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Serum levels of tumor markers and their clinical significance in epithelial ovarian cancer

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ABSTRACT

Objective: Tumor markers have been widely used clinically. Detection of serum CA125 is one of the commonly used clinical methods for early screening and early diagnosis of epithelial ovarian cancer, but it is difficult to diagnose epithelial ovarian cancer with a single specific tumor marker. In this study, the combinatorial tumor marker detection method was used to compare the value of each tumor marker alone and different combinations in the diagnosis of epithelial ovarian cancer.

Methods: The clinical data of patients with epithelial ovarian cancer (n=65) and ovarian benign disease (n=29) were collected. Multiple tumor marker protein chip was used to detect cancer antigen 125 (CA125), carbohydrate antigen 242 (CA242), alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (β-HCG), carcinoembryonic antigen (CEA), cancer antigen 199 (CA199), neuron-specific enolase (NSE), Ferritin, cancer antigen 153 (CA153), and human growth hormone (HGH) serum levels, and to compare the differences between the benign and malignant ovarian tumors. The correlation between tumor markers and clinicopathologic features for ovarian epithelial carcinoma was analyzed by χ^2 test. Spearman rank analysis showed the correlation between CA125 expression level and other tumor markers in epithelial ovarian cancer and the correlation between age and the above 10 tumor markers. Sensitivity, specificity, positive predictive value, negative predictive value, Youden index, and diagnostic efficiency were used to evaluate the diagnostic value of single tumor marker and the combination of tumor markers.

Results: The levels of β-HCG, NSE, CA153, and CA125 in the epithelial ovarian cancer group were higher than those in the ovarian benign disease group. The level of NSE in the serum of patients with epithelial ovarian cancer was related to the clinical stage of patients. In addition, the levels of CA242, β-HCG, CEA, NSE, Ferritin, CA153 in the serum of patients with epithelial ovarian cancer were positively correlated with CA125 (r_s=0.497, P<0.001; r_s=0.612, P<0.001; r_s=0.358, P=0.003; r_s=0.680, P<0.001; r_s=0.322, P=0.009; r_s=0.609, P<0.001, respectively), and the levels of β-HCG, Ferritin, CA153 were positively

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correlated with the patient's age (r_s=0.256, P=0.040; r_s=0.325, P=0.008; r_s=0.249, P=0.046, respectively). In the diagnosis of epithelial ovarian cancer, the sensitivity, Youden index, and diagnostic efficiency of CA125 detection alone were higher than the results of the other 9 separate detections. When CA153, CA199, CA242, Ferritin, and CEA were combined with CA125, the sensitivity of the combined detection of different combinations was higher than that of CA125 alone. The combined detection sensitivities of CA125+CEA and CA125+Ferritin+CEA were 89.2% and 90.8%, respectively, and the diagnostic efficiencies were both 84.1%, which were higher than those of other combinations. The Youden index of CA125+CEA joint detection was 0.616, which was higher than those of other combinations.

Conclusion: CA125 has a high diagnostic value in the diagnosis of epithelial ovarian cancer. The detection of combined tumor markers in serum has higher sensitivity and specificity in epithelial ovarian cancer.

KEY WORDS epithelial ovarian cancer; tumor marker; protein chip-chemiluminescence; combined assessments; diagnostic value

上皮性卵巢癌血清中肿瘤标志物水平及其临床意义

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[摘 要] 目的：肿瘤标志物已广泛应用于临床。血清CA125检测是目前临床常用的上皮卵巢癌早期筛查和早期诊断方法之一，但使用单一特异性肿瘤标志物诊断上皮性卵巢癌比较困难。本研究采用肿瘤标志物组合检测法，比较各肿瘤标志物单独检测与联合检测在上皮性卵巢癌诊断中的价值。**方法：**收集上皮性卵巢癌患者(n=65)和卵巢良性疾病患者(n=29)的临床资料。采用多肿瘤标志物蛋白质芯片检测癌抗原125(cancer antigen 125，CA125)、糖类抗原242(carbohydrate antigen 242，CA242)、甲胎蛋白(alpha-fetoprotein，AFP)、β-人绒毛膜促性腺激素(beta-human chorionic gonadotropin，β-HCG)、癌胚抗原(carcinoembryonic antigen，CEA)、癌抗原199(cancer antigen 199，CA1990)、神经元-特性烯醇化酶(neuron-specific enolase，NSE)、铁蛋白(Ferritin)、癌抗原153(cancer antigen 153，CA153)以及人生长激素(human growth hormone，HGH)的血清水平，比较其在卵巢良恶性肿瘤中的差异；χ^2检验分析肿瘤标志物与卵巢上皮癌患者临床病理特征的相关性；Spearman秩关性分析上皮性卵巢癌CA125与其他肿瘤标志物表达水平及年龄与上述10种肿瘤标志物的相关性；采用灵敏度、特异度、阳性预测值、阴性预测值、约登指数及诊断效率分别评价各肿瘤标志物单项检测及联合检测的诊断价值。**结果：**上皮性卵巢癌组中的β-HCG、NSE、CA153和CA125水平均高于卵巢良性疾病组。上皮性卵巢癌患者血清中NSE的水平与患者的临床分期相关。此外，上皮性卵巢癌患者血清中CA242、β-HCG、CEA、NSE、Ferritin、CA153水平与CA125水平呈正相关(分别r_s=0.497、P<0.001；r_s=0.612、P<0.001；r_s=0.358、P=0.003；r_s=0.680、P<0.001；r_s=0.322、P=0.009；r_s=0.609、P<0.001)，β-HCG、Ferritin、CA153水平与患者年龄呈正相关(分别r_s=0.256、P=0.040；r_s=0.325、P=0.008；r_s=0.249、P=0.046)。在上皮性卵巢癌诊断中，CA125单独检测的灵敏度、约登指数及诊断效率均高于其他9种肿瘤标志物单独检测的结果；CA153、CA199、CA242、Ferritin、CEA与CA125进行联合检测时，其灵敏度均高于CA125单独检测的灵敏度，其中CA125+CEA、CA125+Ferritin+CEA这2种组合的灵敏度分别为89.2%和90.8%，诊断效率均为84.1%，高于其他组合的诊断效率。CA125+CEA联合检测时其约登指数为0.616，高于其他组合。**结论：**CA125在诊断上皮性卵巢癌方面具有较高的诊断价值。血清中的肿瘤标志物组合检测在上皮性卵巢癌中具有更高的灵敏度和特异度。

