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*Research Article*

# The Clinical Value Of Inflammatory Factors, Coagulation Indexes And Ca125 In The Diagnosis Of Ovarian Endometriosis.

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## Abstract

**Purpose:** Nowadays the diagnosis of ovarian endometriosis is mainly through laparoscopy. The purpose of this study is to explore the clinical value of multiple noninvasive tests such as carbohydrate antigen 125 (CA125), inflammatory factors and coagulation indexes in the diagnosis of ovarian endometriosis.

**Methods:** We retrospectively analyzed the general clinical data, inflammatory factors, coagulation indexes and CA125 of patients in our hospital. SPSS26.0 and R4.2.2 were used for statistical analysis.

**Results:** CA125 and prothrombin time (TT) were statistically different between ovarian endometriosis and control groups ($p<0.05$). Correlation analysis showed that CA125, fibrinogen (FIB) and lymphocyte count were positively correlated with the stage ($p<0.05$). The diagnostic value of CA125, TT and combined-markers was compared using receiver operating characteristic (ROC) curves. The area under the curve (AUC) of CA125, TT and the combined-marker were 0.819, 0.601 and 0.714 respectively, with the sensitivity 82.9%, 36.8% and 59.0% respectively, the specificity 75.9%, 80.2% and 79.2% respectively.

**Conclusion:** TT is associated with the occurrence and has no relation with stage. FIB was related to the stage. The model established by CA125 and TT has good predictive value in the diagnosis of ovarian endometriosis.

**Keywords:** Ovarian endometriosis, Carbohydrate antigen 125, Fibrinogen, Thrombin time.

## INTRODUCTION

Endometriosis is a common gynecologic condition in which endometrial glands and stroma appear outside the body of the uterus[1]. It can occur anywhere in the body, although most of which occur in the pelvis. It is divided into three phenotypes, including superficial peritoneal lesions, ovarian endometriosis, and deep infiltrative endometriosis[2]. Endometriotic lesions appearing in the gastrointestinal tract, urinary tract, upper and lower respiratory system, diaphragm, pleura and pericardium, and abdominal cesarean scar have been reported in the literature[3, 4, 5, 6, 7].

Although endometriosis is a benign gynecological condition, it can seriously affect a woman's quality of life. It's clinical manifestations mainly include lower abdominal pain or dysmenorrhea, infertility, deep intercourse pain, and menstrual abnormalities. About 50% of infertility patients which have regular menstrual cycles and whose husbands have normal semen suffer from endometriosis[8]. Epidemiological studies demonstrated that women with endometriosis are at higher risk for malignancies such as ovarian cancer, breast cancer, melanoma, thyroid cancer, and endometrial cancer[9, 10, 11, 12, 13]. Therefore, it is particularly important to identify the cause of endometriosis and diagnostic criteria to improve patient's prognosis.

Nowadays, researches on non-invasive biomarkers for the diagnosis of endome triosis has been slow to meet clinical needs. Although clinical symptoms combined with ultrasonography or MRI are currently used to predict endometriosis, but they cannot diagnose microscopic or deep lesions. So some endometriosis only can be diagnosed during operation, even though, deeply located endometriotic lesions also may be missed during laparoscopy[14, 15].

Studies have shown that endometriosis may lead to change in the levels of inflammatory, coagulation markers and tumor markers[2, 16, 17]. In order to construct a more efficient model to predict the occurrence of endometriosis, we retrospectively analyzed coagulation indexes, inflammatory

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factors, and CA125 in patients with ovarian endometriosis in hope of exploring the relationship between these indexes and ovarian endometriosis.

## MATERIALS AND METHODS

### General information

117 patients with ovarian endometriosis were admitted in our hospital from January 2017 to August 2022, who were defined as the endometriosis group. The diagnosis was confirmed by postoperative pathological examination. Meanwhile, 96 patients with benign ovarian cysts which includes 17 cases of mature teratoma, 2 cases of serous cystadenoma, 3 cases of mucinous cystadenoma, 11 cases of simple cyst, 10 cases of follicular cyst, 3 cases of ovarian fibroma and 50 cases of mixed cyst were selected as the control group.

