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ORIGINAL RESEARCH

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Diagnostic value of transvaginal ultrasound combined with serum CA125 and HE4 in differentiating benign and malignant ovarian tumors

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Abstract

Background: This study aimed to evaluate the diagnostic value of transvaginal ultrasound combined with the serum carbohydrate antigen125 (CA125) and Human Epididymis Protein 4 (HE4) in distinguishing benign from malignant ovarian tumors. **Methods**: The data of 140 patients with ovarian tumors were retrospectively analyzed. According to the histopathological diagnosis divided into benign group (109 cases) and malignant group (31 cases). Clinical data, serum biomarkers and transvaginal ultrasound were collected. Multivariate logistic regression and receiver operating characteristic (ROC) curve were used to analyze the diagnostic value of each parameter. **Results**: No significant differences in body mass index (BMI) or history of abortion between the two groups ($p > 0.05$). The proportion of postmenopausal patients was significantly higher in malignant group than benign group ($p < 0.05$). The pulsatility index (PI) and systolic-to-diastolic ratio (S/D) were significantly lower in the benign group than malignant group ($p < 0.05$), the resistance index (RI) was lower in the benign group but did not reach statistical significance ($p > 0.05$). Serum CA125 and HE4 levels were significantly higher in the malignant group than benign group ($p < 0.05$). Multivariate logistic regression analysis showed that RI, PI, S/D, CA125 and HE4 were independent influencing factors for benign and malignant diagnosis of ovarian tumors ($p < 0.05$). ROC showed that RI, PI, S/D, CA125 and HE4 had diagnostic value, and the area under the curve (AUC) was 0.588, 0.643, 0.698, 0.735 and 0.711, respectively. The diagnostic accuracy of the above combination was the highest, with an AUC of 0.856. **Conclusions**: The diagnosis of benign and malignant ovarian tumors by transvaginal ultrasound is limited, and the detection of serum markers is not high. Transvaginal ultrasound combined with CA125 and HE4 can significantly improve the accuracy of diagnosis, and has high clinical application value.

Keywords

Transvaginal ultrasound; Ovarian tumor; Serum biomarkers

1. Introduction

Ovarian tumors primarily originate from epithelial tissue, germ cells and sex cord-stromal cells and are among the most common diseases affecting the female reproductive system. These tumors often develop insidiously and exhibit diverse anatomical locations, making early detection challenging [1]. Cystadenocarcinoma and cystadenoma, which arise from epithelial tissue, are among the most frequently encountered malignant and benign ovarian tumors in gynecological practice, respectively [2]. Due to the absence of distinct early clinical symptoms, ovarian tumors are often diagnosed at an advanced stage, resulting in poor prognosis and low survival rates [3]. Thus, early detection and timely intervention are crucial for improving patient outcomes and optimizing treatment strategies.

Ultrasound is widely used for the evaluation of pelvic masses, as it provides a clear depiction of pelvic organ morphology [4]. In particular, transvaginal ultrasound enables detailed visualization of ovarian structures, facilitating the assessment of abnormal echogenic masses. The size, shape, location, echogenic characteristics and blood flow patterns of ovarian masses can be analyzed to distinguish between benign and malignant tumors. Typically, benign tumors exhibit slow growth, well-defined margins, smooth surfaces and limited vascularization, while malignant tumors tend to be aggressive, rapidly growing, and associated with irregular margins, restricted mobility, abundant vascularization, and occasional calcifications.

Doppler ultrasound parameters, including the resistance index (RI) and pulsatility index (PI), provide insight into tumor vascularity and hemodynamics. Malignant tumors, characterized by extensive neovascularization and arteriovenous

shunting, generally exhibit lower RI and PI values due to reduced vascular resistance. In contrast, benign tumors usually demonstrate higher RI and PI values. The systolic-to-diastolic ratio (S/D) also provides information on tumor perfusion, and although its standalone diagnostic utility is limited, its combination with RI and PI enhances the accuracy of differentiating ovarian tumors.