[关键词] 上皮性卵巢癌；肿瘤标志物；蛋白质芯片化学发光；联合评估；诊断价值

Ovarian cancer is one of the most common malignant tumors of female reproductive system. The global incidence of ovarian cancer is only after cervical cancer and endometrial cancer. Ovarian cancer is the leading cause of the gynecologic malignancies related death[1], and the 5-year overall survival (OS) rate is 20% to 30%.

According to the tissue type and the direction of differentiation, ovarian cancer can be divided into 3 main types, including epithelial ovarian cancer, germ cell tumor, and sex cord-stromal cell tumor[2], of which epithelial ovary cancer is the most common, accounting for about 90%. The causes of ovarian cancer are complicated and haven't been studied clearly yet. The occurrence of ovarian cancer is mainly related to heredity, reproduction, environment, behavioral habits, and psychology. The protective factors of ovarian cancer include prolificacy, multiple pregnancy, breastfeeding, oral contraceptives, tubal ligation, and double attachment resection[3], and the risk factors include early menarche, late menopause, long menstrual years, homologous recombinant gene mutations [such as breast cancer susceptibility genes 1/2 (BRCA1/2), ataxia telangiectasia-mutated (ATM), BRCA1-associated RING domain 1 (BARD1), BRCA1 interacting protein C-terminal helicase 1 (BRIP1), checkpoint kinase 1 (CHEK1), recombination protein A paralog C (RAD51C)], obesity or weight gain, high-fat diet, occupational exposure, and mental stress[4-6].

Tumor markers have been widely used in clinical practice. Detection of tumor markers can be used for screening high-risk populations for tumors, and also for diagnosis, monitoring, and prognosis. At present, the common method for early screening and the diagnosis of ovarian cancer is ultrasound and the detection of tumor marker—cancer antigen 125 (CA125)[7]. Vaginal ultrasonography can be used to examine female genital organs, but there are certain requirements for the professional level of doctors. As for the detection of CA125, the increased CA125 level is also reported in other physiological or pathological conditions, such as menstruation, pregnancy, endometriosis, and inflammatory diseases of the peritoneum, and this marker has a low sensitivity in the early stages of ovarian cancer, which may lead to false negative or false positive[8]. Other biomarkers have been developed in order to improve specificity for ovarian carcinomas, such as carcinoembryonic antigen (CEA), carbohydrate antigen 242 (CA242), alpha-fetoprotein (AFP), neuron-specific enolase (NSE), beta-human chorionic gonadotropin (β-HCG), Ferritin, cancer antigen 153 (CA153), and cancer antigen 199 (CA199), but each marker has certain limitations in clinical application. It is urgently needed to find a combination of tumor markers that can bring more benefits to patients by combined detection with CA125[9].

1 Subjects and methods

1.1 Subjects

Patients with ovarian disease who were diagnosed in Hunan Cancer Hospital from July 2021 to March 2022 were enrolled. The inclusion criteria were newly diagnosed, without tumor surgery, radiotherapy, chemotherapy or other anti-tumor treatment, and the clinical data were complete. Patients with pregnancy, liver or kidney dysfunction, cardiac insufficiency or other systemic tumors were excluded. The requirement for informed consent was waived because of the retrospective nature of this study. This study was approved by the Ethics Committee of the Third Xiangya Hospital of Central South University (No. 2017-S263).

1.2 Data collection

The clinical data of patients with epithelial ovarian cancer were collected, including age, blood group, life history, menstrual history, marriage and family history, treatment process, pathological type, clinical stage, and lymphatic metastasis. At the same time, 10 tumor markers were detected by multi-tumor marker protein chip method at the initial diagnosis, including CA125, CEA, CA242, AFP, NSE, β-HCG, CA153, CA199, Ferritin, and human growth hormone (HGH).

According to the gold standard of pathological examination, 94 patients were divided into an epithelial ovarian cancer group (n=65) and an ovarian benign disease group (n=29). The age of the epithelial ovarian cancer group was 25－66 (51.5±20.5) years old and that of the ovarian benign disease group was 23－67 (46.5± 3.5) years old. There was no statistical difference in age between the 2 groups (P>0.05).

1.3 Positive standard

The positive criteria for each tumor marker detected by protein chip were: CA125>35.00 U/mL, CA242>20.00 kU/L, AFP>20.00 ng/mL, β-HCG>3.00 mU/L, CEA>5.00 mg/L, CA199>35.00 U/mL, NSE>13.00 ng/mL, Ferritin>219.00 ng/mL (female), HGH>7.50 ng/mL, CA153>35.00 kU/L.

