****
Smoking	58 (54.7 %)	23 (53.5 %)	0.891 [c]
OMA dimension	6 (5-7)	6 (5-8)	0.495

Variables are given as median (25-75 percentile values), mean ±SD and n (%).
[a] Mann Whitney U test, [b] Student-t test
[c] Chi-square test, **** Bold/italics value signifies statistical significance.***

In Table 2, preoperative blood test results were compared between women with and without DIE. In the group of patients with DIE, HB (hemoglobin) value was lower (p=0.014), PLR (platelet-to-lymphocyte ratio), CA125, CA19-9, CA15-3 values were higher (p=0.028, P =0.00, p=0.004, p=0.003, respectively). There was no significant difference between the two groups with and without DIE in terms of TSH, neutrophil count, lymphocyte count, platelet count, NLR (neutrophil-to-lymphocyte ratio), CRP, PT, APTT, INR and CEA values (p> 0.05 for all).

The predictive performances of HB, PLR, CA125, CA19-9 and CA15-3 values in the diagnosis of DIE in patients with OMA were evaluated using ROC analysis. In addition, the predictive performances of the three combination models for the diagnosis of DIE in OMA patients were also analyzed by ROC analysis. The combination of values CA125, CA19-9, and CA15-3 was considered "Combination 1", the combination of PLR and CA125 values was considered "Combination 2", and the combination of PLR, CA125, CA19-9 and CA15-3 values was considered "Combination 3". Analysis results are shown in Table 3. The ROC curve for the Hb value is shown in figure-1, and the ROC curve for the PLR value is shown in figure 2. In Figure 3, the ROC curves of CA125, CA19-9 and CA15-3 values are shown. In Figure 4, the ROC curves of Combination1 Combination 2 and Combination 3 are shown on the same graph. ROC curves showed that HGB, PLR, CA125, CA15-3, CA19-9, Combination1, Combination 2 and Combination 3 had AUC (area under the curve) of 0.629, 0.615, 0.701, 0.650, 0.656, 0.705, 0.698 and 0.759, respectively (p < 0.05).

Table 2. Comparison of Preoperative Blood Test Results Between Women with and Without DIE

	DIE negative (n=106)	DIE positive (n=43)	P [a]
TSH (µIU/ml)	1.68 (1.09-2.72)	1.75 (1.20-2.75)	0.618
HB (g/dL)	12.50 (11.70-13.42)	12 (9.70-13.20)	***0.014 ****
Neutrophil count (×10⁹/L)	4.1 (3.5-5.85)	5 (3.30-8.2)	0.192
Lymphocyte count (×10⁹/L)	2.1 (1.7-2.5)	2.1 (1.4-2.45)	0.162
PLT (×10⁹/L)	276 (232-338)	279 (238.5-326)	0.541
NLR	1.94 (1.6-2.53)	2.27 (1.52-4.77)	0.107
PLR	136.61 (101.2-167.14)	150.71 (119.10-197.54)	***0.028 ****
CRP (mg/L)	3.47 (2-7.17)	5.33 (3.03-11.70)	0.103
PT (s)	12.9 (12.1-13.8)	12.50 (11.8-13.55)	0.143
APTT (s)	26.35 (24.90-28.40)	25.70 (24.90-27.00))	0.108
INR	1.07 (1.02-1.12)	1.06 (0.99-1.14)	0.634
CA125 (U/mL)	23.55 (12.30-58.57)	61.2 (31-152)	***0.000***
CEA (ng/mL)	1.71 (0.51-11.2)	1.53 (0.53-15)	0.782
CA15-3 (U/mL)	10.95 (7.6-15.82)	14.80 (9.6-28)	***0.004 ****
CA19-9 (U/mL)	18.01 (8.99-34.89)	41.45 (10.4-98)	***0.003 ****

Variables are given as median (25-75 percentile values), [a] Mann Whitney U test
**** Bold/italics value signifies statistical significance.***
Abbreviations: TSH=Thyroid Stimulating Hormone, HB=Hemoglobin, PLT: Platelet count, NLR=Neutrophil-to-lymphocyte ratio, PLR=Platelet-to-lymphocyte ratio, CRP=C-reactive protein, PT=Prothrombin time,
APTT=Activated partial thromboplastin time, INR=International standardized ratio

