International Journal of Women's Health

Dovepress

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ORIGINAL RESEARCH

Tumor Markers in Differential Diagnosis of Benign Ovarian Masses

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Background: Although there are many benign tumors in the ovarian adnexal area, the four most common types are still luteal cyst, ovarian mature cystic teratoma (OMCT), ovarian endometriosis, and benign epithelial tumors of the ovary.

Purpose: This study aimed to examine the correlation between six tumor markers (CEA, AFP, CA125, CA19-9, SCC, HE4) in the differential diagnosis of female adnexal benign masses and assess their diagnostic value.

Patients and Methods: In this study, 135 patients with adnexal benign masses were treated in Zhengzhou first people's Hospital from January 2018 to January 2023. 135 patients were divided into four groups: luteal cyst (13.3%), OMCT (42.2%), ovarian endometriosis (23.7%) and benign epithelial tumors of the ovary (including mucinous cystadenoma and serous cystadenoma) in group D. The receiver-operating characteristic (ROC) curve was used to assess the diagnostic value of each marker and combined detection.

Results: The diameter of luteal cysts was significantly smaller than that of benign ovarian tumors ($p < 0.001$). ROC analysis showed that the combination of AFP, CA125, CA19-9, and SCC had a higher diagnostic rate for luteal cysts (AUC=0.871; sensitivity: 71.8%; specificity: 88.9). The SCC level in OMCT was significantly higher than in other benign ovarian tumors (p=0.007). ROC analysis indicated that the combination of AFP, HE4, and SCC had a higher diagnostic rate for OMCT (AUC=0.753; sensitivity: 65.4%; specificity: 75.4%). The CA125 level in ovarian endometriosis was significantly higher than in other accessory benign tumors ($p < 0.001$). ROC analysis demonstrated that the combination of AFP, CA125, and CA19-9 had a higher diagnostic rate for ovarian endometriosis (AUC=0.935; sensitivity: 76.7%; specificity: 96.9%). The tumor diameter of benign epithelial tumors of the ovary was significantly larger than that of other benign ovarian tumors ($p < 0.001$). ROC analysis revealed that the combination of CA125 and CA19-9 had a higher diagnostic rate for benign epithelial tumors of the ovary (AUC=0.792; sensitivity: 64.5%; specificity: 85.7%).

Conclusion: The findings of this study demonstrate that the combined use of tumor markers (CEA, AFP, CA125, CA19-9, SCC, and HE4) has value in diagnosing benign ovarian tumors, including luteal cysts, OMCT, ovarian endometriosis, and benign epithelial tumors of the ovary. However, it is important to acknowledge the limitations of this study, which include its single-center nature and the small sample size. Despite these limitations, the results highlight the potential utility of these markers in clinical practice.

Keywords: luteal cyst, OMCT, ovarian endometriosis, ovarian epithelial benign tumors, tumor markers

Introduction

Women's adnexal mass is one of the common gynecological diseases, can be seen in women of all ages, and occurs in women of childbearing age. Ovarian masses may be neoplastic or physiologic, and most neoplastic adnexal masses are benign.[1] Ovarian tumor encompasses multiple types of tumors, including epithelial ovarian tumor, germ cell ovarian tumors, stromal tumors and ovarian carcinosarcomas.[2,3] In recent years, the incidence of female reproductive system tumors has been increasing year by year, especially ovarian benign tumors.[4] Moreover, the number of asymptomatic ovarian masses has increased with the use of prenatal ultrasonography. Among ovarian tumours that complicate pregnancies, approximately 5% are malignant. Currently surgical intervention is indicated for an ovarian mass over 6 cm in diameter or when symptomatic.[5]

Received: 27 March 2024
Accepted: 2 September 2024
Published: 16 September 2024

Despite the numerous classifications of benign ovarian tumors, the most common types encountered in clinical practice are luteal cyst, OMCT, ovarian endometriosis, and benign epithelial tumors of the ovary, which will also be the focus of this discussion. A simple corpus luteum cyst is actually a physiological cyst; normal women experience cyclical changes in the ovaries, and physiological ovarian cysts will gradually decrease in size and naturally resolve. However, when a corpus luteum cyst does not resolve naturally and ruptures due to other causes, resulting in bleeding, emergency surgery may be required for treatment.[6,7] Study has shown that enlargement and cyst formation in the ovaries of women may be caused by chronic stimulation from luteinizing hormone (LH), as a correlation between high levels of LH and cyst development has been reported.[8,9] Mature cystic teratomas are common benign tumors of the ovary. OMCT is also called dermoid cyst, is a teratoma of a cystic nature that contains kinds of developmentally mature, solid tissues originating from all three germ-cell layers.[10] OMCT is a common neoplasm accounting for 10–20% of all ovarian tumors, and most of OMCT occur in women of reproductive age.[11] Endometriosis is a common disease due to the implantation of active endometrial cells outside the endometrium.[12] Endocrine dysfunction, immune defense deficiency and genetic and physical factors are the main causes of endometriosis.[13] Ovarian endometriosis cyst is the most common form of endometriosis, up to 25–35% of patients with endometriosis.[14] The epithelial tumors of the ovary are derived from surface epithelium of the ovary.[15] Among them, benign epithelial tumors account for 57–60% of all epithelial tumors.[16] Despite the unclear etiology of ovarian epithelial tumors, study has shown that the up-regulation of VEGF has been shown to be a pivotal component of the pathogenesis of epithelial ovarian tumors, in part through increased tumor angiogenesis and/or vasculogenesis.[17]

Although benign ovarian tumor is far less harmful to the physical and mental health of women than malignant ovarian tumor, its wide audience is still one of the diseases that afflict many patients, and the treatment plan of different benign tumors is not the same, and the clear diagnosis will help the treatment and prognosis of patients. Therefore, we need a more specific indicator for the differential diagnosis of various types of ovarian benign tumors.

Tumor markers (TM) are substances that change abnormally due to the expression of related genes in tumor cells or the body's response to tumors during the development and proliferation of malignant tumors.[18] Tumor markers have been discovered for more than 100 years. Since the 1960s, they have been widely used in clinical practice and played an important role in the discovery and treatment of tumors. With the development of biotechnology, a variety of new markers have been gradually discovered with increasing specificity and sensitivity. The representative markers include oncogenes, tumor suppressor genes and their products, tumor DNA, cytokines and their receptors, tumor miRNAs and tumor stem cells, etc. At present, the biomarkers CA125 and HE4 are the only ones authorized for utilization in diagnosing epithelial ovarian cancer. Nevertheless, these markers are inadequate for the purpose of early detection. To address this limitation, Multivariate Index (MVI) tests have been formulated, particularly aimed at enhancing the diagnostic accuracy during the pre-operative assessment of adnexal masses in epithelial ovarian cancer. The Risk of Ovarian Malignancy Algorithm (ROMA) merges information on menopausal status, along with the concentrations of CA125 and HE4, to evaluate women presenting with a pelvic mass. Additionally, microRNAs (miRNAs) showcase considerable potential in various facets of predicting epithelial ovarian cancer. However, there is a need to standardize the procedures involved in sample preparation and to enhance the methodologies used for detecting miRNA in tumors and blood samples. It is worth noting that the application of tumor markers in the past is often in the identification of benign tumors and malignant tumors, and many scholars even believe that tumor markers must be produced by malignant tumor cells.[19] However, recent studies have shown that elevated levels of serum tumor markers also have a suggestive effect on benign tumors.[20,21] For example, tumor marker levels for benign diseases such as endometriosis, pelvic inflammatory disease and early pregnancy all showed significant changes.