1.4 Statistical analysis

Statistical analysis was performed by SPSS 25.0 software. Due to the characteristics of each tumor marker and the difference of the marker levels in the individual serum, the serum level of each tumor marker did not follow a normal distribution. Therefore, the overall level was expressed by the median and the quartile [$M(P_{25}, P_{75})$], and the measurement data were compared by median test and Mann-Whitney U test between the 2 groups. Qualitative data were compared by χ^2 test. The correlation between age and 10 tumor markers or CA125 and other 9 tumor markers were analyzed by Spearman rank correlation analysis. Sensitivity, specificity, positive predictive value, negative predictive value, Youden index, and diagnostic efficiency were used to evaluate the diagnostic value of individual tumor marker and their combination. The closer the value was to 1, the greater the diagnostic value was. P<0.05 was considered statistically significant.

2 Results

2.1 Comparison of 10 tumor markers between the 2 groups

The levels of β-HCG, NSE, CA153, and CA125 in the epithelial ovarian cancer group were higher than those in the ovarian benign disease group (all P<0.05). However, the other 6 tumor markers showed no significant difference between the 2 groups (all P>0.05, Table 1).

Table 1 Ten tumor markers in epithelial ovarian cancer group and ovarian benign disease group

Groups	CA242/(kU·L^{-1})	AFP/(ng·mL^{-1})	β-HCG/(mU·L^{-1})	CEA/(mg·L^{-1})	CA199/(U·L^{-1})
Epithelial ovarian cancer	6.39(3.31, 12.58)	1.92(1.36, 3.01)	0.92(0.55, 1.86)	1.18(0.64, 2.62)	7.73(2.64, 32.90)
Ovarian benign disease	4.85(2.59, 9.95)	2.36(1.21, 6.10)	0.30(0.14, 0.70)	1.11(0.58, 1.59)	9.62(5.83, 28.54)
P	0.180	0.655	<0.001	1.000	1.000
Groups	NSE/(ng·mL^{-1})	Ferritin/(ng·mL^{-1})	HGH/(ng·mL^{-1})	CA153/(kU·L^{-1})	CA125/(U·mL^{-1})
Epithelial ovarian cancer	8.98(4.32, 14.42)	160.12(71.04, 308.60)	0.14(0.01, 0.72)	27.36(8.61, 64.39)	490.75(119.45, 675.35)
Ovarian benign disease	3.38(2.52, 4.34)	61.27(25.75, 172.57)	0.23(0.02, 1.59)	11.70(6.00, 18.44)	23.76(8.76, 74.11)
P	<0.001	0.180	0.372	0.026	<0.001

Non-normal distribution data are expressed as $M(P_{25}, P_{75})$. CA242: Carbohydrate antigen 242; AFP: Alpha-fetoprotein; β-HCG: Beta-human chorionic gonadotropin; CEA: Carcinoembryonic antigen; CA199: Cancer antigen 199; NSE: Neuron-specific enolase; HGH: Human growth hormone; CA153: Cancer antigen 153; CA125: Cancer antigen 125. Statistical methods were Median test, Mann-Whitney U test, and χ^2 test.

2.2 Relationship between tumor markers and clinical stages

According to the positive criteria of each tumor marker and the FIGO staging criteria, the relationship between the level of each tumor marker and the clinical stages or lymphatic metastasis in the epithelial ovarian cancer group was performed. The results indicated that only the difference of NSE levels between patients with different clinical stages was statistically significant (χ^2=4.52, P=0.004), the differences of the other 9 tumor markers between different clinical stages were all not statistically significant (all P>0.05, Table 2). In addition, serum levels of the 10 tumor markers had no significant difference in patients with or without lymphatic metastasis.

2.3 Relationship between the expression of β-HCG, CA153, CA199, and related factors of ovarian cancer

Patients in the epithelial ovarian cancer group were

divided according to 7 factors related to ovarian cancer, which was the age of marriage, the number of pregnancies, the number of abortions, the age of menarche, the menstrual cycle, the menstrual years (ovulation year), and whether menopause was reached. The results were shown in Table 3. It showed that the expression of β-HCG in patients with the number of pregnancies (≤1 time vs >1 time), the expression of CA153 in patients with the menstrual cycle (<30 d vs ≥30 d), and the expression of CA199 in patients with the menstrual years (ovulation year) (<34 years vs ≥34 years) were statistically significant (all P<0.05, Table 3). Except for the above 3 items, there was no significant difference in the expression of other tumor markers between the groups.

Table 2 Relationship between tumor markers and clinical stages

Phases	CA242		AFP		β-HCG		CEA		NSE		Ferritin		CA199		HGH		CA153		CA125	
	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−
I-II	2	16	0	18	3	15	1	17	2	16	6	12	3	15	0	18	4	14	14	4
III-IV	3	44	0	47	4	43	6	41	18	29	18	29	12	35	0	47	19	28	43	4
P	0.500		0.763		0.200		0.455		0.004		0.714		0.792		0.394		0.370		0.060	

Non-normal distribution data are expressed as $M(P_{25}, P_{75})$. CA242: Carbohydrate antigen 242; AFP: Alpha-fetoprotein; β-HCG: Beta-human chorionic gonadotropin; CEA: Carcinoembryonic antigen; CA199: Cancer antigen 199; NSE: Neuron-specific enolase; HGH: Human growth hormone; CA153: Cancer antigen 153; CA125: Cancer antigen 125. +: The number of positive case; −: The number of negative case. The positive criteria for each tumor marker were: CA242>20.00 kU/L, AFP>20.00 ng/mL, β-HCG> 3.00 mU/L, CEA>5.00 mG/L, CA199>35.00 U/mL, NSE>13.00 ng/mL, Ferritin>219.00 ng/mL(female), HGH>7.50 ng/mL, CA153> 35.00 kU/L, CA125>35.00 U/mL. Statistical methods were Median test, Mann-Whitney U test, and χ^2 test.