The accuracy of differentiating benign from malignant ovarian tumors can be further improved by combining transvaginal ultrasound with serum tumor marker detection. For instance, carbohydrate antigen 125 (CA125) is a widely used biomarker in clinical practice for ovarian cancer, and its elevation has been significantly associated with epithelial ovarian cancer, making it valuable for both diagnosis and recurrence monitoring in early-stage ovarian cancer. Additionally, CA125 serves as a useful marker for assessing treatment response, as changes in its levels can indicate tumor progression or remission. However, an elevated CA125 level does not necessarily indicate malignancy, as it can also be mildly increased in various benign conditions, including ovarian cysts, uterine fibroids, endometriosis and pelvic inflammatory disease. The human epididymis protein 4 (HE4) has been recently proposed as a promising tumor marker due to its high specificity for ovarian cancer. Compared with CA125, HE4 demonstrates superior sensitivity and specificity in distinguishing benign from malignant ovarian tumors, with an increase in HE4 levels often associated with a higher risk of malignancy, making it a valuable diagnostic tool. When ovarian cancer is suspected, clinicians frequently measure HE4 alongside CA125 to improve diagnostic accuracy. Thus, frequent monitoring of HE4 levels allows for better assessment of tumor characteristics and treatment effectiveness, contributing significantly to the early detection of ovarian cancer [5].

Based on these considerations, we designed this present study to evaluate the diagnostic value of transvaginal ultrasound combined with serum markers in differentiating benign and malignant ovarian tumors.

2. Methods and materials

2.1 Clinical data

This study initially identified 146 patients diagnosed with ovarian tumors and treated at our hospital between July 2022 and May 2024. Based on the exclusion criteria, four patients with a history of chemoradiation or chemotherapy and two patients with no history of sexual activity were excluded. Therefore, 140 patients met the inclusion criteria and were categorized into a benign group (109 cases) and a malignant group (31 cases) based on pathological results. This study was approved by the hospital's Ethics Committee, and written informed consent was obtained from all patients and their families.

Patients were included in this study if they had (1) ovarian tumors confirmed as benign or malignant through pathological examination, (2) no prior history of radiotherapy or chemotherapy, (3) a history of sexual activity, and (4) complete clinical data for analysis. Patients were excluded if they had coagulation disorders, a diagnosis of other malignant tumors, or any form of organ dysfunction. Individuals with cardiovascular or cerebrovascular diseases were also excluded. Furthermore, pregnant or lactating patients were not eligible for participation in the study.

2.2 Assessments

2.2.1 Transvaginal ultrasonography

Color Doppler ultrasonography (Philips, Den Haag, Netherlands, Model: CX50) was used to assess ovarian blood flow parameters. After having emptied their bladder, the patients were positioned in the lithotomy position, and a transvaginal ultrasound examination was performed using a Doppler probe with a frequency of 7.5 MHz. The probe was covered with a sterile sleeve and inserted vaginally. The instrument capacity was set to 15 mm^3, and the parameters measured included peak systolic velocity (S), low diastolic velocity (D), PI, RI and the S/D. Each parameter was measured three times per patient, and the average value was recorded.

2.2.2 Serum levels

A 5 mL sample of fasting venous blood was collected from each patient, centrifuged at 3000 rpm for 10 minutes, and the serum was stored at −80 °C. The levels of CA125 were determined using chemiluminescence analysis, while HE4 levels were measured using enzyme-linked immunosorbent assay (ELISA), following the manufacturer's instructions.

2.3 Statistical analysis

Data were analyzed using the SPSS 22.0 software (IBM, Armonk, NY, USA). Outliers were removed, and missing values were imputed using the median method. Normally distributed continuous variables are expressed as mean ± standard deviation ($\bar{x} \pm s$) and analyzed using the Student's *t*-test. Categorical variables are expressed as rates and analyzed using the χ^2 test. Logistic regression analysis was performed to identify risk factors associated with benign and malignant ovarian tumors. The diagnostic performance of the parameters was assessed using receiver operating characteristic (ROC) curve analysis. Multiple comparisons were conducted using the least significant difference (LSD) method, with Bonferroni correction applied where necessary. Non-normally distributed data were analyzed using non-parametric tests, and multiple regression analysis was performed to control for confounding factors. A *p*-value of < 0.05 was considered statistically significant.