Exclusion criteria: (1) anemic patients (HGB<110G/L); (2) combined with hypertension and diabetes mellitus; (3) combination with clinically or pathologically diagnosed systemic or local infections; (4) taking drugs related to inflammatory factors and coagulation; (5) combination with uterine smooth muscle tumors or adenomyosis; (6) patients who have a combination of psychiatric disorders; (7) combination with malignant tumors, rheumatic immune diseases, heart, liver, kidney, and hematologic related diseases; (8) hepatitis B surface antigen carriers.

Based on the staging method of endometriosis proposed by the American Society for Reproductive Medicine (ASRM.1997). The staging of endometriosis patients was further determined with reference to the size, number, location, and adhesion range of the endometriosis foci in the surgical records. According to the criteria, 20 cases were stage I, 23 cases were stage II, 46 cases were stage III, and 28 cases were stage IV.

### Sample testing

Clinical data of the patients were recorded, including age, number of pregnancy and delivery, number of cesarean delivery. 3-5 ml of peripheral venous blood was drawn from ovarian endometriosis patients before surgery to test blood routine, coagulation index and CA125 level. Blood results were obtained by BECKMAN COULTER AC.TTM5 Automatic Hematology Analyzer. The results of coagulation indexes were obtained by TSA 8000 automatic coagulation detector and CS-1300 automatic coagulation analyzer. CA125 was measured by microparticle enzyme immunoassay (MEIA) to determine CA125 antigen in serum, and the testing equipment and kits were provided by Abbott. The above specimens were processed by the Clinical Laboratory Center of the First Affiliated Hospital of Jinan University. The criteria of the testing instruments were in accordance with the requirements, and the errors were within the permissible range. Blood routine results included platelet count (PLT), white blood cell count (WBC), neutrophil count, lymphocyte count, neutrophil percentage, and lymphocyte percentage, prothrombin time (PT), fibrinogen (FIB), thromboplastin time (TT), partial thromboplastin time (APTT) were measured with an automated coagulation tester. The concentration of CA125 was expressed as U/ml. PLR was defined as platelet count divided by lymphocyte count; NLR was defined as neutrophil count divided by lymphocyte count.

### Statistical analysis

The patient's clinical data were statistically analyzed using SPSS (Statistical Package for the Social Sciences) 26.0 and R 4.4.2 software. The Shapiro-Wilk test was used to test whether the distributions were normal or not, and for the sake of uniformity of format, the median (M25, M75) was used throughout the text. Group comparisons of normally distributed indicators were performed using the t-test, and non-normally distributed indicators were tested using the Mann-Whitney U-test. Spearman's correlation coefficient was used for correlation analysis. Binary logistic regression analysis was applied to establish a diagnostic model and AUC was calculated to analyze the diagnostic efficiency of different diagnostic indicators. The 117 cases in the endometriosis group and 96 cases in the control group were randomly assigned to the training set (85 cases) and the validation set (32 cases) in the ratio of 85 %:15 %. The training set was used to construct a predictive model using the risk factors screened by binary logistic regression analysis, and then the validation set was used to verify the performance of the model. Using the rms package to draw nomogram. Individual prediction curves for CA125, TT and combined markers were constructed using the data from the training set, and the predictive efficacy of the three models was compared using ROC curves and AUC. $p<0.05$ was considered statistically significant. The reporting of this study conforms to STROBE guidelines[18].

## RESULTS

### Comparison of general information and various biological indicators between the two group

There were no statistically significant differences in terms of age, number of pregnancy, number of cesarean section, WBC (×109/L), Neutrophil% (%), Lymphocyte (%), Neutrophil count (×109/L), Lymphocyte count (×109/L), NLR and PLR ($p > 0.05$) between the ovarian endometriosis group and the control group. CA125 and TT values were statistically different in the ovarian endometriosis group and control group ($p < 0.05$) (**Table. 1**).