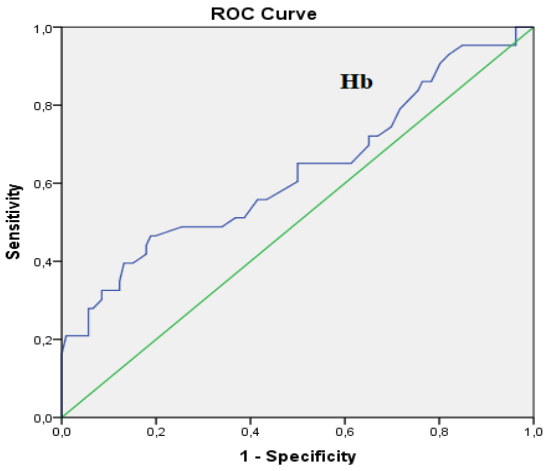

Figure 1. The ROC curve for the Hb value

Table 3. Diagnostic Efficacy of HB, PLR, CA125, CA15-3, CA19-9 Values and Three Combination Models in the Diagnosis of DIE in Patients with OMA

	AUC (95% CI)	Sensitivity, %	Specifity, %	Cutoff value	P*
HB (g/dL)	0.629 (0.523-0.735)	46	81	11.55	0.014
PLR	0.615 (0.514-0.716)	44	78	172.32	0.028
CA125 (U/mL)	0.701 (0.608-0.795)	81	52	26.6	0.000
CA15-3 (U/mL)	0.650 (0.548-0.752)	70	55	11.85	0.004
CA19-9 (U/mL)	0.656 (0.545-0.768)	46	90	54.76	0.003
Combination 1 (CA125, CA15-3, CA19-9)	0.705 (0.613-0.798)	70	63	0.25	0.000
Combination 2 (PLR and CA125)	0.698 (0.604-0.792)	82	56	0.24	0.000
Combination 3 (PLR, CA125, CA15-3, CA19-9)	0.759 (0.673-0.844)	63	78	0.28	0.000

P*<0.05 was considered statistically significant.

Abbreviations: AUC=Area under the curve, CI=Confidence interval, HB=Hemoglobin, PLR=Platelet-to-lymphocyte ratio