Table 3 Relationship between the expression of β-HCG, CA153, CA199, and related factors of ovarian cancer

Related factors	CA242/(kU·L^{-1})	AFP/(ng·mL^{-1})	β-HCG/(mU·L^{-1})	CEA/(mg·L^{-1})	CA199/(U·mL^{-1})
Age of marriage/years					
≤22	6.39(3.49, 13.53)	1.97(1.36, 3.58)	0.92(0.59, 1.88)	1.53(0.80, 2.78)	7.28(2.61, 20.33)
>22	6.50(3.09, 12.04)	1.83(1.18, 2.53)	1.00(0.49, 1.86)	0.88(0.58, 1.87)	15.08(2.65, 42.13)
P	0.808	0.575	0.757	0.182	0.330
Number of pregnancies/times					
≤1	5.76(3.31, 11.95)	2.16(1.16, 3.84)	0.68（0.63, 1.19）	0.87(0.58, 1.70)	11.12(3.54, 39.46)
>1	6.46(3.25, 13.02)	1.89(1.36, 2.61)	1.35(0.62, 2.13)	1.57(0.75, 2.94)	7.28(2.55, 32.82)
P	0.742	0.956	0.012	0.071	0.588
Number of abortions/times					
≤1	6.46(3.12, 11.93)	1.72(1.23, 2.60)	0.79(0.43, 1.75)	1.12(0.57, 2.75)	7.29(2.62, 37.86)
>1	5.76(3.56, 14, 31)	2.36(1.36, 3.59)	1.20(0.76, 2.15)	1.22(0.76, 2.47)	10.49(3.47, 29.93)
P	0.756	0.358	0.068	0.540	0.599
Age of menarche/year					
<13	10.14(2.97, 12.88)	2.36(1.63, 3.44)	0.79(0.34, 1.81)	1.15(0.46, 2.25)	12.77(3.15, 44.16)
13−16	5.89(3.45, 13.13)	1.67(0.64, 3.40)	0.96(0.59, 1.87)	1.07(0.74, 2.60)	7.52(3.44, 25.64)
>16	6.44(3.05, 12.03)	1.61(1.31, 2.73)	1.04(0.55, 2.24)	1.37(0.65, 3.34)	6.57(2.49, 28.51)
P	0.948	0.304	0.835	0.769	0.537
Menstrual cycle/d					
<30	9.16(3.69, 13.48)	1.93(1.36, 2, 42)	0.79(0.36, 1.87)	1.36(0.56, 2.87)	11.55(4.55, 34.77)
≥30	5.84(3.05, 11.84)	1.92(0.83, 3.58)	1.10(0.58, 1.86）	1.08(0.67, 2.06)	7.27(2.55, 22.85)
P	0.318	0.564	0.478	0.836	0.236

Table 3 (to be continued)

Related factors	CA242/(kU·L^{-1})	AFP/(ng·mL^{-1})	β-HCG/(mU·L^{-1})	CEA/(mg·L^{-1})	CA199/(U·mL^{-1})
Menstrual years/years					
<34	5.84(2.82, 13.64)	2.07(1.36, 2.83)	0.85(0.37, 2.13)	1.00(0.56, 1.72)	5.96(2.55, 30.19)
≥34	6.97(3.96, 11.95)	1.92(1.16, 3.34)	1.19(0.62, 1.75)	1.62(0.78, 2.92)	15.51(5.67, 33.04)
P	0.608	0.818	0.608	0.093	0.035
Menopause					
Yes	7.86(2.89, 13.59)	1.82(1.36, 2.53)	0.84(0.43, 1.62)	1.25(0.58, 2.08)	10.89(2.55, 39.98)
No	5.84(3.49, 11.95)	1.97(1.18, 3.58)	1.24(0.62, 1.88)	1.15(0.78, 2.78)	7.50(3.73, 22.00)
P	0.478	0.727	0.198	0.613	0.813