**Table 1.** Comparison of general information and biological indicators between the endometriosis group and the control groups.

| Variables | Endometriosis group (n=117) | Control group (n=96) | p |
|---|---|---|---|
| Age (years) | 26.00(30.00 ~ 37.00) | 30.50(24.25 ~ 39.00) | 0.947 |
| Gravidity (n) | 1.00(0 ~ 2.00) | 1.00(0 ~ 3.00) | 0.080 |
| Parity (n) | 0(0 ~ 1.00) | 1.00(0 ~ 2.00) | 0.050 |
| Cesarean section(n) | 0(0 ~ 0) | 0(0 ~ 0) | 0.238 |
| ATPP(s) | 38.50(36.10 ~ 41.50) | 38.30(35.90 ~ 41.40) | 0.651 |
| PT(s) | 13.30(12.95 ~ 13.80) | 13.45(12.90 ~ 13.90) | 0.539 |
| TT(s) | 16.60(16.10 ~ 17.35) | 16.30(15.70 ~ 16.80) | 0.012 |
| FIB(g/L) | 3.08(2.74 ~ 3.41) | 2.98(2.62 ~ 3.31) | 0.246 |
| PLT(×109/L) | 264.00(229.40 ~ 299.90) | 247.50(219.25 ~ 277.08) | 0.056 |
| WBC(×109/L) | 6.52(5.48 ~ 8.18) | 6.70(5.66 ~ 7.90) | 0.542 |
| Neutrophil(%) | 62.57(55.94 ~ 68.63) | 62.49(55.95 ~ 70.13) | 0.783 |
| Lymphocyte(%) | 28.20(23.41 ~ 33.49) | 29.07(21.57 ~ 34.25) | 0.897 |
| Neutrophil count(×109/L) | 4.12(3.10 ~ 5.34) | 4.35(3.30 ~ 5.35) | 0.526 |
| Lymphocyte count(×109/L) | 1.83(1.50 ~ 2.19) | 1.77(1.45 ~ 2.23) | 0.574 |
| PLR | 140.00(115.41 ~ 172.64) | 131.69(109.19 ~ 165.41) | 0.387 |
| NLR | 2.22(1.66 ~ 2.86) | 2.17(1.65 ~ 3.25) | 0.638 |
| CA125(U/ml) | 44.72(26.05 ~ 79.50) | 16.99(11.00 ~ 23.45) | <0.001 |

**Comparison of biological indicators of patients with ovarian endometriosis at different stages**

We analyzed the correlation of general clinical data with routine blood results, coagulation results, NLR, PLR and CA125 values in the ovarian endometriosis and control groups. The results showed that CA125 (Rho=0.269, p=0.003), FIB (Rho =0.273, p=0.003) and lymphocyte counts (Rho=0.195, p=0.035) were positively correlated with the stage (**Table.2**).