However, due to the wide variety of benign ovarian tumors and the varying treatment approaches required for different types of benign tumors, it is crucial to accurately diagnose these tumors before surgery. Ultrasonography is currently one of the most commonly used diagnostic methods.[22] Yet, in certain cases, such as when tumor size and blood flow signals are nonspecific, ultrasonography still faces significant challenges in distinguishing ovarian tumors. Under these circumstances, relying solely on ultrasonography for diagnosis becomes very difficult.[23] Naturally, serum tumor markers play a crucial role in this context. However, the limitations in sensitivity and specificity of individual tumor markers still prevent them from being decisive. For example, CEA is a broad-spectrum tumor marker that is elevated in

numerous tumors, while CA125 is a nonspecific tumor marker frequently used in the treatment and prognostic monitoring of patients with ovarian tumors.[24] Therefore, exploring the combined application of tumor markers may be a better approach for the differential diagnosis of ovarian tumors.In this study, we collected 135 cases of adjunctive benign masses, including endometriosis, luteal cyst of the ovary, serous cystadenoma of the ovary, mucinous cystadenoma of the ovary, and OMCT. Collecting and analyzing serum tumor markers aims to identify the differences and connections in tumor marker levels among benign ovarian tumors, providing insights and guidance for the differential diagnosis of benign ovarian tumors through the combined application of tumor markers. This is beneficial for the clinical treatment of benign ovarian tumors.

Methods

Ethics Statement

This was a retrospective study and all aspects of the study design were retrospective. All procedures involving human subjects meet the ethical standards of the Medical Ethics Committee of Zhengzhou First People's Hospital. Since this study is a retrospective research, it does not involve human materials/data that can identify individuals, and the risk to patients is no greater than minimal risk. Therefore, this study has been granted a waiver of informed consent by the Ethics Committee of the First People's Hospital of Zhengzhou City (2024–022).

Research Object

This study was conducted on all cases with obvious diagnosis of adnexal mass referring to Zhengzhou First People's Hospital. The total of patients was counted as 135 during 2018–2023 and the convenience sampling method was used. Patients with appendicular masses admitted to the gynecology department of Zhengzhou First People's Hospital during the past 5 years were included in the study who were pathologically diagnosed as luteal cyst, OMCT, ovarian endometriosis, serous cystadenoma, mucinous cystadenoma, and mixed cystadenoma. Patients who were pregnant, had or have had malignant tumors, had taken medications that may alter serum tumor marker levels, had not undergone serum tumor marker testing before surgery, did not wish to undergo ultrasound, did not have surgery, and were unable to obtain pathological results were excluded from the study.

Method

All patient information, including name, age, and hospital number, is extracted from the patient's hospital record and recorded in a pre-constructed examination form. Preoperative ultrasonography was performed and blood was drawn upon admission for tumor markers (CEA, AFP, CA125, CA19-9, SCC, and HE4).CEA and AFP were detected by a chemiluminescent microparticle immunoassay (*ADIVIA Centaur*, Siemens). SCC was detected by a chemiluminescent microparticle immunoassay (*I2000SR*, Abbott, USA). CA125, CA153 and HE4 were detected by an automatic electrochemical luminescence analyzer (*Cobas e601*, Roche, Germany). According to the normal range values of our hospital laboratory, the respective ranges for the tumor markers are as follows: CEA (0–2.5 ng/mL), AFP (0–8 ng/mL), CA125 (0–35 U/mL), CA19-9 (0–34 U/mL), SCC (0–1.5 ng/mL), and HE4 (premenopausal 0–70 pmol/L; postmenopausal 0–140 pmol/L).All these patients underwent surgical treatment in Zhengzhou First People's Hospital. The excised masses were sent for frozen pathological examination during the operation and routine pathological examination after the operation. The pathological examination was carried out by the Department of Pathology of Zhengzhou First People's Hospital and has its own unique pathological number.

Group

We divided all patients into four groups: Group A (corpus luteum cyst, a total of 18 cases), Group B (OMCT, a total of 57 cases), group C (ovarian endometriosis, a total of 32 cases), and group D (ovarian epithelial benign tumors, including serous cystadenoma, mucinous cystadenoma and mixed cystadenoma, a total of 28 cases).

Statistical Analyses

SPSS26.0 software was used for statistical analysis of data. The measurement data were described as Mean±SD; the measurement data conforming to normal distribution and approximate normal distribution were compared by one-way ANOVA and compared by LSD test. The measurement data that did not conform to the normal distribution were compared between groups using the rank sum test. Counting data were expressed as rate (%), and Chi-square test was used to compare between groups. $P<0.05$ was considered to be statistically significant. ROC curve analysis was performed with MedCalc20.022 software to explore the diagnostic value of tumor markers for different types of adnexal benign masses.

Results

Ovarian Benign Tumors are Correlated with Tumor Size, Unilateral Tumor and Partial Tumor Markers, but Not with Age

We collected the data of a total of 135 patients with appendicular mass, ranging in age from 21 to 71 years old (mean age 32.00 ± 8.92 years old). Pathological findings showed that all of them were benign masses, including 18 cases of simple luteal cyst, 57 cases of OMCT, and 32 cases of ovarian endometriosis (chocolate cyst). There were 28 cases of ovarian epithelial tumors (serous cystadenoma, mucinous cystadenoma and mixed cystadenoma), which were divided into four groups A, B, C and D. Serum tumor marker levels of carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), CA125, CA19-9, squamous cell carcinoma antigen (SCC), and human epididymis protein 4 (HE4) were collected in all patients. And collect the diameter of the tumor, either on one or both sides.

As shown in Table 1, a total of 135 patients were diagnosed. Group A had simple luteal cyst (n=18, 13.3%), group B had OMCT (n= 57, 42.2%), group C had ovarian endometriosis (n= 32, 23.7%), and group D had ovarian epithelial tumors, including mucinous cystadenoma and serous cystadenoma (n=28, 20.8), statistical differences were compared between the data among the groups. Except for the tumors that met the normal distribution on one or both sides, Chi-square test was used, and the rest did not meet the normal distribution. Data analysis was performed using rank sum test. We could see that there were no statistical differences in age, CEA and HE4 among all groups, while there were statistical differences in AFP, CA125, CA19-9, and SCC and tumor diameter among all groups.

The mean age of the four groups was 32.0, 35.1, 36.0, 39.3 years, respectively, and the mean tumor diameter was 3.80, 8.14, 7.09, 10.47 cm. The tumors in group A were significantly smaller than those in other groups, and those in group D were significantly larger than those in other groups. In addition, the incidence of tumors in group C was more bilateral. Our results showed that there was no significant difference in age among patients with benign ovarian tumors,

Table 1 The General Situation of 135 Patients and the Expression Differences Between Each Tumor Marker Were Analyzed

	Group A, n=18	Group B, n=57	Group C, n=32	Group D, n=28	H/X^2	P
Age	32.00±8.92	35.12±9.60	36.00±8.56	39.36±15.07	4.719*	0.136
CEA	0.52±0.39	0.73±0.64	0.80±0.89	0.88±0.77	1.279*	0.400
AFP	0.93±0.72	2.61±2.08	1.73±3.12	3.09±4.79	16.331*	0.062
CA125	15.01±4.28^{c}	23.40±16.74^{c}	89.83±91.50^{abd}	15.97±12.11^{c}	60.106*	<0.001
CA199	14.93±7.20^{bc}	51.81±77.50 ^{ad}	53.73±44.91^{ad}	14.10±12.40^{bc}	29.144*	0.003
SCC	0.72±0.51^{b}	1.19±0.52^{acd}	0.90±0.74^{b}	0.91±0.40^{b}	20.665*	0.007
HE4	51.64±9.10	47.17±9.93	50.98±10.89	50.95±10.90	5.696*	0.181
Diameter of Tumor	3.80±1.23^{bcd}	8.14±5.25^{ad}	7.09±4.09^{ad}	10.47±3.88^{abc}	35.606*	<0.001
Unilateral (%)	100 (18)	71.9 (41)	62.5 (20)^{ad}	92.9 (26)	14.276$^{\#}$	0.003
Bilateral (%)	0 (0)	28.1(16)	37.5 (12)^{ad}	7.1(2)		

Notes: a: different from group A; b: different from group B; c: different from group C; d: different from group D; *: rank sum test value (H); #: chi-square test value (X2).

