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Original Article

Prediction models of endometriosis stage generated from potential hematological biomarkers

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ABSTRACT

Objective: The aim of the study assess efficacy of hematological biomarkers for predicting the stage of endometriosis.

Materials and methods: Patients who underwent surgery and were diagnosed with endometriosis confirmed by pathology report between January 2015-December 2020 were included. Individuals were divided into two groups as stage 1-2-3 and stage 4 patients.

Results: Ninety one patients with stage 1-2-3 and 105 with stage 4 endometriosis were identified. There was no significant relationship between endometriosis score and complete blood count parameters. However, the endometriosis score revealed a significant correlation between serum CA125 level and the combined markers including CA125. The logarithm of the CA 125 was used to predict the endometriosis score. In order to quantify the relationship, a univariate linear model was performed to predict the endometriosis score with log (CA 125). It demonstrated for every increase in the level of log (CA 125), endometriosis score increased by 8.57 (β=8.57. R2=0.115. p<0.001). The p values of alternative parameters analyzed to predict the stage of endometriosis. p-values were 0.263 for neutrophile/lymphocyte; 0.457 for platelet/lymphocyte; 0.790 for red cell distribution width/lymphocyte and 0.842 for mean platelet volume/lymphocyte ratios.

Conclusion: CA 125 alone was found substantially efficient in predicting the endometriosis stage preoperatively.

Keywords: biomarkers; endometriosis; mean platelet volume; neutrophils

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Introduction

Endometriosis is a chronic inflammatory disease which occurs 6 to 10 %, varies within the population [1]. It affects women during their premenarcheal, reproductive, and postmenopausal hormonal stages [2–4]. Endometriosis is definitively diagnosed by histologic evaluation of a lesion biopsied during typically laparoscopic surgery or laparotomic surgery [3,5]. It is staged as minimal, mild, moderate and severe by revised American Society for Reproductive Medicine's (ASRM) classification system [5]. This classification provides standardized approach to present surgical findings methodically. Stage of endometriosis and severeness of symptoms were reported irrelevant [6–8]. The pathogenesis of endometriosis appears to be multifactorial, however stil unexplained. Recent studies commonly stated theroies on altered immunity and inflammatory response [9–13]. According to some researchers lymphocyte-to-monocyte ratio [LMR] and neutrophil-to-lymphocyte ratio (NLR) also platelet index may be used to diagnose endometriosis [9] . In addition some studies focused on platelet distrubiton width (PDW), mean platele volume (MPV) and platecrite (PCT) parameters with Cancer Antigen 125 (CA 125) levels to be considered for clinical endometriosis staging [10–12].

In our study, we aim to examine the ability of MPV, PCT, PDW, LMR, NLR, and CA 125, which are considered to play critical roles in the inflammatory process, to predict the stage of endometriosis.

Material and methods

Operated and pathologically confirmed endometriosis patients' medical records between January 2015 and December 2020 were recruited. Demographics, laboratory and ultrasonography findings, and surgery reports of the cases were analyzed. Patients with chronic diseases which could affect hematological profile, hemoglobin<10 mg/dl cases, and individuals with cancer or cervical intraepithelial neoplasia were excluded. Age, gravida, parity, antecedent surgeries, surgery method, location of the lesions, endometriosis score, preoperative complete blood cound parameters and CA 125 levels were noted. Cases were staged as minimal (1-5 points), mild (6-15 points), moderate (16-40 points) and severe (>40 points) by revised ASRM classification system. Patients were divided into two groups; patients with stages 1-2-3 combined and stage 4.

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All parameters and ratios which were found allegedly significant in previous studies, were used to design a model for predicting the stage of endometriosis lesions in our patients. Models' capacity of predicting were analyzed. Statistical analyses were performed using SPSS statistical software (version 25.0; SPSS Inc., Chicago, IL, USA) and R statistical computing software (version 3.6.1, https://www.r-project.org/). The normality of the distribution of the variables was tested with the Kolmogorov Smirnov test. Continuous variables between the two groups were compared by the Independent Sample T test or Mann Whitney U test. The relationship between the endometriosis score and the variables was analyzed by using Spearmen correlation coefficient. In order to avoid missing non-linear relations, the CA125 level and complete blood count ratios were investigated using generalized additive model. Restricted maximum likelihood was used to fit the model. In order to investigate the endometriosis classifying potential of the related markers and ratios, ROC analysis was performed. The area under the curve values were calculated for each marker. The mean, standard deviation, median (interquartile range) and sample size values of the variables were presented in the tables. A two-tailed p value of <0.05 was considered as significant. Approval was obtained from the local ethics committee. Decision number is 2020/6-25.