**Table 2.** Comparison of biological indicators of patients with endometriosis at different clinical stages

| Variable | Stage I (n = 20) | Stage II (n = 23) | Stage III (n = 46) | Stage IV (n = 28) | r | p |
|---|---|---|---|---|---|---|
| Age (years) | 30.00(27.0 ~ 37.00) | 31.00(26.0 ~ 35.00) | 28.50(25.0 ~ 37.00) | 30.00(26.00 ~ 36.50) | -0.015 | 0.870 |
| Gravidity (n) | 1(0 ~ 1) | 0(0 ~ 1) | 1(0 ~ 2) | 1(0 ~ 3) | 0.096 | 0.303 |
| Parity (n) | 0(0 ~ 1) | 0(0 ~ 1) | 0(0 ~ 1) | 1(0 ~ 1) | 0.109 | 0.244 |
| Cesarean section(n) | 0(0 ~ 1) | 0(0 ~ 0) | 0(0 ~ 0) | 0(0 ~ 0.75) | 0.124 | 0.182 |
| ATPP(s) | 39.60(37.7 ~ 42.18) | 37.70(36.0 ~ 40.60) | 37.80(36.1 ~ 41.55) | 38.60(35.73 ~ 41.20) | -0.102 | 0.275 |
| PT(s) | 13.30(12.95 ~ 13.78) | 13.60(13.20 ~ 14.20) | 13.40(12.7 ~ 13.80) | 13.10(12.83 ~ 13.40) | -0.155 | 0.095 |
| TT(s) | 16.75(16.1 ~ 17.60) | 16.70(16.0 ~ 17.40) | 16.45(15.8 ~ 17.40) | 16.65(16.10 ~ 17.28) | -0.027 | 0.769 |
| FIB(g/L) | 2.78(2.37 ~ 3.05) | 3.08(2.81 ~ 33.24) | 3.15(2.85 ~ 3.52) | 3.22(2.68 ~ 3.56) | 0.273 | 0.003 |
| PLT(×109/L) | 259.90(22 ~ 298.90) | 242.20(21 ~ 293.00) | 271.00(2 ~ 296.13) | 268.50(244.8 ~ 320.93) | 0.133 | 0.153 |
| WBC(×109/L) | 6.17(5.30 ~ 7.48) | 6.44(5.52 ~ 7.69) | 6.35(5.30 ~ 7.94) | 7.30(5.74 ~ 9.20) | 0.148 | 0.112 |
| Neutrophil%(%) | 62.80(55.5 ~ 70.68) | 64.30(55.8 ~ 68.60) | 62.67(55.9 ~ 67.53) | 61.12(56.30 ~ 68.83) | -0.028 | 0.766 |
| Lymphocyte(%) | 30.10(22.2 ~ 34.06) | 26.71(23.1 ~ 32.71) | 28.40(24.5 ~ 32.95) | 28.22(23.62 ~ 34.79) | 0.020 | 0.830 |
| Neutrophil count(×109/L) | 3.80(3.09 ~ 5.36) | 3.93(3.18 ~ 5.26) | 4.20(3.01 ~ 5.29) | 4.39(3.17 ~ 6.52) | 0.096 | 0.302 |
| Lymphocyte count(×109/L) | 1.78(1.45 ~ 2.20) | 1.74(1.46 ~ 2.05) | 1.81(1.51 ~ 2.16) | 2.08(1.61 ~ 2.72) | 0.195 | 0.035 |
| PLR | 143.03(11 ~ 212.89) | 137.13(12 ~ 163.71) | 141.84(1 ~ 176.57) | 134.71(105.6 ~ 157.39) | -0.114 | 0.221 |
| NLR | 2.05(1.64 ~ 3.16) | 2.43(1.77 ~ 2.87) | 2.21(1.66 ~ 2.72) | 2.12(1.62 ~ 2.83) | -0.048 | 0.609 |
| CA125(U/ml) | 34.65(18.2 ~ 48.80) | 48.60(26.9 ~ 95.50) | 45.31(26.0 ~ 75.80) | 76.12(32.53 ~ 152.58) | 0.269 | 0.003 |

*PT, prothrombin time; ATPP, activated partial thromboplastin time; TT, thrombin time; FIB, fibrinogen; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; CA125, carbohydrate antigen 125. P <0.05 was considered statistically significant.*

**Diagnostic efficacy TT and CA125 for ovarian endometriosis**

Binary logistic correlation analysis showed that CA125 and TT were relevant to the development of ovarian endometriosis (p=0.038 and p=0.017, respectively) (**Table. 3**). ROC curve was used to compare the diagnostic value of CA125, TT, and combined markers for ovarian endometriosis (**Fig.1**). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), cutoff value, and Youden index for CA125, TT, and the combined markers are shown in **Table 4**. CA125 exhibited the highest AUC value of 0.819 (95% confidence interval: 0.759–0.878), with a maximum sensitivity of 82.9% and specificity of 75.9%. TT demonstrated an AUC of 0.601 (95% confidence interval: 0.525–0.676), with a sensitivity of 36.8% and specificity of 80.2%. The AUC value for the combined markers was 0.714 (95% confidence interval: 0.644–0.783), with a sensitivity of 59.0% and specificity of 79.2%.