3. Results

3.1 Comparison of general data

There were no significant differences in body mass index (BMI) or history of abortion between the benign and malignant groups ($p > 0.05$). However, the proportion of postmenopausal patients was significantly higher in the malignant group compared to the benign group ($p < 0.05$), indicating a potential association between menopause and malignancy. The detailed comparisons of general patient characteristics are presented in Table 1.

TABLE 1. Comparison of the patients' baseline characteristics ($\bar{x} \pm s$).

Variables	Benign group (n = 109)	Malignant group (n = 31)	t/χ^2	p
BMI (kg/m^2)	22.14 ± 3.04	22.80 ± 3.38	0.987	0.329
Menopausal or not				
Yes	47 (43.12)	25 (80.65)	13.606	<0.001
No	62 (56.88)	6 (19.35)		
History of abortion				
Yes	18 (17.31)	7 (22.58)	0.606	0.436
No	91 (87.50)	24 (77.42)		

Note: BMI, Body Mass Index.

3.2 Ultrasonic indicators

The PI and S/D values were significantly lower in the benign group compared to the malignant group ($p < 0.05$), and although RI was numerically lower in the benign group, the difference was not statistically significant ($p > 0.05$). These findings suggest that PI and S/D may be useful parameters for distinguishing benign from malignant ovarian tumors, whereas RI alone may have limited diagnostic value. The detailed comparisons of ultrasonic indicators are presented in Table 2 and Fig. 1.

3.3 Serum indexes

Serum levels of CA125 and HE4 were significantly higher in the malignant group compared to the benign group ($p < 0.05$). The detailed comparison of serum markers between the two groups is presented in Table 3 and Fig. 2.

3.4 Multivariate logistic analysis of the benign and malignant factors of ovarian tumors

Multivariate logistic regression analysis revealed that the ultrasound parameters PI and S/D, along with the serum biomarkers CA125 and HE4, were significant factors associated with the differentiation of benign and malignant ovarian tumors ($p < 0.05$). Although RI showed an increasing trend, it did not reach statistical significance ($p = 0.157$) (Table 4), suggesting that combining ultrasound and serum markers may enhance diagnostic accuracy.

3.5 ROC curve analysis for the diagnosis of benign and malignant ovarian tumors

ROC curve analysis demonstrated that RI, PI, S/D, CA125 and HE4 each had a certain degree of diagnostic value in differentiating benign from malignant ovarian tumors, with the corresponding AUC being 0.588, 0.643, 0.698, 0.735 and 0.711, respectively. When these parameters were combined, the diagnostic accuracy significantly improved, yielding an AUC of 0.856. Fig. 3 and Table 5 illustrate the ROC curves for the different diagnostic indicators.

4. Discussion

Ovarian cancer is one of the most common gynecological malignancies and is associated with high mortality and poor postoperative survival rates [6]. In its early stages, tumor lesions are typically small and lack distinct characteristics, making early detection difficult. Consequently, many cases are diagnosed at advanced stages, by which time optimal treatment opportunities may have been missed [7]. Therefore, early detection and timely intervention are crucial for improving prognosis and increasing survival rates.

Transvaginal ultrasound is a widely used imaging modality for the preliminary assessment and monitoring of ovarian lesions. It provides valuable information on tumor size, shape and blood flow, aiding in the differentiation between benign and malignant tumors. However, its diagnostic accuracy is influenced by the expertise of the sonographer and the clinical judgment of the physician, introducing variability in results [8]. Serum biomarkers such as CA125 may exhibit early elevation in ovarian cancer, offering a complementary approach for early diagnosis. Regular monitoring of serum marker levels can facilitate the tracking of disease progression

TABLE 2. Comparison of the ultrasound-related indicators.