Related factors	NSE/(ng·mL^{-1})	Ferritin/(ng·mL^{-1})	HGH/(ng·mL^{-1})	CA153/(kU·L^{-1})	CA125/(U·mL^{-1})
Age of marriage/years					
≤22	9.18(4.98,13.74)	193.70(61.25,353,94)	0.16(0.01,0.78)	31.11(8.38,69.26)	514.69(166.12,744.30)
>22	7.03(3.87,14.82)	144.63(73.73,263.00)	0.12(0.01,0. 64)	21.93(8.62,54.99)	439.33(78.21,620.88)
P	0.453	0.617	0.699	0.636	0.304
Number of pregnancies/ times					
≤1	6.37(4.16, 11.65)	110.96(70.66, 180.73)	0.22(0.01, 0.84)	13.04(7.08, 52.06)	419.33(89.84, 558.64)
>1	10.99(4.61, 16.42)	203.52(66.87, 337.61)	0.12(0.01, 0.68)	27.65(11.12, 70.80)	617.45(157.22, 783.43)
P	0.156	0.188	0.586	0.174	0.131
Number of abortions/ times					
≤1	6.59(4.05, 13.80)	150.90(55.72, 302.46)	0.20(0.01, 0.98)	21.96(7.94, 61.77)	425.75(117.62, 705.08)
>1	12.18(5.36, 14.44)	180.73(95.62, 319.06)	0.01(0.01, 0.25)	30.33(9.86, 69.58)	558.64(167.78, 661.17)
P	0.227	0.345	0.137	0.434	0.882
Age of menarche/years					
<13	6.08(3.53, 14.29)	109.92(50.92, 268.59)	0.19(0.01, 1.18)	20.60(7.17, 68.96)	419.33(84.64, 661.89)
13−16	10.04(5.09, 14.82)	184.58(101.61, 300.45)	0.01(0.01, 0.59)	24.01(8.73, 85.97)	518.83(354.11, 805.55)
>16	8.86(4.03, 12.85)	119.80(57.15, 455.95)	0.22(0.05, 0.59)	29.42(8.94, 49.65)	463.31(73.62, 630.50)
P	0.548	0.503	0.294	0.890	0.356
Menstrual cycle/d					
<30	8.34(4.02, 13.98)	150.90(84.85, 341.59)	0.12(0.01, 0.89)	15.80(6.98, 57.27)	491.14(76.53, 658.60)
≥30	8.98(5.19, 14.42)	171.52(61.25, 299.45)	0.16(0.01, 0.57)	32.06(9.39, 65.00)	490.75(271.64, 744.30)
P	0.606	0.779	0.920	0.029	0.413
Menstrual years/years					
<34	8.13(4.15, 13.76)	161.20(64.95, 368.42)	0.75(0.01, 0.59)	25.55(6.98, 47.99)	425.75(87.24, 674.57)
≥34	9.18(4.48, 15.91)	160.12(74.75, 226.75)	0.22(0.01, 0.84)	27.36(10.78, 72.9)	514.70(130.50, 715.51)
P	0.660	0.503	0.237	0.344	0.590
Menopause					
Yes	9.04(4.13, 13.91)	94.31(46.50, 267.00)	0.12(0.01, 0.80)	21.93(7.85, 47.00)	439.33(109.30, 691.42)
No	7.58(4.48, 15.91)	196.08(109.92, 324.38)	0.17(0.01, 0.51)	32.81(9.40, 75.38)	514.69(166.12, 676.91)
P	0.793	0.634	0.589	0.232	0.762

Non-normal distribution data are expressed as $M(P_{25}, P_{75})$. CA242: Carbohydrate antigen 242; AFP: Alpha-fetoprotein; β-HCG: Beta-human chorionic gonadotropin; CEA: Carcinoembryonic antigen; CA199: Cancer antigen 199; NSE: Neuron-specific enolase; HGH: Human growth hormone; CA153: Cancer antigen 153; CA125: Cancer antigen 125. Statistical methods were median test and χ^2 test.

2.4 Correlation between CA125 and the other 9 tumor markers or age and the 10 tumor markers

The serum levels of CA242, β-HCG, CEA, NSE, Ferritin, and CA153 of patients with epithelial ovarian cancer were positively correlated with the level of CA125, while the other 3 tumor markers were not significantly associated with the level of CA125.

In addition, the correlation analysis between age and the 10 tumor markers showed that the levels of β-HCG, Ferritin, and CA153 in patients with epithelial ovarian cancer were positively correlated with the age of the patients, while the other 7 tumor markers were not significantly associated with the age (all P>0.05, Table 4).

2.5 Comparison of the diagnostic value between individual tumor marker and combined assessments for epithelial ovarian cancer

The sensitivity, negative predictive value, Youden index, and diagnostic efficiency of CA125 alone were higher than those of the other tumor markers alone, and the sensitivity of AFP and HGH alone both were 0 (Table 5). When CA153, CA199, CA242, Ferritin, and CEA were combined with CA125 respectively, the sensitivity of the combined detection was higher than that of CA125 alone. Among them, CA125+CA153+CA199, CA125+CA153+CA242, CA125+Ferritin+CA199, CA125+Ferritin+CA242, CA125+CA153+CEA, CA125+Ferritin+CEA had highest sensitivity, all of which were 90.8%. The sensitivity of CA125+CEA and CA125+Ferritin+CEA was 89.2% and 90.8%, and the diagnostic efficiency both were 84.1%, which was higher than the diagnostic efficiency of other combinations. The Youden index of CA125+CEA was 0.616, which was higher than that of the other combinations (Table 6).

Table 4 Correlation between CA125 and the other 9 tumor marker and correlation between age and the 10 tumor markers in the epithelial ovarian cancer group

Tumor markers	CA125		Age	
	r_s	P	r_s	P
CA242	0.497	<0.001	−0.093	0.461
AFP	−0.058	0.648	0.006	0.959
β-HCG	0.612	<0.001	0.256	0.040
CEA	0.358	0.003	0.237	0.057
CA199	0.141	0.263	−0.074	0.556
NSE	0.680	<0.001	0.093	0.462
Ferritin	0.322	0.009	0.325	0.008
HGH	−0.167	0.184	0.012	0.926
CA153	0.609	<0.001	0.249	0.046
CA125			0.117	0.352

CA242: Carbohydrate antigen 242; AFP: Alpha-fetoprotein; β-HCG: Beta-human chorionic gonadotropin; CEA: Carcinoembryonic antigen; CA199: Cancer antigen 199; NSE: Neuron-specific enolase; HGH: Human growth hormone; CA153: Cancer antigen 153; CA125: Cancer antigen 125. Statistical method was Spearman rank analysis.