**Table 3.** Binary Logistic Regression to Construct a Predictive Model for Endometriosis.

| Parameters | OR | 95%CI | p |
|---|---|---|---|
| CA125 | 1.005 | 1.000,1.010 | 0.038 |
| TT | 1.349 | 1.005,1.724 | 0.017 |

*PT, prothrombin time; CA125, carbohydrate antigen 125.*

*P <0.05 was considered statistically significant.*

**Figure 1.** ROC curves of CA125, TT, and the combined marker for discriminating between the endometriosis and control group.

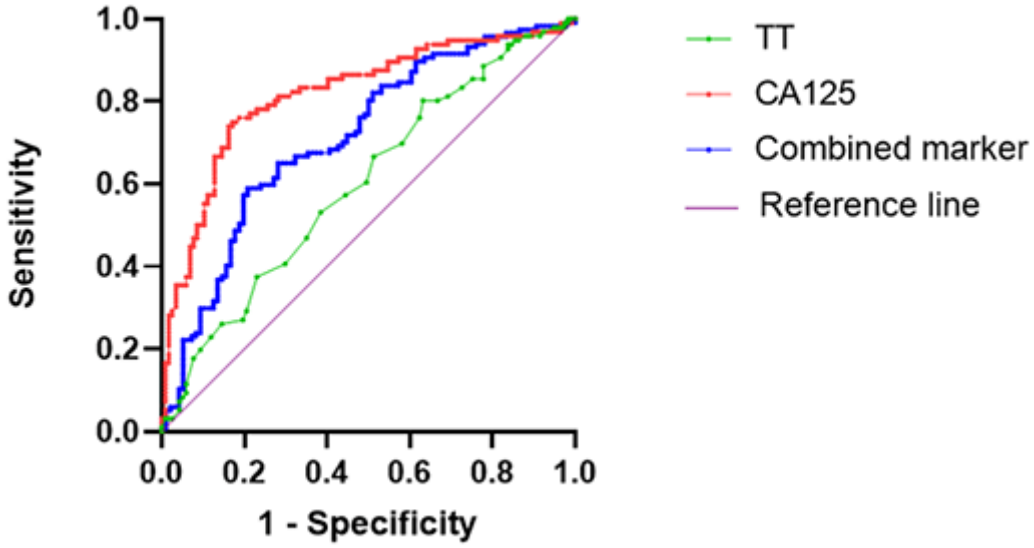



**Table 4.** Diagnostic value of CA125, and TT in endometriosis.

| Parameters | AUC | 95% CI | Sensitivity (%) | Specificity (%) | Yoden Index | p |
|---|---|---|---|---|---|---|
| CA125 | 0.819 | 0.759~0.878 | 0.829 | 0.750 | 0.579 | 0.000 |
| TT | 0.601 | 0.525~0.676 | 0.368 | 0.802 | 0.170 | 0.012 |
| Combined markers | 0.714 | 0.644~0.783 | 0.590 | 0.792 | 0.381 | 0.000 |

*PT, prothrombin time; CA125, carbohydrate antigen 125; Combined markers, CA125+TT*

*P <0.05 was considered statistically significant.*

**Ovarian endometriosis prediction model column line plot and model evaluation results**

The data collected in this study were divided into a training set and a validation set. The predictive models of CA125, TT and combined markers for the diagnosis of ovarian endometriosis were constructed using the data in the training set. AUCs of the ROC curves were for CA125, TT and combined markers were 0.8156, 0.6118 and 0.7038, respectively. The AUC of ROC curves plotted using the data in the validation set showed that the diagnostic models for the evaluation of ovarian endometriosis by CA125, TT and combined markers were 0.9004, 0.5519, and 0.6623 respectively. (**Table 5, Figure.2**).