Group	n	RI	PI	S/D
Benign group	109	0.48 ± 0.19	0.56 ± 0.20	1.68 ± 0.37
Malignant group	31	0.52 ± 0.11	0.70 ± 0.25	2.06 ± 0.65
t		−1.809	−2.817	−3.176
p		0.074	0.007	0.003

Note: RI, Resistance Index; PI, Perfusion Index; S/D, Systolic Peak Velocity/Ovarian Diastolic Low Velocity.

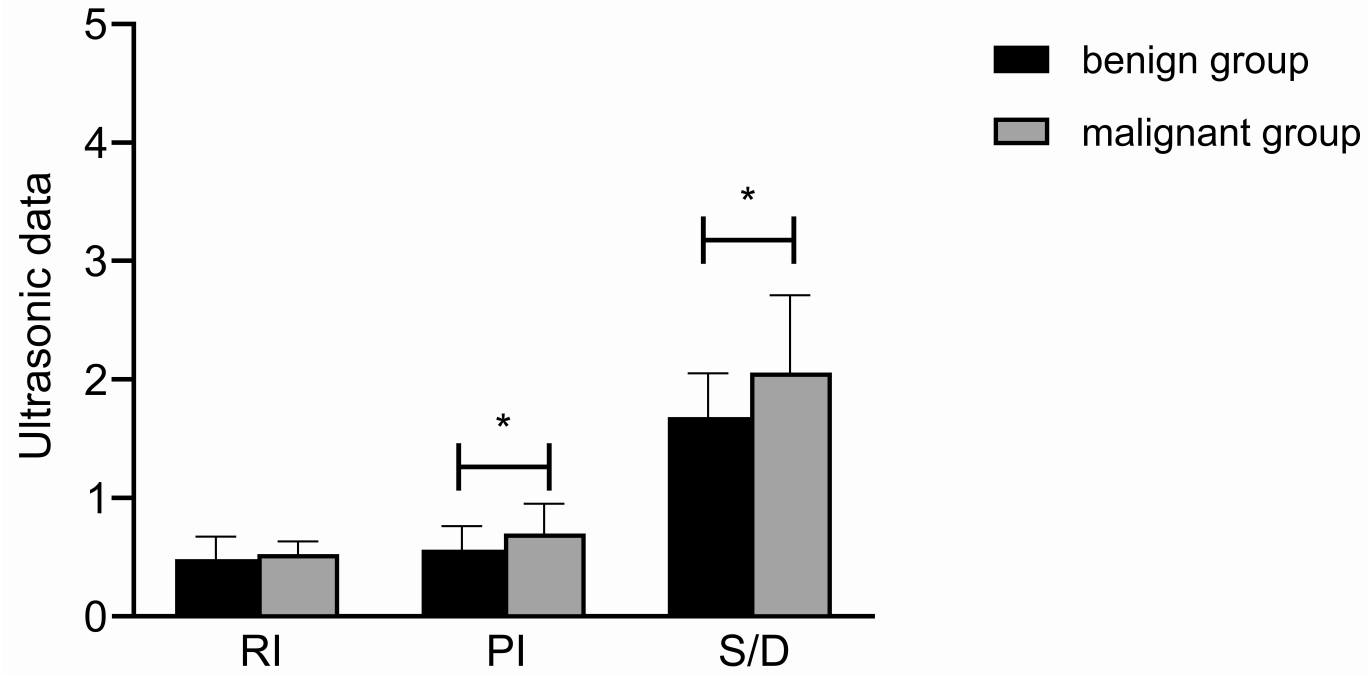

FIGURE 1. Comparison of the ultrasonic indexes. *$p < 0.05$. RI, Resistance Index; PI, Perfusion Index; S/D, Systolic Peak Velocity/Ovarian Diastolic Low Velocity.

TABLE 3. Comparison of serum indexes between the study groups.