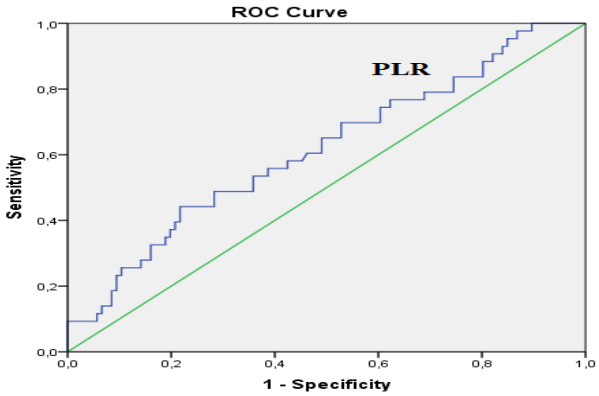

Figure 2. The ROC curve for the PLR value

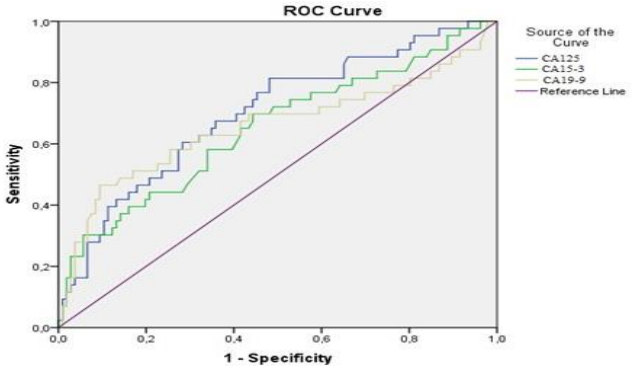

Figure 3. The ROC curves of CA125, CA19-9 and CA15-3 values

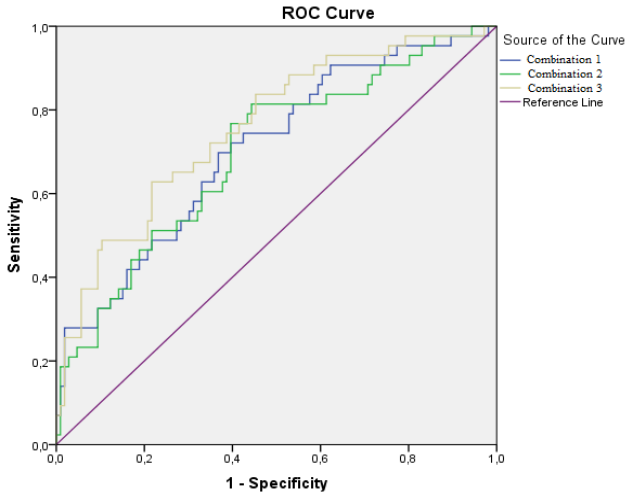

Figure 4. The ROC curves of Combination1 Combination 2 and Combination 3

DISCUSSION

Endometriosis is assumed to occur by ectopic implantation of the endometrium into the pelvic cavity, and it is thought that the implanted endometrium may lead to recurrent bleeding, recurrent tissue injury and inflammation (1). In addition, it is thought that there may be a potential hypercoagulation condition in women with endometriosis (13,14). Although there are many studies in the literature examining the effects of endometriosis and its stages on hematological, coagulation and biochemical laboratory markers, there are few studies (8,9,30,32) examining whether these markers differ between endometriosis subtypes (SUP, OMA, DIE). In addition, an important study examining the effect of the presence of additional DIE on these markers in OMA patients may not be available in the literature so far. Future studies on this subject, like our study, will help to detect the presence of DIE in OMA patients before the operation. One of the most important studies in the literature that could contribute to the preoperative prediction of the presence of DIE in OMA patients was based on the clinical findings of the patients (7). Our study will be one of the first studies in the literature that can contribute to the preoperative prediction of the presence of DIE in OMA patients with the help of serum biomarkers.One of the most well-known biomarkers associated with endometriosis is CA125, and the relationship between CA125 and endometriosis has been known since the 1980s (15,16).

Yılmaz et al. observed higher CA125 values in patients with advanced-stage endometriosis/DIE than in patients with OMA alone. In addition, they found that the CA125 value increased as the number of endometriotic nodules increased in patients with endometriosis (9). In our study, in line with the study of Yılmaz et al., we found that the CA125 level increased in patients with OMA in the presence of DIE, that is, in the case of more advanced endometriosis, compared to patients with only OMA. When we look at the studies in the literature examining the relationship between endometriosis and other tumor markers other than CA125, we see that CA19-9, like CA125, may be useful in the diagnosis of endometriosis. CA19 seems to have a high predictive value, especially in the diagnosis of advanced endometriosis (17-18).

According to meta-analysis studies published by Shen et al. in 2015, endometriosis is significantly associated with higher serum concentrations of CA125 and CA19-9, and CA19-9 is further increased in more advanced stages of disease. In addition, this study found that CA15-3 is not useful for the general diagnosis of endometriosis, but may be a valid biomarker of advanced disease (18). In our study, we found that CA125, CA15-3 and CA19-9 levels were increased in patients with OMA in the presence of DIE, that is, in the presence of more advanced endometriosis, compared to the absence of DIE. The ROC curve in our study showed that the combination of three tumor markers (CA125, CA15-3, CA19-9) had a slightly higher AUC (0.705) than each individual index in diagnosing the presence of DIE in patients with OMA. In addition, we did not observe any significant difference between the groups in terms of CEA level. Our study shows parallelism with most of the studies in the literature in terms of increased CA125 and CA19-9 levels in advanced endometriosis. However, in the study conducted by Kim et al. in 2014, it was determined that there was no significant difference between patients with stage 3 and stage 4 endometriosis in terms of tumor markers CA125, CAE and CA19-9 (19). More randomized controlled controls and meta-analyses are needed to examine the relationship between tumor markers and predictivity, type, and score of endometriosis.