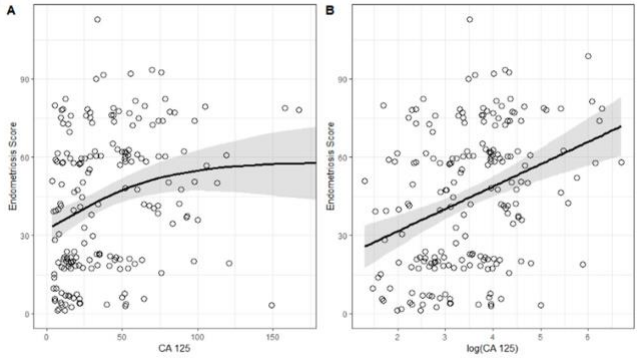
Results

A total of 244 women who underwent endometriosis surgery were included. 202 of them only had intra-abdominal endometriotic lesions or cysts. 6 of them were excluded due to missing values of CA 125 levels. All in all, 196 patients were included in the analysis. In Table 1, the correlation between endometriosis score and demographic characteristics, preoperative hematologic markers and combined markers were presented. No significant relationship is detected between the endometriosis score and the complete blood count parameters. However, the endometriosis score reveals a significant correlation between serum CA125 level and the combined markers including multiplication of CA125.

Table 2 presents the comparison of the demographic characteristics and hematologic parameters for the endometriosis stage. A statistically significant difference was found between the two groups in terms of CA125, PLR*CA125 and NLR*CA125 value (respectively p<0.001; <0.001; <0.001). The area under curve value of these characteristics to discriminate the endometriosis stage 4 disease from diseases with lower stage, was shown.

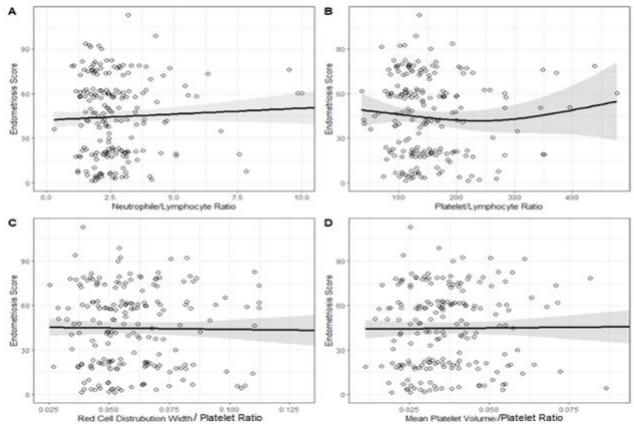
In order to investigate a potential non-linear relationship between the endometriosis score and the serum parameters, the generalized additive model (GAM) with restricted maximum likelihood method was used. In Figure 1.A.

Figure 1. The relationship of endometriosis score with respect to A. CA 125 and B. log[CA 125] levels [Due to the low number of observations with CA 125 levels higher than 175, the maximum value for Figure A's x axis is set at 175].



GAM analysis demonstrates a smooth with logarithmic pattern between the endometriosis score and CA 125 levels. In order to verify this relationship, the logarithm of the CA 125 was used to predict the endometriosis score. As presented in Figure 2.B. the GAM analysis shows a smooth with one degree of freedom, verifying the linear relationship between the endometriosis score and the logarithm of CA 125.

Figure 2. The relationship of endometriosis score with respect to A. Neutrophile/Lymphocyte B. Platelet/Lymphocyte C. Red Cell Distribution Width/Platelet D. Mean Platelet Volume/Platelet ratios [The range of the x coordinates of the figures were truncated to the interval where most observations were concentrated.]