The AUC of the CA125 prediction model is the highest in both the training set and the validation set, and the nomograms are plotted. Baseline CA125 values for all patients were used to predict ovarian endometriosis. In the nomogram, CA125 is located on the variable axis, and a vertical line is drawn upward to determine the score on the integral axis (**Figure.3**).

**Table 5.** Training set and experimental set ROC curves to evaluate the predictive value of CA125, TT and combined markers.

| Parameters | Train | Test |
|---|---|---|
| CA125 | 0.8156 | 0.9004 |
| TT | 0.6118 | 0.5519 |
| Combined markers | 0.7038 | 0.6623 |

*PT, prothrombin time; CA125, carbohydrate antigen 125; Combined markers, CA125+TT*

*P <0.05 was considered statistically significant.*

**Figure 2.** The ROC curve of CA125, TT and the combined marker in training and testing set. a. ROC curves for CA125 in training set. b. ROC curves for CA125 in testing set. c. ROC curves for TT in training set. d. ROC curves for TT in testing set. e. ROC curves for combined marker in training set. f. ROC curves for combined marker in testing set.

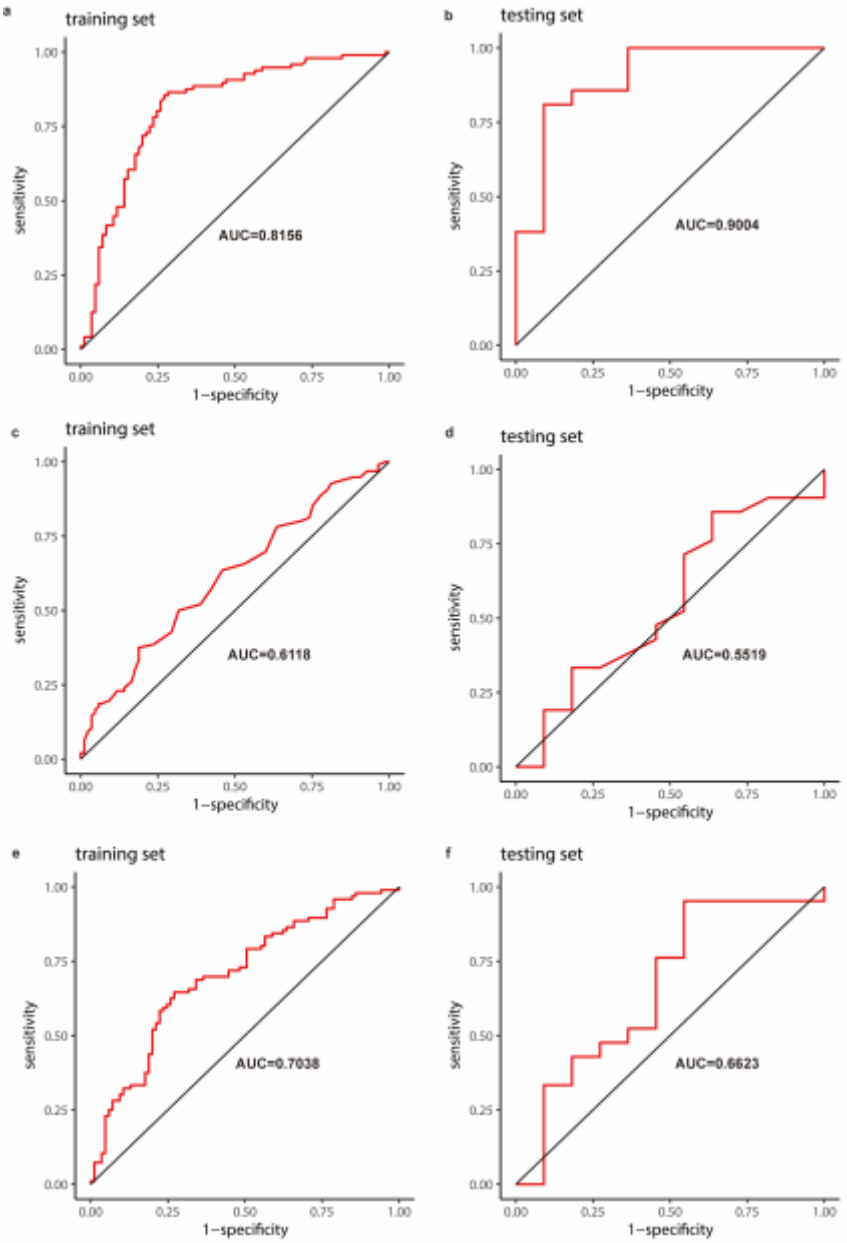
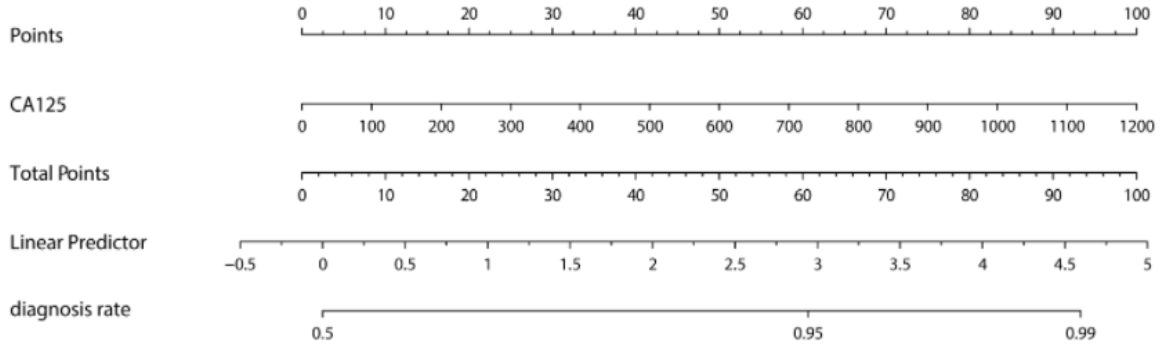