In most of the studies evaluating the relationship between endometriosis and hematological parameters, endometriosis was associated with low hemoglobin value (9,20-22). In some of these studies, the decrease in hemoglobin became more pronounced as the stage of endometriosis progressed (9,22), while in some, no significant difference was observed between different stages of endometriosis in terms of hemoglobin value (20,21). The reason for the relationship between the presence of endometriosis and low hemoglobin value has not been determined exactly. There are opinions that the disorder in iron metabolism triggers endometriosis (23-25). Low hemoglobin levels in patients with endometriosis may be associated with disturbances in iron metabolism. In addition, the opinion that hypoxia may facilitate the formation of endometriosis may explain the low hemoglobin level in endometriosis (26). In the study of Chen et al. published in 2021, hemoglobin values of patients with DIE were significantly lower than patients with benign gynecological diseases in the control group (1). Although the control groups of Chen et al.'s study and our study are different, our study and Chen et al.'s study are compatible in terms of the result that the presence of deep endometriosis reduces the hemoglobin value. DIE is the most aggressive form of endometriosis, and the presence of DIE in patients with OMA makes endometriosis more severe and complicates endometriosis surgery (12). Therefore, our study is consistent with the studies of Cho et al. (22) and Yılmaz et al. (9), which showed that as the severity of endometriosis increases, the hemoglobin value decreases.

Endometriosis is thought to be a chronic inflammatory disease associated with local and systemic inflammatory response (8,19,22,27,28). Neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) are simple systemic inflammatory response (SIR) markers and are evaluated by blood parameters (9). C-reactive protein (CRP), a member of the pentraxin protein family, is known as a useful biomarker for detecting inflammation and is elevated in peripheral blood during inflammation.

CRP level can be routinely measured in peripheral blood using either a conventional method or the more recently described high-sensitivity CRP (hsCRP) technique (8). There are various studies evaluating the relationship between CRP, NLR and PLR values and endometriosis. In their study conducted in 2014, Thubert et al. found that hsCRP values were not affected by the presence of endometriosis, the stage of endometriosis, and the type of endometriosis (SUP, OMA and DIE) (8). In other words, they argued that hsCRP measurement is not useful in the diagnosis and/or staging of endometriosis. This is compatible with the result of our study that DIE presence does not change the CRP level in OMA patients. We found that the CRP level has not changed when endometriosis becomes more serious with the presence of DIE. In the study of Cho et al. in 2008, the NLR alone and the combined marker value for which CA125 and NLR were calculated together were significantly higher in patients with endometriosis than in patients without endometriosis. In this study, NLR was able to distinguish patients with endometriosis from those with benign ovarian tumors and healthy controls (29). In their study published in 2013, Yang et al., serum CA125, NLR, and combined biomarkers were able to significantly distinguish the stage III and IV endometriosis group from patients with benign tumors and healthy controls. In particular, the combined evaluation of both biomarkers was found to have high sensitivity and specificity in the diagnosis of endometriosis. Additionally, they found that NLR level may be an important diagnostic tool in detecting stage 3 and stage 4 endometriosis in patients with negative CA125 levels (27). In their study published in 2021, Chen et al. observed higher CRP, CA125 and fibrinogen values in patients with DIE compared to patients with benign gynecological disease, and they did not observe any significant difference between the two groups in terms of NLR and PLR (1). While Yılmaz et al. observed higher CRP values in advanced endometriosis/DIE patients compared to OMA patients alone, they did not observe any significant difference between the groups in terms of NLR and PLR values (9). Guo and Zhang evaluated the relationship of the presence of endometriosis and the degree of pelvic adhesion with PLR, CA125 and combined biomarker values in their study published in 2022. They found that these values were positively correlated with both the presence of endometriosis and the severity of adhesion (28). Considering that the presence of DIE in patients with OMA will aggravate the disease, this is consistent with our study. As can be seen from the studies in the literature, although there is a relationship between endometriosis and inflammation, there is no clear consensus on the increased inflammation markers in endometriosis. In addition, the relationship between the stages and types of endometriosis and inflammation markers is not clear. In our study, we observed that the presence of DIE in OMA patients increased the PLR value, but did not statistically significantly change the NLR and CRP values.

The ROC curve in our study showed that the combination of PLR and three tumor markers (CA125, CA15-3, CA19-9) had a higher AUC (0.759) than each index and the combination of the three tumor markers in diagnosing the presence of DIE in patients with OMA.