In order to quantify the relationship, a univariate linear model was performed to predict the endometriosis score with log [CA 125]. It showed that the endometriosis score increased by 8.57 for every increase in the level of log [CA 125] by one [β=8.57. R2=0.115. <0.001]. Lastly GAM analysis for the alternate ratios did not demonstrate a significant relationship with respect to the endometriosis score. The smooths' p-values were 0.263 for neutrophile/lymphocyte; 0.457 for platelet/lymphocyte; 0.790 for red cell distribution width/lymphocyte and 0.842 for mean platelet volume/lymphocyte ratios.

Discussion

Endometriosis results when ectopic endometrial cells implant, grow, and elicit an inflammatory response[1]. Even though definitive diagnosis requires biopsy and histological confirmation; sypmtoms and imaging combined could also be used for hypothetical and non-surgical diagnosis of endometriosis [13,14]. Recent studies focused on association of endometriosis and hemotological markers, and also non-invasive diagnostic methods [10,12,15]. Additionally markers such as NLR, PLR, PCT were suggested to be effective on staging endometriosis [12,15,16]. In our study we did not observe a supposed correlation between inflammatory markers and endometriosis stage.

Nevertheless, we could only verify one between the CA 125 level and endometriosis. No lineer relation was detected between endometriosis score and CA 125 yet an association was found between endometriosis score and [log] CA125. Also analysis did not show any significant difference between two groups in NLR, PLR, LMR, RDW/PLT and MPV/PLT levels. Endometriosis is more common in nulliparous women [4,17,18]. Furthermore multiple births were found associated with decreased risk [19,20].

Table 1. Correlations between the endometriosis score and demographic characteristics, preoperative hematologic markers, and combined markers.

Parameter	Correlation Coefficient[1]	p-value
Age [year]	-0.24	<0.001*
Gravida	-0.30	<0.001*
Parity	-0.30	<0.001*
CA125 [U/mL]	0.34	<0.001*
White Blood Count	0.11	0.135
Neutrophile [x10^3/µl]	0.06	0.373
Lymphocyte [x10^3/µl]	0.11	0.139
Monocyte [x10^3/µl]	0.05	0.518
Eosonophile [x10^3/µl]	-0.01	0.912
Basophile [x10^3/µl]	-0.07	0.325
Red Blood Count	0.07	0.308
Hemoglobin /g/dL]	0.08	0.260
Hematocrite [%]	0.09	0.225
MCV [fL]	-0.01	0.916
MCH [pg]	0.02	0.794
MCHC [g/dL]	0.07	0.334
RDW [%]	-0.11	0.134
Platelet	-0.03	0.702
MPV [fL]	0.10	0.165
Platecrite [%]	0.01	0.932
PDW [%]	0.04	0.622
NLR	-0.02	0.790
PLR	-0.08	0.273
LMR	0.03	0.701
PLR*CA125	0.30	<0.001*
NLR*CA125	0.31	<0.001*
RDW/PLT	-0.01	0.906
MPV/PLT	0.05	0.449

CA, cancer antigen; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width; MPV, mean platelet volume; PDW, platelet distribution width; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR,lymphocyte-to-monocyte ratio. [1]Spearman correlation coefficient were given.
*Statistically significant correlations were indicated with *.*

Consisting with our data of decreased gravida and parity numbers in advanced staged patients, Ding et al. reported higher nulliparity and less multiple births in women with advanced stage endometriosis [9]. The own pathophysiological process of endometriosis appears to be the cause of inflammatory response [21]. Probably this leaded researchers to examine the role of hematological markers further in endometriosis diagnose and staging.

Cho et al. reported 69.3% sensivity and 83.9% specifity in NLR and CA 125 levels combined to detect endometriosis [15]. Yet other study observed 71.6% sensivitiy of CA 125 alone to diagnose moderate and severe endometriosis, however CA 125 and PLR rates together increased sensivity to 90.4% [12]. Also some researchers demonstrated MPV and PDW rates were significantly lower [p=0.003, p=0.002 respectively] but PLT and PCT rates were significantly higher in advanced endometriosis [p=0.001, p=0.001] [16].

Table 2. Comparison of demographic characteristics, preoperative hematologic markers and combined parameters between women with endometriosis stage 1, 2, 3, and stage 4 and Area under curve [AUC] values of these parameters to discriminate endometriosis stage 4 from lower stage diseases.