**Figure 3.** Nomogram based on CA125 for predicting the occurrence of ovarian endometriosis. The nomogram is used by summing the points determined by each predictor on the integral scale.




## DISCUSSION

CA125 is derived from somatic epithelial cells and is most commonly used in the diagnosis of ovarian cancer. Patton et al. demonstrated that CA125 was significantly elevated in patients with endometriosis and has been used as a noninvasive serologic marker for the diagnosis of endometriosis. Another research demonstrated a significant correlation between CA125 and disease severity[19]. In stage III/IV, CA125 can be elevated to 1000 IU/mL or higher[20]. However, the sensitivity and specificity of CA125 for the diagnosis of endometriosis is very low, suggesting a high false-negative rate for CA125 as a predictor of endometriosis. It was reported that the sensitivity and specificity of CA125 used for the diagnosis of abdominal wall endometriosis were high when it was over 19.9 U/L[21] in prediction of advanced endometriosis, ruptured endometriotic cysts, or adenomyosis and the value of CA125 is of little value in the diagnosis of early ovarian endometriosis. So it is imperative to combination CA125 with other index to precisely predict the existence of early ovarian endometriosis. Multicenter studies have been done to investigate whether CA125 can be combined with serological markers to predict ovarian endometriosis. Some studies reported that the area under the ROC curve of CA125 combined with Fib or PLR was higher than that predicted by CA125 alone, demonstrating that the combined prediction is more accurate[22, 23]. A growing body of research confirms that endometriosis is a systemic, heterogeneous disease associated with estrogen-dependent chronic inflammation, as ectopic endometrium in the pelvic abdomen is associated with overexpression of prostaglandins, cytokines, and chemokines[24]. PLR and NLR, as ratio parameters of inflammation, have been reported to be elevated in the peripheral blood of patients with endometriosis in several published studies[25]. Neutrophils as primary inflammatory response cells in peripheral blood have higher chemotactic activity in patients with endometriosis, and lymphocytes as inflammatory mediators have also been reported to be involved in the inflammatory response to endometriosis[26]. Inversely, some researches demonstrated the above mentioned inflammation factors have no role on the endometriosis. Although we did not find statistically significant difference in leukocyte count, neutrophil count, lymphocyte count, NLR, and PLR between the endometriosis and control group, lymphocyte count was found to be positively correlated with the stage of ovarian endometriosis in the correlation analysis. The reason may be that the sample size included in this study for analysis was too little and inflammatory indicators such as hypersensitive C-reactive protein (CRP), procalcitonin (PCT) and interleukin 6 (IL-6) were not included. CRP is an acute-phase reactant protein produced by the liver. The chronic inflammatory state present in endometriosis continuously stimulates the immune system, with pro-inflammatory cytokines such as IL-6, IL-1, and TNF-α promoting its production[27]. However, CRP has low specificity and can be influenced by any infection, trauma, other autoimmune diseases, obesity, or even smoking. Research indicates that IL-6 is significantly elevated in the serum, peritoneal fluid, and ectopic lesions of endometriosis patients, serving as a more direct indicator of local lesion activity[28]. PCT is a highly specific marker for systemic bacterial infections and can be used for differential diagnosis. In future research, IL-6, given its central role in disease mechanisms, should be prioritized as the primary biomarker for investigation; CRP can be utilized in epidemiological studies; and PCT can be employed to rule out bacterial infections. Furthermore, future efforts should focus on developing multi-marker combination models rather than relying on a single indicator.