Table 5 Diagnostic value of each tumor marker for epithelial ovarian cancer

Tumor markers	Sensitivity/%	Specificity/%	Positive predictive value/%	Negative predictive value/%	Youden index	Diagnostic efficiency/%
CA125	87.7	72.4	87.7	72.4	0.601	83.0
CA242	7.7	79.3	45.5	27.7		29.8
β-HCG	10.8	100.0	100.0	33.3	0.108	38.3
CEA	10.8	93.1	77.8	31.8	0.039	36.2
CA199	23.1	82.8	75.0	32.4	0.059	41.5
NSE	30.8	100.0	100.0	39.2	0.308	52.1
Ferritin	36.9	86.2	85.7	37.9	0.231	52.1
CA153	36.9	89.7	88.9	38.8	0.266	53.2
AFP	0	96.6	0	43.1		29.8
HGH	0	96.6	0	43.1		29.8

CA125: Cancer antigen 125; CA242: Carbohydrate antigen 242; β-HCG: Beta-human chorionic gonadotropin; CEA: Carcinoembryonic antigen; CA199: Cancer antigen 199; NSE: Neuron-specific enolase; CA153: Cancer antigen 153; AFP: Alpha-fetoprotein; HGH: Human growth hormone.

Table 6 Diagnostic value of difference combined detection for epithelial ovarian cancer

Tumor marker	Sensitivity/%	Specificity/%	Positive predictive value/%	Negative predictive value/%	Youden index	Diagnostic efficiency/%
CA125+CA153	89.2	65.5	85.3	73.1	0.547	82.0
CA125+CA199	89.2	69.0	86.6	74.1	0.582	83.0
CA125+CA242	89.2	69.0	86.6	74.1	0.582	83.0
CA125+Ferritin	89.2	69.0	86.6	74.1	0.582	83.0
CA125+CEA	89.2	72.4	87.9	75.0	0.616	84.1
CA125+Ferritin+CA153	89.2	62.1	84.1	72.0	0.513	80.9
CA125+CA153+CA199	90.8	62.1	84.3	75.0	0.529	82.0
CA125+CA153+CA242	90.8	62.1	84.3	75.0	0.529	82.0
CA125+Ferritin+CA199	90.8	65.5	85.5	76.0	0.563	83.0
CA125+Ferritin+CA242	90.8	65.5	85.5	76.0	0.563	83.0
CA125+CEA+CA199	89.2	69.0	86.6	74.1	0.582	83.0
CA125+CEA+CA242	89.2	69.0	86.6	74.1	0.582	83.0
CA125+CA153+CEA	90.8	65.5	85.5	76.0	0.563	83.0
CA125+Ferritin+CEA	90.8	69.0	86.8	76.9	0.598	84.1

CA125: Cancer antigen 125; CA153: Cancer antigen 153; CA199: Cancer antigen 199; CA242: Carbohydrate antigen 242; CEA: Carcinoembryonic antigen.

3 Discussion

Owing to the unique and complex physiological structure of the ovaries themselves, the onset of ovarian cancer is relatively insidious, the early clinical manifestations are not obvious, and there are no specific symptoms, so it is easy to miss the diagnosis or misdiagnosis [10].

The most widely used tumor marker in the diagnosis of ovarian cancer is CA125. CA125, also known as mucin 16, which is a cell surface glycoprotein antigen molecule encoded by the *MUC16* gene on chromosome 19. It is the preferred marker for epithelial ovarian cancer, especially for serous ovarian cancer. The results of this study showed that the median serum level of CA125 in the epithelial ovarian cancer group was much higher than the positive judgment standard, and had significant differences when compared with the serum level of CA125 in the benign ovarian disease group, which indicated that CA125 has high application value in differentiating epithelial ovarian cancer from benign ovarian diseases. The serum level of CA125 can be increased one year before the clinical symptoms appear[11], so it can be used for early screening of ovarian cancer. CA125 can also be used for the diagnosis, efficacy monitoring, prognosis, and the judgment of recurrence [12]. CA125 is elevated in the serum of 65% endometrioid, 40% clear cells, and 12% mucinous ovarian cancer. However, the serum CA125 level is still within the normal range in about 20% of ovarian cancer patients, which raises the concern of the sensitivity of CA125 alone in the diagnosis of ovarian cancer[13]. Of the 65 patients with epithelial ovarian cancer collected in this study, 8 patients had lower serum CA125 levels than the positive criteria, indicating that CA125 is still insufficient in the diagnosis of epithelial ovarian cancer. In addition, CA125 is not only expressed in various benign and malignant tumors derived from mesothelial cells[14], but also expressed in some normal body cavity epithelial tissues such as ovary, fallopian tube, peritoneum, pleura, pericardium, and colon. CA125 increases in many benign diseases such as endometriosis, uterine leiomyoma, pelvic inflammatory disease, kidney disease, heart failure, and about 1% of healthy women and some early pregnancy women. Inflammation, tuberculosis, and many other factors also affect the serum level of CA125[15], which led to the low specificity. In this study, the sensitivity, specificity, and diagnostic efficiency of CA125 in the diagnosis of epithelial ovarian cancer were 87.7%,

72.4%, and 83.0%, respectively, the results of the other 9 markers alone showed that CA125 has a good diagnostic value for epithelial ovarian cancer. Combined detection of tumor markers is often used to solve these limitations[9]. Many studies[8, 16-17] have suggested that the combination of CA125 and HE4 is an efficient biological diagnostic tool to diagnose ovarian cancer, the ROC AUC is high, varying from 0.91 (95% *CI* 86.70−96.00) to 0.96 (95% *CI* 0.93−1.00).