	Stage 1-2-3 [n=91]	Stage 4 [n=105]	p-value	AUC [95% CI]
Age [year]	42.16±13.08 43.0 [33.0;48.0]	39.93±9.64 41.0 [34.0; 45.0]	0.185[a]	0.555 [0.473 – 0.637][c]
Gravida	2.46±1.56 3.0 [1.0; 3.0]	1.95±1.37 2.0 [1.0; 3.0]	0.012[a]	0.601 [0.521 – 0.681][c,*]
Parity	2.41±1.53 22.0 [11.8; 51.7]	1.90±1.32 11.8[51.7;105.0]	0.012[a]	0.601 [0.521 – 0.681][c,*]
CA125 [U/mL]	39.19±51.10 22.0 [11.8; 51.7]	82.19±125.24 48.7 [23.2; 75.9]	<0.001[a]	0.670 [0.595 – 0.746][d,*]
White Blood Count	7.80±2.83 7.4 [6.1; 8.6]	8.07±2.56 7.3 [6.1; 9.3]	0.376[a]	0.537 [0.456 – 0.618][d]
Neutrophile [x10^3/µl]	5.15±2.67 4.7 [3.7; 5.8]	5.32±2.39 4.6 [3.6; 6.1]	0.643[a]	0.519 [0.438 – 0.601][d]
Lymphocyte [x10^3/µl]	1.97±0.82 1.9 [1.6; 2.2]	2.02±0.65 2.0 [1.6; 2.4]	0.210[a]	0.552 [0.471 – 0.632][d]
Monocyte [x10^3/µl]	0.48±0.15 0.5 [0.4; 0.6]	0.52±0.38 0.5 [0.4; 0.6]	0.950[a]	0.503 [0.422 – 0.584][d]
Eosonophile [x10^3/µl]	0.13±0.11 0.1 [0.0; 0.2]	0.12±0.12 0.1 [0.0; 0.2]	0.765[a]	0.512 [0.430 – 0.593][c]
Basophile [x10^3/µl]	0.05±0.08 0.0 [0.0; 0.1]	0.05±0.11 0.0 [0.0; 0.1]	0.330[a]	0.534 [0.453 – 0.615][c]
Red Blood Count	4.37±0.67 4.5 [4.2; 4.7]	4.46±0.45 4.5 [4.1; 4.8]	0.703[a]	0.516 [0.435 – 0.597][d]
Hemoglobin [g/dL]	11.88±1.65 12.3 [10.5; 13.1]	12.03±1.43 12.2 [11.0; 13.1]	0.589[a]	0.522 [0.441 – 0.604][d]
Hematocrite [%]	36.23±4.50 36.7 [33.7; 39.6]	36.55±3.84 37.1 [34.2; 39.4]	0.592[b]	0.524 [0.442 – 0.605][d]
MCV [fL]	81.45±8.43 83.1 [76.9; 87.2]	82.21±6.48 82.2 [79.1; 87.0]	0.985[a]	0.501 [0.418 – 0.583][c]
MCH [pg]	26.85±3.24 27.5 [25.1; 29.1]	27.08±2.72 27.3 [25.7; 29.1]	0.867[a]	0.507 [0.425 – 0.589][d]
MCHC [g/dL]	32.74±1.22 32.7 [32.0; 33.6]	32.89±1.13 32.9 [32.3; 33.5]	0.382[b]	0.533 [0.451 – 0.615][d]
RDW [%]	15.56±3.02 14.6 [13.5; 16.2]	15.24±3.17 13.9 [13.3; 16.3]	0.132[a]	0.562 [0.482 – 0.643][c]
Platelet	279.12±89.08 269.0 [218; 335]	276.35±80.01 262.0 [229; 329]	0.768[a]	0.512 [0.431 – 0.594][c]
MPV [fL]	9.15±1.14 9.0 [8.3; 10.0]	9.34±1.14 9.3 [8.6; 10.1]	0.258[b]	0.555 [0.474 – 0.636][d]
Platecrite [%]	0.25±0.07 0.3 [0.2; 0.3]	0.25±0.07 0.3 [0.2; 0.3]	0.781[a]	0.512 [0.430 – 0.593][d]
PDW [%]	16.73±0.57 16.6 [16.3; 17.1]	16.75±0.68 16.7 [16.2; 17.1]	0.841[a]	0.508 [0.427 – 0.590][d]
NLR	2.85±1.94 2.4 [2.0; 3.1]	3.20±3.21 2.4 [1.8; 3.2]	0.475[a]	0.530 [0.449 – 0.611][c]
PLR	151.52±60.24 136.3[112.5;174]	153.19±77.45 131.3[108.4;176]	0.380[a]	0.536 [0.455 – 0.618][c]
LMR	4.23±1.37 4.2 [3.3; 5.0]	4.58±2.17 4.5 [3.3; 5.5]	0.330[a]	0.540 [0.460 – 0.621][d]
PLR*CA125	6505±14010 3080[1653;6899]	12628±19821 6393[2887;11325]	<0.001[a]	0.656 [0.580 – 0.732][d,*]
NLR*CA125	111.43±161.88 55.8[28.5;135.5]	267.36±596.14 106.5[53.4;231.3	<0.001[a]	0.660 [0.583 – 0.736][d,*]
RDW/PLT	0.063±0.036 0.054[0.046;0.07]	0.059±0.020 0.056[0.045;.069]	0.980[a]	0.501 [0.419 – 0.583][c]
MPV/PLT	0.039±0.026 0.033[0.025;0.04]	0.037±0.013 0.035[0.028;0.04]	0.423[a]	0.533 [0.452 – 0.615][d]