Abbreviations: CEA, carcinoembryonic antigen; AFP, alpha-fetoprotein; CA125, carbohydrate antigen 125; CA19-9, carbohydrate antigen 19–9; SCC, squamous cell carcinoma antigen; HE4, human epididymis protein 4.

with smaller tumors for simple luteal cysts and larger tumors for epithelial tumors, and patients with bilateral ovarian cysts were at higher risk for ciliary sac.

Among the 6 tumor markers, only AFP, CA125, CA19-9 and SCC had differences. The AFP level of group A was 0.93 (SD 0.72) mg/l, which was significantly lower than that of group B 2.61 (SD 2.08) and group D 3.09 (SD 4.79). The CA125 level of group C was 89.83 (SD 91.5), which was significantly higher than that of the other three groups (15.01, SD 4.28; 23.40, SD 16.74; 15.97, SD 12.11); the level of CA19-9 in group B was 51.81 (SD 77.50) and 53.73 (SD 44.91), which were significantly higher than those in group A (14.93, SD 7.2) and group B (14.10, SD 12.40). The SCC level of group B was 1.19 (SD 0.52), which was significantly higher than that of the other three groups (0.72, SD 0.51; 0.90, SD 0.74; 0.91, SD 0.40). These results suggest that CA125 levels in the endometriosis and SCC levels in OMCT may have certain diagnostic value.

Establish a Diagnostic Model to Determine the Diagnostic Ability of Each Tumor Marker

In order to further evaluate the differential ability of each tumor marker for ovarian benign tumors, we constructed diagnostic models for each group to evaluate and compare their differential diagnostic ability.

ROC curve analysis showed that AFP, CA125, CA19-9 and SCC were significantly different in simple luteal cysts (p=0.01; p=0.011; p=0.026; p=0.003), and AUC were 0.690, 0.686, 0.663, and 0.714, respectively. Only SCC belonged to the medium diagnostic efficacy, while AFP, CA125, and CA19-9 all belonged to the low diagnostic efficacy. Therefore, we combined the four indexes for analysis, and the AUC was 0.871. The 95% CI was 0.803–0.923, the sensitivity was 71.8, and the specificity was 88.9, all of which were higher than that of single tumor markers. (Table 2, Figure 1, Figure 2).

In OMCT, there were significant differences in AFP, SCC and HE4 tumor markers (p=0.01; p < 0.001; p=0.029), AUC was 0.665, 0.710, 0.610 respectively, among which SCC belonged to medium diagnostic efficacy, AFP and HE4 both belonged to low diagnostic efficacy. Therefore, we conducted a joint analysis of these three indicators, and the AUC was 0.753, with a 95% CI of 0.671 to 0.823 and a sensitivity of 65.4. The specificity was 75.4, higher than that of the tumor markers alone. (Table 3, Figure 3, Figure 4).

The three tumor markers of AFP, CA125 and CA19-9 were significantly different in the endometriosis (p=0.021; p < 0.001; p < 0.001), AUC was 0.635, 0.936, 0.719, respectively, in which CA125 was high diagnostic efficacy, CA19-9 was medium diagnostic efficacy, and AFP was low diagnostic efficacy. Combined analysis of the three showed that AUC was 0.935, 95% CI was 0.879–0.970, and sensitivity was 76.7. The specificity was 96.9, but its indexes were not superior to those of CA125. (Table 4, Figure 5, Figure 6).

In epithelial benign tumors, there were significant differences between CA125 and CA19-9 tumor markers (p < 0.001; p < 0.001), and AUC were 0.728 and 0.746, respectively, indicating moderate diagnostic efficacy. Combined analysis showed that AUC was 0.792, 95% CI was 0.713–0.857, sensitivity was 64.5, and specificity was 85.7, which was higher than the diagnostic value of single tumor markers. (Table 5, Figure 7, Figure 8).

Table 2 ROC Curve of Luteal Cyst

Variate	AUC	95% CI	P	Youden Index J	Cut-off Value	Sensitivity (%)	Specificity (%)
CEA	0.573	[0.485, 0.658]	0.319	0.222	>1.39	22.2	100.0
AFP	0.690	[0.605, 0.767]	0.010	0.427	>1.40	53.8	88.9
CA125	0.686	[0.600, 0.763]	0.011	0.432	>20.92	48.7	94.4
CA199	0.663	[0.577, 0.742]	0.026	0.393	>32.08	39.3	100.0
SCC	0.714	[0.630, 0.789]	0.003	0.432	>0.70	70.9	72.22
HE4	0.620	[0.533, 0.702]	0.101	0.363	≤44.11	41.9	94.44
AFP+CA125+CA199+SCC	0.871	[0.803, 0.923]	<0.001	0.607	>0.90	71.8	88.9

Abbreviation: AUC, area under the curve.