As a unique kind of acidic protease to neurons and neuroendocrine cells, NSE is a valuable tumor marker of decarboxylated cells. Its main function is to convert glycerol diphosphate into enol phosphate, which can reflect cell renewal and apoptosis[18]. When the transferred tumor cells invade the nerve cells, the cell membrane is destroyed, then NSE is released from the cells into the peripheral blood, so the level of NSE in the serum can reflect the degree of the nerve's damage. Study[19] has found that there are also neuroendocrine cells in epithelial ovarian cancer, especially mucinous and serous ovarian cancer. Neuroendocrine cells appear in the epithelial-stromal tumor of the ovary means the tumor is more invasive[20]. In addition, the differentiation degree of the neuroendocrine cells is enhanced with the degree of malignancy and clinical stage of epithelial ovarian cancer, and neuroendocrine proliferates with the proliferation of epithelial ovarian cancer cells[21]. According to FIGO stage of ovarian cancer, in stage I-II, the tumor is confined to the ovary, occasionally accompanied by pelvic cavity diffusion. In stage III-IV, tumor cells are further proliferated and spread, accompanied by distant metastasis, such as pelvic external peritoneal implantation, lymph node metastasis, liver, and the other organ metastasis[22]. The results of this study showed that the level of NSE in the serum of patients with epithelial ovarian cancer was related to the clinical stage, the positive rate of NSE in patients with stage III-IV was significantly higher than that in patients with stage I-II. That probably due to the proliferation and spread of tumor cells in stage III-IV, which lead the neuroendocrine cells to proliferate and secrete higher NSE, but the clearly mechanism remains to be further studied.

Correlation analysis between tumor markers and factors related to ovarian cancer showed that the serum level of β-HCG in patients with epithelial ovarian cancer was related to the number of pregnancies. As the number of pregnancies increased, the serum level of β-HCG in patients with epithelial ovarian cancer also increase. β-HCG has important application value and can be used for the diagnosis of early pregnancy, ectopic pregnancy, abortion, and the prediction of pregnancy outcome. However, the relationship between the serum level of β-HCG and the number of pregnancies in cancer patients have not been studied. This study also showed that the serum level of CA153 was related to the patient's menstrual cycle. In patients with menstrual cycle ≥30 d, the serum level of CA153 was higher than that of menstrual cycle <30 d. The serum level of CA199 was related to the patient's menstrual years, with the prolongation of the patient's menstrual years, the serum level of CA199 was increased. Menstrual cycle and menstrual years both are related factors of ovarian cancer which are related to female ovulation. At present, the correlation between CA153 and CA199 and the above factors has not been found.

In epithelial ovarian cancer, β-HCG, CA153, and NSE levels have a certain degree. The results of this study showed that the serum levels of these 3 tumor markers were significantly different between the epithelial ovarian cancer group and the ovarian benign disease group. In addition, the serum levels of β-HCG, Ferritin, and CA153 were positively correlated with the age of patients with epithelial ovarian cancer. In the correlation study, it was found that the serum levels of CA242, β-HCG, CEA, NSE, Ferritin, and CA153 of patients with epithelial ovarian cancer were positively correlated with CA125, indicating that they can be used for combined detection to improve the detection rate of epithelial ovarian cancer. The multi-tumor markers protein chip detection system can simultaneously detect various tumor markers in serum, combined detection of markers can improve the diagnostic value. This study showed that the sensitivity of the combination of other tumor markers with CA125 was higher than that of CA125 alone, indicating that the combined detection of 2 or more tumor markers can improve sensitivity. Among them, the sensitivity and the Youden index of the combination of CA125, Ferritin, and CEA were the highest. The combination of CA125+CEA and the combination of CA125+Ferritin+CEA had the highest diagnostic efficiency, which was up to 84.1%. These

combinations have a significant advantage in the detection of epithelial ovarian cancer compared with the separate detection, and can improve the detection and diagnosis rate of ovarian cancer. Therefore, CA125+CEA and CA125+Ferritin+CEA may be used as a new combination of detection for early screening and the diagnosis of epithelial ovarian cancer.

This study has some limitations. First, there are inadequate clinical samples, which cann't reflect the overall situation comprehensively. In addition, the pathological types in the epithelial ovarian cancer group are mainly serous, and there are not enough patients with other pathological types; the relationship between each tumor marker and different pathological types have not been explored. Second, For the detection of tumor marker, the multi-tumor marker protein chip technology is used, and the detection technology itself has certain limitations. Last, the conclusions made in this study that the serum level of β-HCG is related to the number of pregnancies, the level of CA153 is related to patient's menstrual cycle and the level of CA199 is related to patient's menstrual years, have not been reported previously, and no reasonable explanation has been made in this study, so it remains to be further explored.

With the application of new diagnostic techniques such as liquid biopsy[23] and new biomarkers of ovarian cancer such as miRNA[24], the detection rate of ovarian cancer is gradually increasing. However, to explore the levels and the clinical significance of known tumor markers is equally important.

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References

[1] Lheureux S, Gourley C, Vergote I, et al. Epithelial ovarian cancer[J]. Lancet, 2019, 393(10177): 1240-1253. https://doi.org/10.1016/S0140-6736(18)32552-

[2] Colombo N, Sessa C, Bois AD, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease[J]. Int J Gynecol Cancer, 2019: ijgc-2019-000308. https://doi.org/10.1136/ijgc-2019-000308.

[3] Troisi R, Bjørge T, Gissler M, et al. The role of pregnancy, perinatal factors and hormones in maternal cancer risk: a review of the evidence[J]. J Intern Med, 2018, 283(5): 430-445. https://doi.org/10.1111/joim.12747.