APTT is significantly shorter in patients with ovarian endometriosis and correlates with the stage of the disease, with slightly shorter APTT values in patients with stage I-II endometriosis, but significantly higher than in patients with stage III-IV[22, 29]. Shaojie Ding reported that TT and PT values were significantly shorter and FIB was significantly longer in the ovarian endometriosis. In addition, FIB levels were found to be positively correlated with CRP, NLR, and PLR, which indicated that patients with endometriosis were in a hypercoagulable state[30]. In our study, we found TT in the ovarian endometriosis group was significantly increased, meanwhile, FIB was positively correlated with stage and progression of endometriosis. The retrograde menstrual flow theory is the primary pathogenesis model for endometriosis. Retrograde menstrual blood contains endometrial fragments, and fibrin (FIB) enhances cellular adhesion, facilitating the attachment of these fragments to the peritoneum. Elevated FIB levels further activate immune cells, promoting the release of inflammatory mediators. This process stimulates endometrial cell proliferation and inhibits apoptosis, thereby accelerating disease progression[31]. However, previous studies have observed shortened TT in endometriosis patients, indicating a hypercoagulable state. This may indirectly reflect an imbalance in the body's coagulation and fibrinolytic systems, potentially correlating with disease severity and activity. Inflammation at lesion sites may persistently activate the coagulation system, leading to alterations in TT values. We inferred CA125 combined with TT or FIB could provide good sensitivity and specificity for ovarian endometriosis, which was verified by our further analysis.

As a retrospective study, our study had many limitations, firstly the samples were from the same hospital. Secondly, we did not limit the duration of the disease and did not consider the possibility of deep invasive endometriosis or endometrioma or peritoneal endometriosis. What's more we did not follow up the patients to dynamically detect changes in their laboratory parameters. In addition, we should include D-dimer, CRP and PCT for further analysis. Even with those shortcomings, we still can conclude that the value of CA125 combined with inflammatory factors and coagulation indexes can provide early information for the diagnosis of ovarian endometriosis.

## Disclosure Statement

### Acknowledgements

No application

### Ethics Statement

We got ethics approval from our hospital, the Issue Number: KY-2025-371. We got written consent to participate the research.

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### Availability of data and materials

The authors declare that all of the data and material are freely accessible on reasonable request.

### Competing interests

The authors declared that they have no competing interests.

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