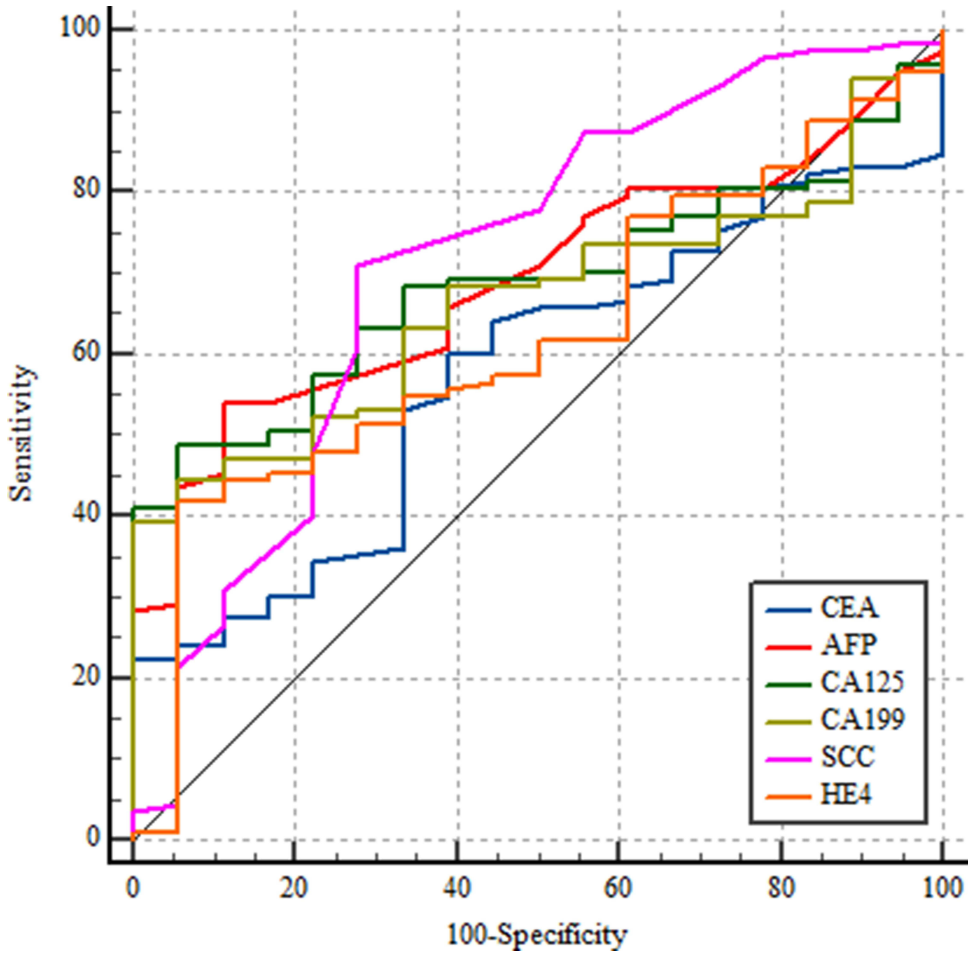

Figure 1 ROC curves for six tumor markers of luteal cyst.

Discussion

Because of the wide variety of adnexal masses, various tissue types and complex classification, the differential diagnosis of ovarian masses is relatively difficult. The diagnosis of benign and malignant adnexal masses has always been an issue of concern in the field of gynecology. Studies have shown that the accuracy of the simple regular model proposed by international tumor analysis to distinguish benign and malignant adnexal tumors can reach 76%-89%. Combined with tumor markers and the clinical judgment of experienced experts, the accuracy can reach more than 90%.[25] However, the identification of benign tumors in the adnexal region is still a thorny problem, and there is no effective method to identify the types of benign tumors. The purpose of this study was to investigate the correlation of preoperative serum tumor markers in the differential diagnosis of benign ovarian masses. By collecting the clinical data and serum tumor marker data of 135 patients with adnexal benign masses, we found that there were significant differences in tumor marker levels among different types of benign ovarian masses. In addition, we collected additional data of patients' age, mass size and unilateral and bilateral masses, and found that four kinds of benign ovarian masses were not related to age, but were related to mass size and unilateral and bilateral masses, and simple luteal cysts were significantly smaller than those in other groups. The incidence of epithelial benign tumors was significantly larger than that of other groups, while the bilateral incidence of ovarian benign tumors was significantly higher in endometriosis

Luteal cyst is actually a physiological disease, normal corpus luteum is a cystic structure, can make the ovary slightly enlarged. If the cystic corpus luteum persists or grows, or the luteal hematoma contains more blood, after the blood is absorbed, it can cause luteal cyst. However, rupture of functional ovarian cysts is a common cause of acute pelvic pain in women of childbearing age.[26] The course of disease ranges from asymptomatic or physical signs to severe peritoneal

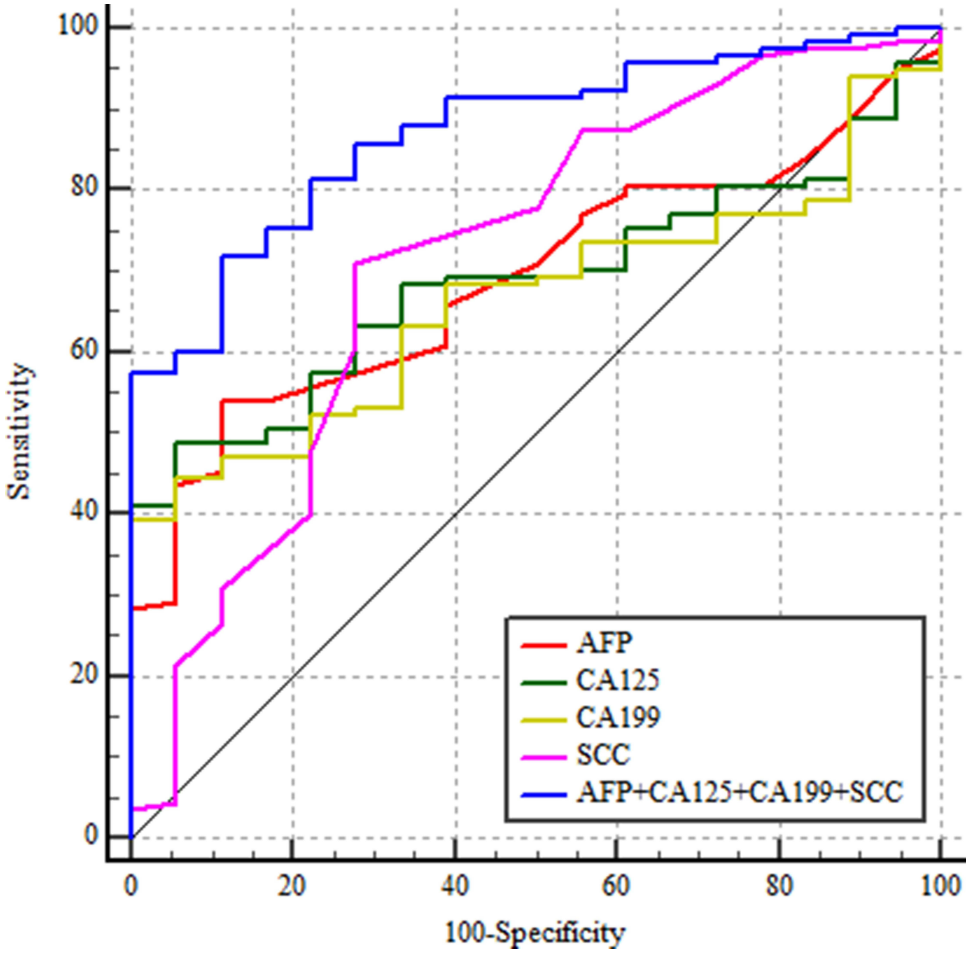

Figure 2 ROC curves of four tumor markers with diagnostic value in luteal cyst and their combined diagnosis.

irritation and even life-threatening shock. Therefore, although ovarian cyst rupture is a self-limited physiological event that can be conservatively treated, surgical intervention is occasionally required when accompanied by hemodynamic instability, severe persistent pain, uncertain diagnosis or massive peritoneal hemorrhage.[27,28] Therefore, it is very important for the non-invasive diagnosis of luteal cyst. In this study, the tumor size of luteal cyst was significantly smaller than that of the other groups. ROC analysis showed that the combination of AFP, CA125, CA19-9, and SCC had a higher diagnostic rate for luteal cysts (AUC=0.871) with a sensitivity of 71.8% and specificity of 88.9%. The sensitivity is slightly low, yet it still exceed single tumor markers, and its and its specificity is relatively high, with a false positive rate of only 11.1%. Therefore, when distinguishing luteal cyst from other benign ovarian tumors, greater attention should be paid to the four tumor markers: AFP, CA125, CA19-9, and SCC. This approach will enhance the preoperative