In the literature, hypercoagulation status in patients with endometriosis has been demonstrated in some studies with the help of laboratory values such as activated partial thromboplastin time (APTT), prothrombin time (PT), international normalization ratio (INR), thrombin

time (TT), platelet count (PLT), D-dimer and fibrinogen (13,14,30,31). In the study of Vigano et al. published in 2018, no difference was found between endometriosis patients and controls in terms of thrombin time and platelet count. The APTT was shorter in patients with endometriosis, but still within the normal range overall. Different subtypes of endometriosis were also evaluated in this study. While shortening in APTT was observed significantly in patients with ovarian endometrioma compared to the control group, no similar significant shortening was observed in patients with deep and peritoneal endometriosis. Additionally, women with stage I to II endometriosis had a significantly shorter APTT than those with stage III to IV disease. It is noteworthy that in the study of Vigano et al., women with more severe disease did not appear to have a shorter APTT, and the shortening in APTT was associated with the presence of endometriotic cyst (30). In our study, patients with OMA were also examined and no significant difference was observed between the two groups with and without DIE in terms of PT, APTT, INR, and PLT values. That is, we found no evidence that the presence of DIE further promoted hypercoagulation in patients with OMA. This is consistent with the study of Vigano et al., in which APTT shortening was associated with the presence of ovarian endometriotic cysts, and the presence of DIE and SPE was not associated with aPTT change. Similarly, in the study of Ottolina et al., published in 2020, shorter APTT was observed in patients with OMA than in patients with DIE and SPE, which are other types of endometriosis, and in the control group without endometriosis (32). A study published in 2018 by Ding et al. revealed that women with OMA had significantly shorter TT, higher platelet activation rate and platelet aggregation rate, and elevated plasma D-dimer, fibrinogen, fibrin degradation products, plasma soluble P-selectin, and prothrombin fragment 1+2 levels compared to women without endometriosis. However, in this study, INR and APTT values were not different in patients with endometriosis. In addition, Ding et al. found in this study that 3 months after surgical removal of endometriotic lesions, TT was prolonged and all other coagulation measures were significantly reduced except for plasma fibrinogen level (14). Although almost all studies to date have shown hypercoagulation of endometriosis, especially OMA, the changes in the values studied have shown differences. This may have occurred due to different sample sizes, conditions and techniques applied between studies (31). In the study of Chen et al. in 2021, shorter TT was found in DIE patients compared to those with benign gynecological disease. However, the association between TT and the presence of DIE was no longer significant after adjusting for confounding factors. Also, APTT and PT were similar between groups with and without DIE (1). Similarly, in our study, we observed that the presence of additional DIE in OMA patients did not affect these coagulation parameters. In addition, in the study of Chen et al., it was determined that the presence of DIE increased the fibrinogen level compared to those with benign gynecological diseases (1). Fibrinogen is an acute phase reactant that plays a role in tissue damage and inflammation, as well as being a coagulation factor that indicates hypercoagulation (1,33). According to Chen et al.'s study (1), whether the presence of DIE causes hypercoagulability or not, the increase in fibrinogen in the DIE patient group may indicate that the presence of DIE causes an inflammatory state. Since our study is a retrospective study and fibrinogen measurement is not routinely performed in every patient in our clinic, we could not evaluate the fibrinogen value in our study.

The strongest aspect of our study is that it will be one of the first studies in the literature that can contribute to the preoperative prediction of the presence of DIE in OMA patients with the help of serum biomarkers. The limitation of our study is that it is retrospective and therefore markers other than those routinely measured preoperatively could not be analyzed.

In conclusion, hemoglobin values tend to decrease and PLR, CA125, CA15-3 and CA19-9 values tend to increase in patients with OMA in the presence of DIE. The combination of PLR, CA125, CA15-3, and CA19-9 values may help detect the presence of DIE preoperatively in patients with OMA.

Ethics Committee Approval: The study was approved by Health Sciences University Derince Training and Research Hospital Ethics Committee, Protocol No: 2022-78. This research was conducted in accordance with the ethical stansdards of the Helsinki declaration and its later amendments.

Author Contributions: MD and ES designed the study. ES collected data. MD performed the data analysis, interpreted the analysis, and reviewed the literature. MD and ES wrote the manuscript, then critically reviewed and made significant corrections. All authors read and approved the final version of the manuscript.

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