CA. cancer antigen; MCV. mean corpuscular volume; MCH. mean corpuscular hemoglobin; MCHC. mean corpuscular hemoglobin concentration; RDW. red cell distribution width; MPV. mean platelet volume; PDW. platelet distribution width; NLR. neutrophil-to-lymphocyte ratio; PLR. platelet-to-lymphocyte ratio; LMR. lymphocyte-to-monocyte ratio.
[a]Independent Sample T test and [b]Mann Whitney U test were used. [c]Smaller test result indicates Stage 4 disease. [d]Larger test result indicates Stage 4 disease.
Statistically significant correlations and AUC values were indicated with *.

Lin et al.'s findings described specified coagulation and inflammatory factors may be the clinical key role in diagnosis and treatment of moderate to severe ovary endometriosis. They also resulted NLR and PLR rates were significantly higher in endometriosis patients than cases with benign cyst (p<0.001) [22].

In contrast to previous studies, we presented no relation between inflammatory paramaters and endometriosis stage. This results correlate favorably well with Yavuzcan et al.'s study as they resulted MPV, NLR and PLR levels were impractical to diagnose severe stage of endometriosis [10].

In a study of Seçkin et al. found PCT, PLT and CA 125 rates were significantly increased in individuals with endometrioma ($p<0,001$). Still these rates were found unable to recognize endometrioma thus they finally stated hematological markers were considered as unable to distinguish endometriomas from ovarian cysts [23]. Coskun et al.'s study with 102 endometriosis and 88 control patients, described PC index alone and also MPV level were not to be found efficient in diagnosis [24]. Results varied widely with various grouping criteria and number of patients in the literature. Noticeable studies showed that CA 125 levels were found higher in advanced stages of endometriosis eventhough it was not described as diagnostic criteria [25,26].

In Myuldermans et al.'s review, it was outlined that CA 125 could be a favorable marker for endometriotic disease yet they resulted this was limited to early stages of illness [27]. Similarly a meta-analysis suggested CA 125 was used to diagnose endometriosis, nevertheless considerably CA 125 <30 units/ml levels could not rule out endometriosis [28]. Dorien et al.'s study also confirmed the most valuable marker to diagnose and follow-up was CA 125 [29]. A recent study found hemoglobin, CA 125 and C reactive protein (CRP) levels significantly increased only in patient with deep infiltrative endometriosis [p=0.007, p=0.00, p=0.036 respectively] [30]. While advanced endometriosis requires more invasive approaches, early stages could benefit from these markers.