Table 3 ROC Curve of OMCT

Variate	AUC	95% CI	P	Youden Index J	Cut-off Value	Sensitivity (%)	Specificity (%)
CEA	0.507	[0.420, 0.594]	0.885	0.121	≤0.56	57.7	54.4
AFP	0.665	[0.579, 0.774]	0.001	0.315	≤0.90	52.6	78.9
CA125	0.582	[0.494, 0.666]	0.105	0.196	>62.48	23.1	96.5
CA199	0.581	[0.493, 0.665]	0.110	0.206	≤23.44	67.9	52.6
SCC	0.710	[0.626, 0.785]	<0.001	0.331	≤0.80	57.7	75.4
HE4	0.610	[0.523, 0.693]	0.029	0.211	>42.6	80.8	40.4
AFP+SCC+HE4	0.753	[0.671, 0.823]	<0.001	0.408	>0.621	65.4	75.4

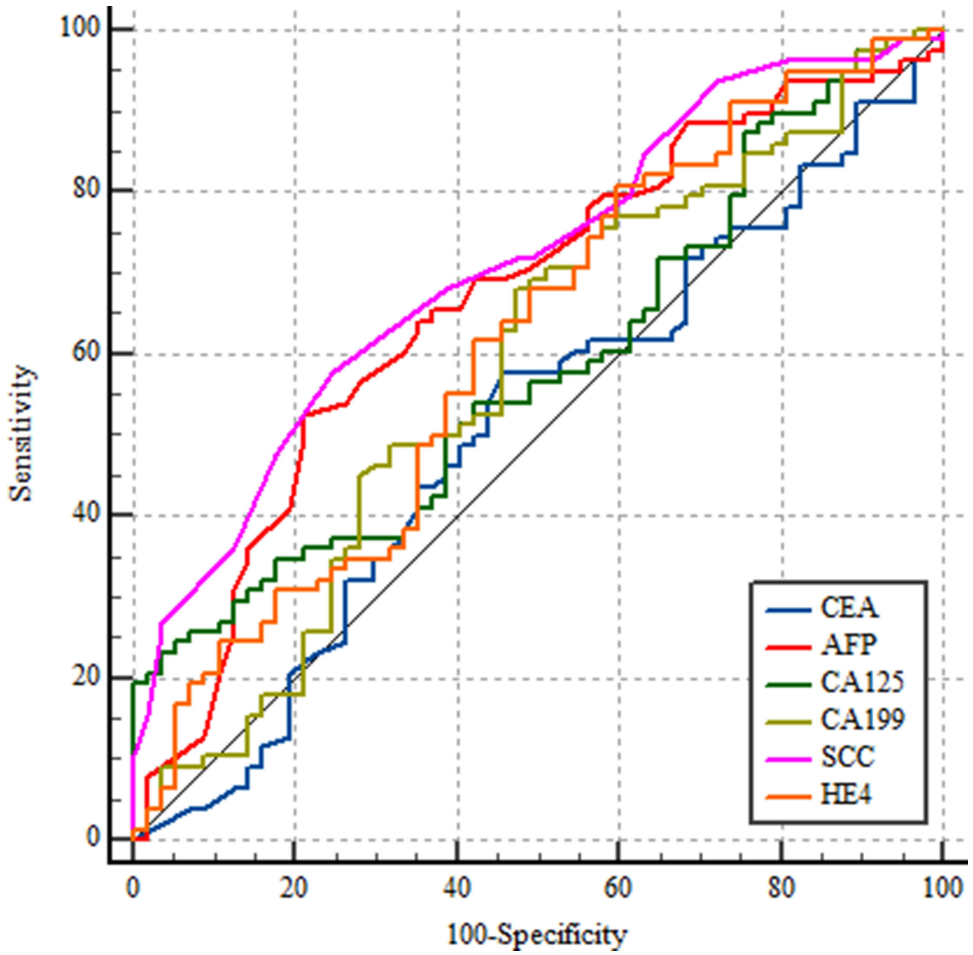

Figure 3 ROC curves for six tumor markers of OMCT.

diagnostic rate of luteal cyst, reduce unnecessary surgical explorations, save medical costs, and alleviate patient suffering.

OMCT is the most common benign germ cell tumor of ovary in women of childbearing age.[29] It accounts for 10–25% of ovarian tumors and 95% of ovarian teratomas.[30] Ovarian teratoma often lacks specific symptoms and signs. Understanding the grading of immature-malignant-teratomas is crucial for prognostic purposes. The grading scale for immature teratomas ranges from 1 to 3, determined by the extent of immature neuroepithelial tissue present per low power field. These tumors exhibit high chemosensitivity and are typically managed with fertility-preserving surgery, making an accurate histological diagnosis essential for selecting the most suitable treatment approach. And so far, there is no clear tumor biomarker for OMCT. However, some literatures still show the relationship between some tumor markers and OMCT. The level of serum CA19-9 as a tool to assist OMCT diagnosis has been proposed in many studies, and the increase rate of CA19-9 is 39.6% Mel 86%.[31,32] This is consistent with our results, which also found a significant increase in CA19-9 in group B. CA19-9 is a salivary Lewis A antigen associated with mucin in gastrointestinal adenocarcinoma.[33] Considering the histological characteristics of multiple tissues in OMCT, it is not surprising that CA19-9 is generally elevated in patients with OMCT. In addition, our study found that the level of SCC in group B was significantly higher than that in the other groups, and the diagnostic value of SCC alone in the ROC curve was also high. Therefore, in clinical practice, we can consider the diagnosis of OMCT combined with imaging when we find that both CA19-9 and SCC are significantly increased. ROC analysis indicated that the combination of AFP, HE4, and SCC had a higher diagnostic rate for OMCT (AUC=0.753) with a sensitivity of 65.4 and specificity of 75.4. We have found that the combined diagnostic efficacy of three tumor markers in OMCT is superior to that of a single tumor marker. Although

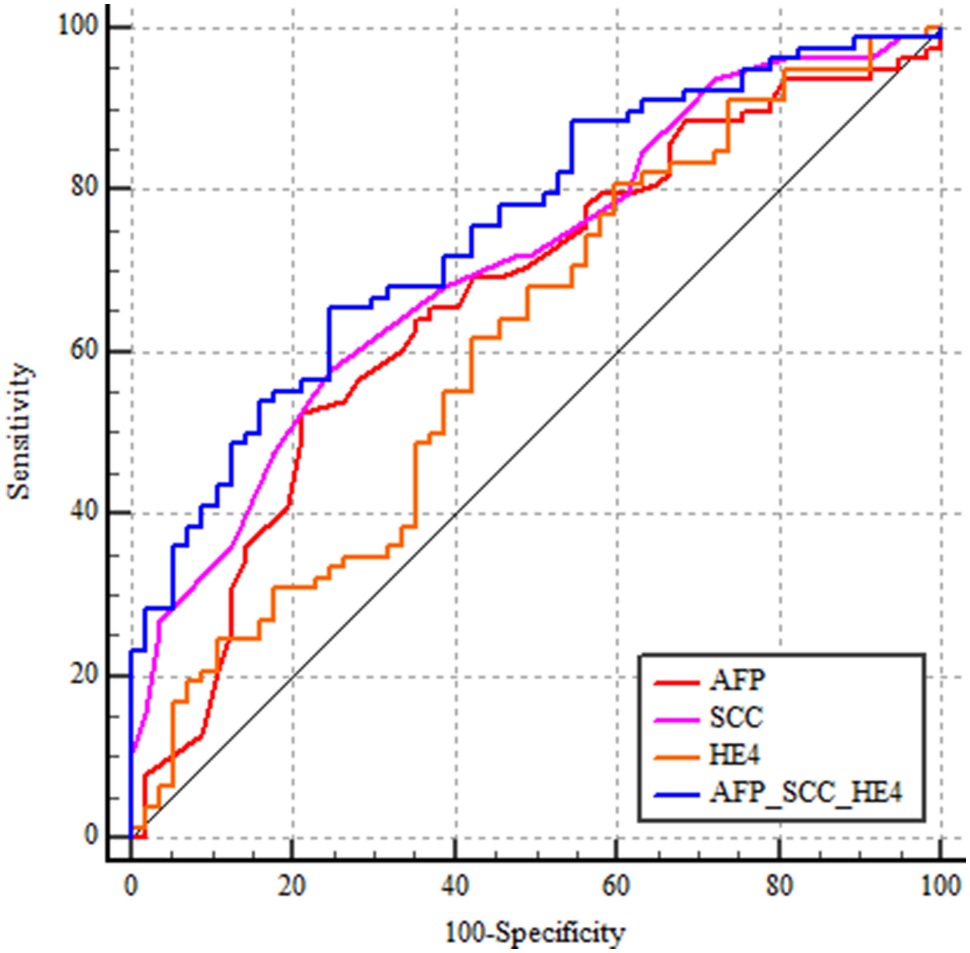

Figure 4 ROC curves of three valuable tumor markers and their combination in the diagnosis of OMCT.