[4] Phung MT, Muthukumar A, Trabert B, et al. Effects of risk factors for ovarian cancer in women with and without endometriosis[J]. Fertil Steril, 2022, 118(5): 960-969. https://doi.org/10.1016/j.fertnstert.2022.07.019.

[5] Tanha K, Mottaghi A, Nojomi M, et al. Investigation on factors associated with ovarian cancer: an umbrella review of systematic review and meta-analyses[J]. J Ovarian Res, 2021, 14(1): 153. https://doi.org/10.1186/s13048-021-00911-z.

[6] Kim SJ, Lubinski J, Huzarski T, et al. Weight gain and the risk of ovarian cancer in *BRCA1* and *BRCA2* mutation carriers[J]. Cancer Epidemiol Biomarkers Prev, 2021, 30(11): 2038-2043. https://doi.org/10.1158/1055-9965.EPI-21-0296.

[7] Nebgen DR, Lu KH, Jr Bast RC. Novel approaches to ovarian cancer screening[J]. Curr Oncol Rep, 2019, 21(8): 75. https://doi.org/10.1007/s11912-019-0816-0.

[8] Dochez V, Caillon H, Vaucel E, et al. Biomarkers and algorithms for diagnosis of ovarian cancer: CA125, HE4, RMI and ROMA, a review[J]. J Ovarian Res, 2019, 12(1): 28. https://doi.org/10.1186/s13048-019-0503-7.

[9] Zhang MH, Cheng SS, Jin Y, et al. Roles of CA125 in diagnosis, prediction, and oncogenesis of ovarian cancer[J]. Biochim Biophys Acta Rev Cancer, 2021, 1875(2): 188503. https://doi.org/10.1016/j.bbcan.2021.188503.

[10] Lheureux S, Braunstein M, Oza AM. Epithelial ovarian cancer: evolution of management in the era of precision medicine[J]. CA Cancer J Clin, 2019, 69(4): 280-304. https://doi. org/10.3322/caac.21559.

[11] Zhang RQ, Siu MKY, Ngan HYS, et al. Molecular biomarkers for the early detection of ovarian cancer[J]. Int J Mol Sci, 2022, 23(19): 12041. https://doi.org/10.3390/ijms231912041.

[12] Ali FT, Soliman RM, Hassan NS, et al. Sensitivity and specificity of microRNA-204, CA125, and CA19.9 as biomarkers for diagnosis of ovarian cancer[J/OL]. PLoS One, 2022, 17(8): e0272308[2022-12-11]. https://doi. org/10.1371/journal.pone.0272308.

[13] Nowak M, Janas Ł, Stachowiak G, et al. Current clinical application of serum biomarkers to detect ovarian cancer[J]. Pm, 2015, 4: 254-259. https://doi.org/10.5114/pm.2015.55887.

[14] Funston G, Hamilton W, Abel G, et al. The diagnostic performance of CA125 for the detection of ovarian and non-ovarian cancer in primary care: a population-based cohort study [J/OL]. PLoS Med, 2020, 17(10): e1003295[2022-12-21]. https://doi.org/10.1371/journal.pmed.1003295.

[15] Lin HX, Ni L. Diagnostic utility of LDH, CA125 and CYFRA21-1 in tuberculosis pleural effusion[J]. Med Clin,

2022, 158(2): 70-72. https://doi. org/10.1016/j. medcli. 2020. 10.017.

[16] Chen X, Zhou H, Chen R, et al. Development of a multimarker assay for differential diagnosis of benign and malignant pelvic masses[J]. Clin Chim Acta. 2014, 440: 57-63. https://doi. org/10.1016/j.cca.2014.11.013.

[17] Moore RG, Brown AK, Miller MC, et al. The use of multiple novel tumor biomarkers for the detection of ovarian carcinoma in patients with a pelvic mass[J]. Gynecol Oncol, 2008, 108(2): 402-408. https://doi.org/10.1016/j.ygyno.2007.10.017.

[18] Zhang M, Yan L, Lippi G, et al. Pleural biomarkers in diagnostics of malignant pleural effusion: a narrative review[J]. Transl Lung Cancer Res, 2021, 10(3): 1557-1570. https://doi. org/10.21037/tlcr-20-1111.

[19] Virarkar M, Vulasala SS, Morani AC, et al. Neuroendocrine neoplasms of the gynecologic tract[J]. Cancers, 2022, 14(7): 1835. https://doi.org/10.3390/cancers14071835.

[20] Shih AJ, Menzin A, Whyte J, et al. Identification of grade and origin specific cell populations in serous epithelial ovarian cancer by single cell RNA-seq[J/OL]. PLoS One, 2018, 13(11): e0206785[2022-12-18]. https://doi. org/10.1371/journal. pone. 0206785.

[21] Jiang LY. Study on the distribution and partial effect of neuroendocrine cells in ovarian epithelial tumors [D]. Jinan: Jinan University, 2006.

[22] Kehoe S. FIGO staging in ovarian carcinoma and histological subtypes[J/OL]. J Gynecol Oncol, 2020, 31(4): e70[2022-12-15]. https://doi.org/10.3802/jgo.2020.31.e70.

[23] Giannopoulou L, Zavridou M, Kasimir-Bauer S, et al. Liquid biopsy in ovarian cancer: the potential of circulating miRNAs and exosomes[J]. Transl Res, 2019, 205: 77-91. https://doi.org/10.1016/j.trsl.2018.10.003.

[24] Yoshida K, Yokoi A, Kato T, et al. The clinical impact of intra- and extracellular miRNAs in ovarian cancer[J]. Cancer Sci, 2020, 111(10): 3435-3444. https://doi.org/10.1111/cas.14599.

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