In our study hematological biomarkers and CA 125 were compared between two groups and revealed only CA 125's area under curve (AUC) value was 0,67 [%95 CI, $p<0,001$]. This correlation between advanced stage endometriosis and CA 125 was noteworthy [0.34]. Inaddition we observed CA 125 was increased with the larger samples. Our findings are consistent with the previous research. Eventhough no significant difference were obtained, we described AUC values 0.656 and 0.66 respectively in PLR*CA 125 and NLR*CA 125 between the groups. Yet as far as we know these combinations restrained the strength of diagnosis with only CA 125.

We are aware that our study had few limitations. First we had small sample size and second lack of control group with benign ovary cyst was identified. These limitations highlight the difficulty of collecting data on this very specific topic.

In conclusion the results of our study indicated preoperative evaluation of hematological biomarkers were not valuable in staging endometrioma. We assumed CA 125 was much more useful to diagnose stage alone than CA 125 plus other hematological biomarkers could determine together. Further studies with larger sample size and control group are needed to be performed to adress this topic.

Disclosure

Authors have no potential conflicts of interest to disclose.

References

[1] Giudice LC, Kao LC. Endometriosis. In: Lancet. 2004; Nov 13-19;364[9447]:1789-99.

[2] Vercellini P, Viganò P, Somigliana E, Fedele L. Endometriosis: Pathogenesis and treatment. Nat Rev Endocrinol. 2014; May;10[5]:261-75

[3] Hickey M, Ballard K, Farquhar C. Endometriosis. BMJ [Online]. 2014; Mar 19;348:g1752.

[4] Hediger ML, Hartnett HJ, Louis GMB. Association of endometriosis with body size and figure. Fertil Steril. 2005;Nov;84[5]:1366-74.

[5] Canis M, Donnez JG, Guzick DS, Halme JK, Rock JA, Schenken RS, et al. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. Fertil Steril. 1997; May;67[5]:817-21.

[6] Vercellini P, Fedele L, Aimi G, Pietropaolo G, Consonni D, Crosignani PG. Association between endometriosis stage, lesion type, patient characteristics and severity of pelvic pain symptoms: A multivariate analysis of over 1000 patients. Hum Reprod. 2007; Jan;22[1]:266-71.

[7] Vercellini P, Trespidi L, De Giorgi O, Cortesi I, Parazzini F, Crosignani PG. Endometriosis and pelvic pain: Relation to disease stage and localization. Fertil Steril. 1996; Feb;65[2]:299-304.

[8] Parazzini F, Cipriani S, Moroni S, Crosignani PG, Ciavattini A, Garzetti G, et al. Relationship between stage, site and morphological characteristics of pelvic endometriosis and pain. Hum Reprod. 2001; Dec;16[12]:2668-71.

[9] Ding S, Lin Q, Zhu T, Li T, Zhu L, Wang J, et al. Is there a correlation between inflammatory markers and coagulation parameters in women with advanced ovarian endometriosis? BMC Womens Health. 2019; Dec 30;19[1]:169.

[10] Yavuzcan A, Caglar M, Ustun Y, Dilbaz S, Ozdemir I, Yildiz E, et al. Evaluation of mean platelet volume, neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in advanced stage endometriosis with endometrioma. J Turkish Ger Gynecol Assoc. 2013; Dec 1;14[4]:210-5.

[11] Kim SK, Park JY, Jee BC, Suh CS, Kim SH. Association of the neutrophil-to-lymphocyte ratio and CA 125 with the endometriosis score. Clin Exp Reprod Med. 2014; Dec;41[4]:151-7.

[12] Yang H, Zhu L, Wang S, Lang J, Xu T. Noninvasive Diagnosis of Moderate to Severe Endometriosis: The Platelet-Lymphocyte Ratio Cannot Be a Neoadjuvant Biomarker for Serum Cancer Antigen 125. J Minim Invasive Gynecol. 2015; Mar-Apr;22[3]:373-7.

[13] Eskenazi B, Warner M, Bonsignore L, Olive D, Samuels S, Vercellini P. Validation study of nonsurgical diagnosis of endometriosis. In: Fertility and Sterility. 2001; Nov;76[5]:929-35.

[14] Barcellos MB, Lasmar B, Lasmar R. Agreement between the preoperative findings and the operative diagnosis in patients with deep endometriosis. Arch Gynecol Obstet. 2016; Apr;293[4]:845-50.