their sensitivity and specificity are not particularly ideal, we can still consider these three tumor markers as auxiliary factors in diagnosing OMCT.

Endometriosis is an estrogen-dependent gynecological disease characterized by the presence of endometriosis tissue outside the uterine cavity, which is related to pelvic pain and low fertility.[34] According to histology, endometriosis can be divided into three types: superficial endometriosis, ovarian endometriosis and deep invasive endometriosis. Ovarian endometriosis is the most common type of endometriosis, with more than 50% of patients with endometriosis.[35] The patients with endometriosis collected in this study are all ovarian endometriosis, which is classified as a kind of benign ovarian tumor in this study. CA125 marker is a glycoprotein found in several epithelial tissues, including ovarian tissue. Its serum levels rise during ovulation and menstruation, as well as during pregnancy and peritoneal inflammation. Among

Table 4 ROC Curve for Ovarian Endometriosis

Variate	AUC	95% CI	P	Youden index J	Cut-off value	Sensitivity (%)	Specificity (%)
CEA	0.503	[0.416, 0.590]	0.959	0.125	>0.22	71.8	15.6
AFP	0.635	[0.548, 0.716]	0.021	0.267	>1.80	48.5	78.1
CA125	0.936	[0.881, 0.971]	<0.001	0.729	≤28.22	85.4	87.5
CA199	0.719	[0.636, 0.793]	<0.001	0.374	≤18.72	59.2	78.1
SCC	0.613	[0.526, 0.696]	0.053	0.205	>0.80	61.2	59.4
HE4	0.538	[0.450, 0.624]	0.516	0.156	≤38.99	15.5	100.0
AFP+CA125+CA199	0.935	[0.879, 0.970]	<0.001	0.736	>0.90	76.7	96.9

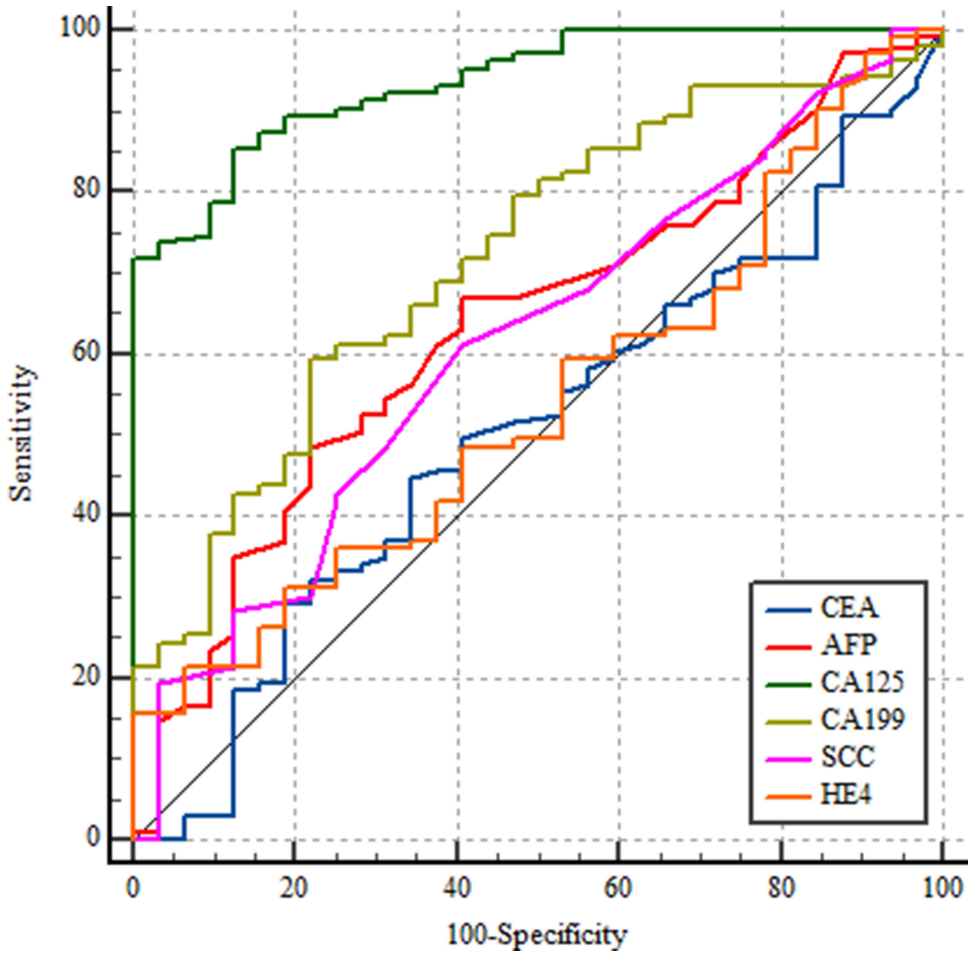

Figure 5 ROC curves for six tumor markers of ovarian endometriosis.

the many tumor markers, CA125 is the most commonly used marker of endometriosis. Compared with other markers, its sensitivity proves that its use as a "gold standard" is reasonable.[36] The results of this study also confirm this conclusion again. In this study, the level of CA125 in group C was significantly higher than that in other groups. CA125 is sensitive to ovarian endometriosis, but its specificity is low because it is also affected by menstruation and pregnancy. ROC analysis demonstrated that the combination of AFP, CA125, and CA19-9 had a higher diagnostic rate for ovarian endometriosis (AUC=0.935) with a sensitivity of 76.7 and specificity of 96.9. Our results have shown that the combined use of AFP, CA125, and CA19-9 in diagnosing ovarian endometriosis yields very good outcomes, with high specificity and a low false positive rate of only 4.1%.

