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 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 neutrophil/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

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 laparotomy 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 still unexplained. Recent studies commonly stated theories 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 distribution width (PDW), mean platele volume (MPV) and plateletcrit (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, gravidity, parity, antecedent surgeries, surgery method, location of the lesions, endometriosis score, preoperative complete blood count 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.
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 Spearman 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 stage and the serum parameters, 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]. Lasty 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; symptoms 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 hematological 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 linear 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].
and PCT rates were significantly higher in advanced stages 
significantly lower \( p=0.003, p=0.002 \) respectively but PLT 
and PLR rates together increased sensitivity to 90.4\% \( 12\). 
other study observed 71.6\% sensitivity of CA 125 alone to 
endometriosis diagnose and staging.

To examine the role of hematological markers further in 
process of endometriosis, Ding et al. reported 
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.

CA and CA125 (U/mL) 
were significantly lower \( p=0.003, p=0.002 \) respectively but PLT 
and PCT rates were significantly higher in advanced 
endometriosis \( p=0.001, p=0.001 \) \(16\).
In contrast to previous studies, we presented no relation between inflammatory markers and endometriosis stage. This result correlates 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<0.01). 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 even though 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]. Dorién 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]. Inadition we observed CA 125 was increased with the larger samples. Our findings are consistent with the previous research. Even though 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 address this topic.

Disclosure

Authors have no potential conflicts of interest to disclose.

References