[15] Cho SH, Cho H, Nam A, Kim HY, Choi YS, Park KH, et al. Neutrophil-to-lymphocyte ratio as an adjunct to CA-125 for the diagnosis of endometriosis. Fertil Steril. 2008; Dec;90[6]:2073-9.

[16] Avcioğlu SN, Altinkaya SÖ, Küçük M, Demircan-Sezer S, Yüksel H. Can Platelet Indices Be New Biomarkers for Severe Endometriosis? ISRN Obstet Gynecol. 2014; Mar 26;2014:713542.

[17] Ballard KD, Seaman HE, De Vries CS, Wright JT. Can symptomatology help in the diagnosis of endometriosis? Findings from a national case-control study - Part 1. BJOG An Int J Obstet Gynaecol. 2008; Oct;115[11]:1382-91.

[18] Sinaii N, Plumb K, Cotton L, Lambert A, Kennedy S, Zondervan K, et al. Differences in characteristics among 1,000 women with endometriosis based on extent of disease. Fertil Steril. 2008; Mar;89[3]:538-45.

[19] Missmer SA, Hankinson SE, Spiegelman D, Barbieri RL, Marshall LM, Hunter DJ. Incidence of laparoscopically confirmed endometriosis by demographic, anthropometric, and lifestyle factors. Am J Epidemiol. 2004; Oct 15;160[8]:784-96.

[20] Parazzini F, Cipriani S, Bianchi S, Gotsch F, Zanconato G, Fedele L. Risk factors for deep endometriosis: a comparison with pelvic and ovarian endometriosis. Fertil Steril. 2008 Jul;90[1]:174-9.

[21] Giudice LC. Clinical practice. Endometriosis. N Engl J Med. 2010 Jun 24;362[25]:2389-98.

[22] Lin Q, Ding SJ, Zhu TH, Li TT, Huang XF, Zhang XM. [Role and clinical significance of coagulation and inflammatory factors in moderate and severe ovarian endometriosis]. Zhonghua Fu Chan Ke Za Zhi. 2018; Mar 25;53[3]:167-171.
[23] Seckin B, Ates MC, Kirbas A, Yesilyurt H. Usefulness of hematological parameters for differential diagnosis of endometriomas in adolescents/young adults and older women. Int J Adolesc Med Health. 2018; Sep 26:/j/ijamh.ahead-of-print/ijamh-2018-0078/ijamh-2018-0078.xml.
[24] Coskun B, Ince O, Erkilinc S, Elmas B, Saridogan E, Coskun B, et al. The feasibility of the platelet count and mean platelet volume as markers of endometriosis and adenomyosis: A case control study. J Gynecol Obstet Hum Reprod. 2019; Sep 6:101626.
[25] Cheng YM, Wang ST, Chou CY. Serum CA-125 in preoperative patients at high risk for endometriosis. Obstet Gynecol. 2002;Mar;99[3]:375-80.
[26] Mol BWJ, Bayram N, Lijmer JG, Wiegerinck MAHM, Bongers MY, Van Der Veen F, et al. The performance of CA-125 measurement in the detection of endometriosis: A meta-analysis. Fertil Steril. 1998; Dec;70[6]:1101-8.
[27] Muyldermans M, Cornillie FJ, Koninckx PR. Ca125 and endometriosis. Hum Reprod Update. 1995; Mar;1[2]:173-87.
[28] Hirsch M, Duffy JMN, Davis CJ, Nieves Plana M, Khan KS. Diagnostic accuracy of cancer antigen 125 for endometriosis: a systematic review and meta-analysis. BJOG: An International Journal of Obstetrics and Gynaecology. 2016; Oct;123[11]:1761-8.
[29] O DF, Flores I, Waelkens E, D'Hooghe T. Noninvasive diagnosis of endometriosis: Review of current peripheral blood and endometrial biomarkers. Best Practice and Research: Clinical Obstetrics and Gynaecology. 2018; Jul; 50:72-83.
[30] Yilmaz EPT, Topdagi YE, Al RA, Kumtepe Y. The relationship between C-reactive protein, carbohydrate antigen 125, and hematological parameters to endometriotic nodule localization in pelvis. J Chinese Med Assoc. 2020; Jun;83[6]:577-581.
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