Epithelial tumor is a common ovarian tumor, and its incidence occupies the first place in ovarian tumors. This is likely due to the fact that there are still no effective tools available for screening the general population. This is also reflected economically and cost-effective strategies for early detection and prevention of ovarian cancer have been investigated over the last decade. The cost of treatment per patient with ovarian cancer remains the highest among all cancer types. As an example, the average initial cost in the first year can amount to around USD 80,000, whereas the final year cost may increase to USD 100,000.[37] Epithelial tumors are tumors originating from the surface epithelial tissue of the ovary, which are mainly divided into three categories: benign, malignant and borderline. Serous cystadenoma is the most common type of ovarian epithelial tumors, and mucinous cystadenoma is relatively rare. Serous cystadenoma, mucinous cystadenoma and serous mucinous mixed cystadenoma were collected in this study. At present, there is still lack of relatively authoritative data to explain the relationship between the level of tumor markers in epithelial ovarian tumors and the differentiation of benign ovarian masses. In this study, we found that the level of CA19-9 in group D was

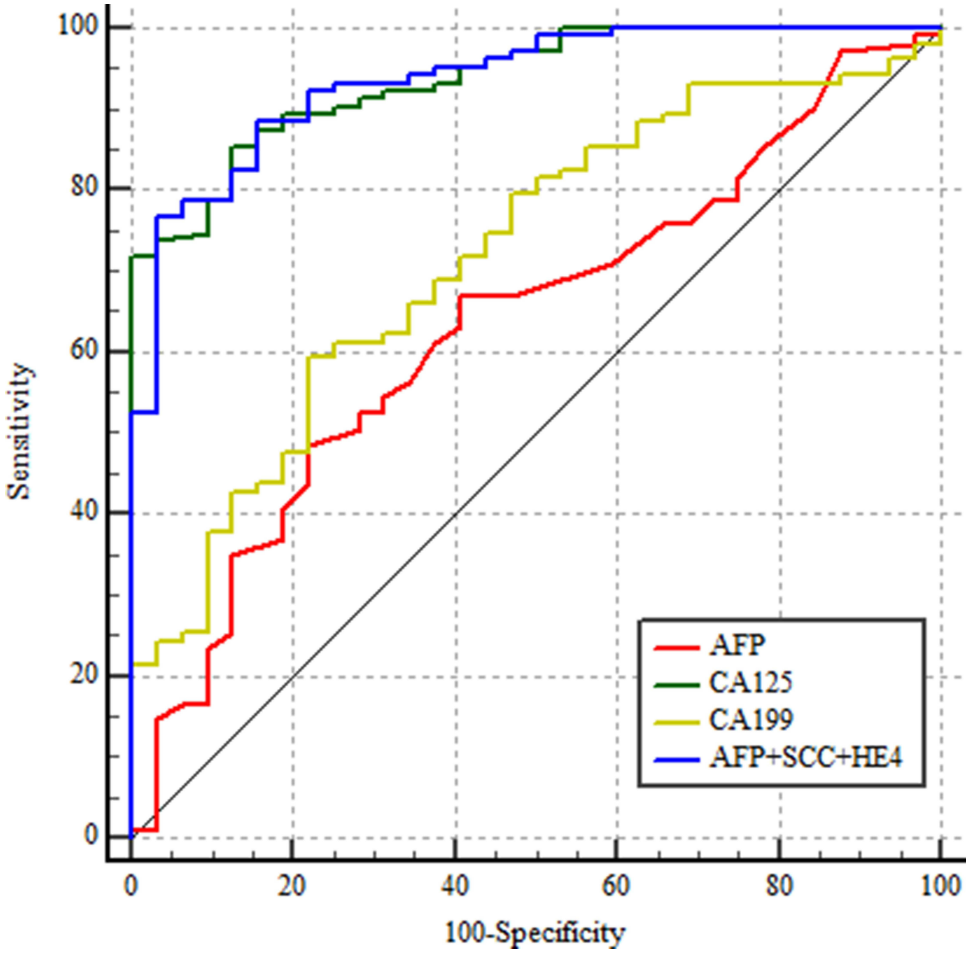

Figure 6 ROC curves of three valuable tumor markers and their combination in the diagnosis of ovarian endometriosis.

significantly lower than that in group B and C, the level of CA125 was lower than that in group C, and the level of SCC in group D was significantly lower than that in group B. However, there was no significant difference in the level of tumor markers between group D and group A. ROC analysis revealed that the combination of CA125 and CA19-9 had a higher diagnostic rate for benign epithelial tumors of the ovary (AUC=0.792) with a sensitivity of 64.5 and specificity of 85.7. The specificity of CA125 and CA19-9 alone is quite good, yet their sensitivity is very poor. When combining the two for diagnosis, there is a significant improvement in sensitivity, although it is still not particularly ideal. This suggests that we may need a wider range of tumor markers for diagnostic purposes.

Overall, our results show that there is a certain correlation between preoperative serum tumor markers and the type and diagnosis of benign ovarian masses. The combination of multiple tumor markers has certain value in the differential

Table 5 ROC Curve for Ovarian Epithelial Benign Tumors

Variate	AUC	95% CI	P	Youden Index J	Cut-off Value	Sensitivity (%)	Specificity (%)
CEA	0.544	[0.456, 0.630]	0.475	0.22	≤1.26	83.2	39.3
AFP	0.537	[0.449, 0.623]	0.551	0.19	≤2.10	65.4	53.6
CA125	0.728	[0.644, 0.801]	<0.001	0.43	>21.92	46.7	96.4
CA199	0.746	[0.644, 0.817]	<0.001	0.39	>21.84	53.3	85.7
SCC	0.536	[0.449, 0.623]	0.554	0.11	>1.30	21.5	89.3
HE4	0.537	[0.449, 0.623]	0.547	0.16	≤57.15	86.0	28.6
CA125+CA199	0.792	[0.713, 0.857]	<0.001	0.50	>0.75	64.5	85.7

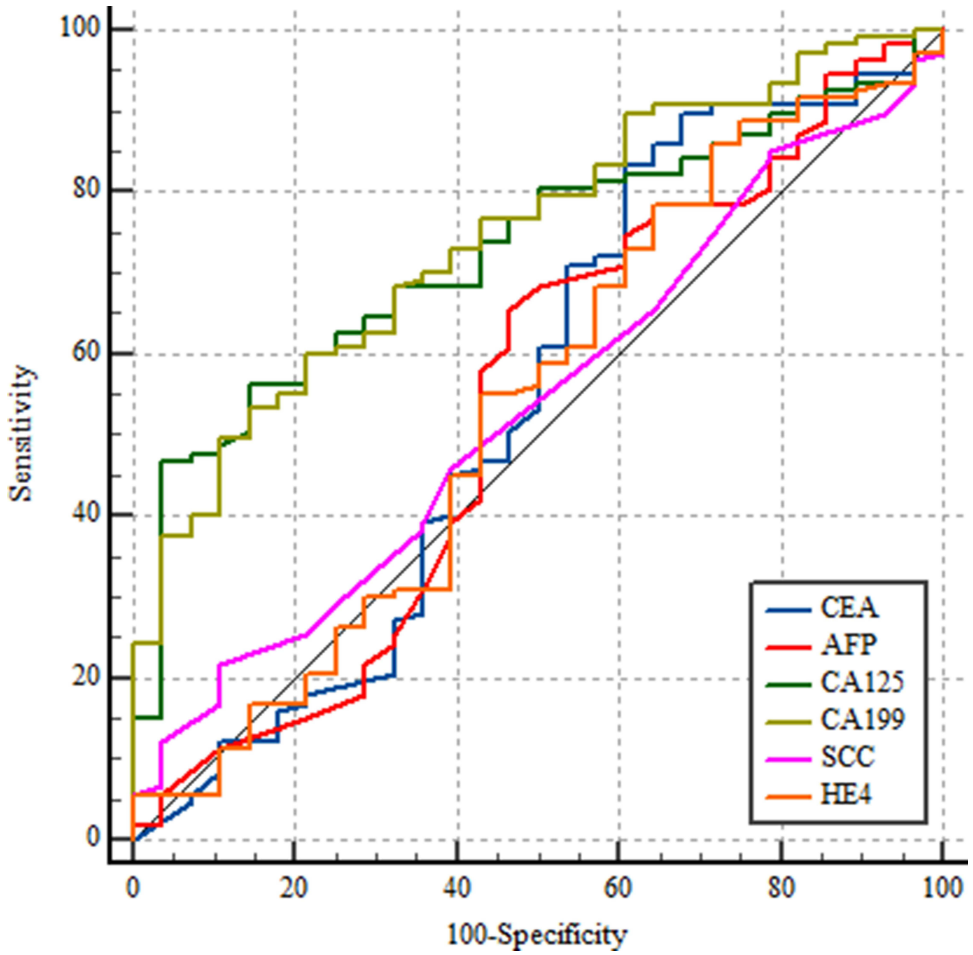

Figure 7 ROC curves for six tumor markers in epithelial benign tumors of the ovary.

diagnosis of benign ovarian tumors. Preoperative diagnosis will effectively change the surgical options for patients. If it is merely a simple corpus luteum cyst without rupture and bleeding, observation and conservative treatment can be considered. Mild pain and bleeding from ovarian endometriosis can attempt drug treatment.[38] Patients with OMCT should pay more attention to some dangerous complications, such as neurological symptoms of anti-NMARD encephalitis.[39] Epithelial tumors can focus on the risk of malignant transformation in advance. Early diagnosis effectively provides clinicians with more effective treatment options, and improves patient prognosis and quality of life. However, because the sample size of this study is relatively small and only a single-center study, our results need to further verify and expand the sample size. Future studies can consider multicenter prospective studies to further evaluate the accuracy and feasibility of different tumor markers in the differential diagnosis of benign ovarian masses and to determine the best diagnostic strategy. In addition, the potential value of other new tumor markers or combinations can be explored to improve the accuracy of differential diagnosis of benign ovarian masses.

Conclusion

In our study, the tumor markers CEA, AFP, CA125, CA199, SCC, and HE4 have diagnostic value for benign ovarian tumors. ROC analysis reveals that the combined use of these tumor markers has significant significance in diagnosing four types of benign ovarian tumors: luteal cysts (sensitivity 71.8, specificity 88.9), OMCT (sensitivity 65.4, specificity 75.4), ovarian endometriosis (sensitivity 76.7, specificity 96.9), and benign epithelial tumors of the ovary (sensitivity 64.5, specificity 85.7). The combined diagnosis demonstrates good accuracy and reliability, utilizing commonly encountered clinical tumor markers without a significant increase in economic cost. Compared to the current diagnostic value of

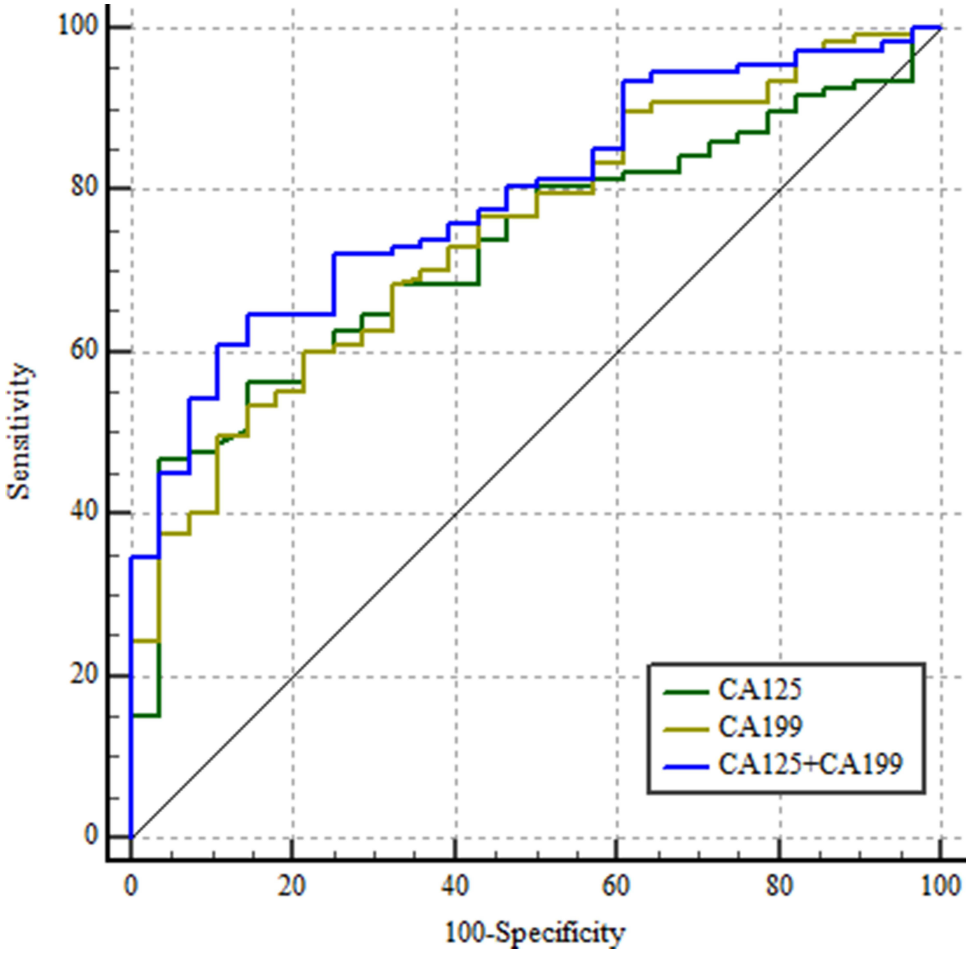

Figure 8 ROC curves of two tumor markers with diagnostic value in benign epithelial ovarian tumors and their combination.

individual tumor markers, there is a significant increase, effectively assisting imaging in the differential diagnosis of benign ovarian tumors. This enhances the diagnostic efficiency of clinicians, thereby optimizing treatment plans, ultimately improving patient prognosis and quality of life. However, this study is limited by the insufficiency of sample size and its single-center design, which constrains the accuracy of its results. In addition, the results of the ROC curve in OMCT and ovarian epithelial tumors are not very ideal. The sensitivity and specificity of the combined diagnosis of OMCT did not exceed 0.8, and the sensitivity in ovarian epithelial tumors was not particularly high. Therefore, we may need other more sensitive and specific tumor markers to study these two benign tumors. Future studies should consider multicenter trials with larger sample sizes to validate these findings and potentially include cost-effectiveness analyses to assess the practicality of implementing this combined diagnostic approach in clinical settings. Such research would not only reinforce the efficacy of using multiple tumor markers in diagnosing benign ovarian tumors but also provide valuable data on the sustainability and broader applicability of this method.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Statement

Studies involving human subjects have been reviewed and approved, and all procedures involving human subjects meet the ethical standards of the Ethics Committee of Zhengzhou First People's Hospital (Zhengzhou, China, 2024-022). This study was conducted in accordance with the principles of the Declaration of Helsinki. This study is a retrospective

research involving the analysis of existing medical records without direct patient contact or intervention. In view of the nature of the study and to ensure patient privacy, the Ethics Committee of Zhengzhou First People's Hospital specifically authorized the waiver of informed consent for this study, in accordance with relevant ethical standards and regulations. The ethics review reference number is (2024-022). All procedures implemented in this study strictly adhered to the guidance and requirements of the Ethics Committee to ensure the security and privacy of patient information.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the 2024 Zhengzhou Medical and health field science and technology innovation guidance plan project (grant number 2024YLZDJH138).

Disclosure

The authors declare that they have no competing interests in this work.

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