Groups	n	CA125 (U/mL)	HE4 (pmol/L)
Benign group	109	285.19 ± 48.16	227.05 ± 42.80
Malignant group	31	330.23 ± 47.19	285.89 ± 100.06
t		−4.667	−3.192
p		<0.001	<0.001

Note: CA125, Carbohydrate Antigen 125; HE4, Human Epididymis Protein 4.

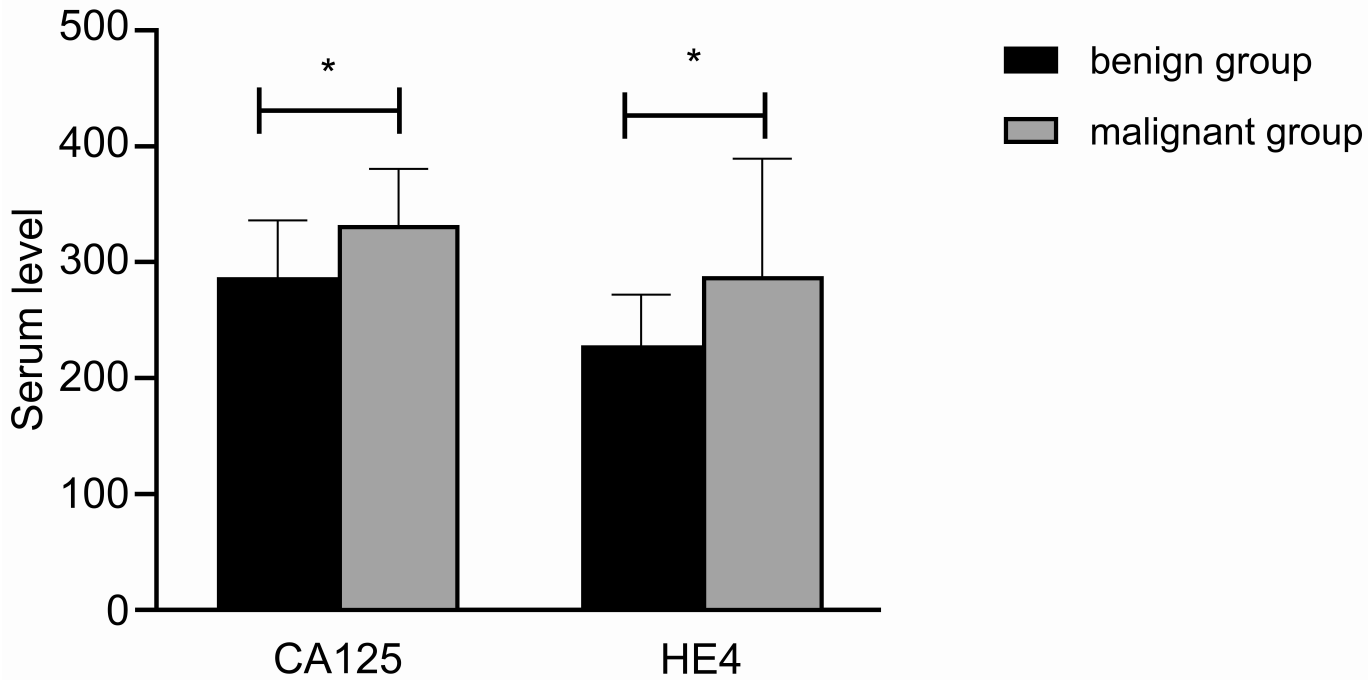

FIGURE 2. Barchart showing the difference in serum indexes between the two groups. *$p < 0.05$. CA125, Carbohydrate Antigen 125; HE4, Human Epididymis Protein 4.

TABLE 4. Multivariate logistic regression analysis of factors associated with benign and malignant ovarian tumors.

Index	b	S.E.	Wald	*p*	OR	95% CI for OR
RI	2.294	1.622	2.002	0.157	9.918	0.413–238.065
PI	2.576	1.248	4.260	0.039	12.147	1.139–151.795
S/D	1.186	0.581	4.170	0.041	3.273	1.049–10.212
CA125	0.022	0.006	12.927	<0.001	1.022	1.010–1.034
HE4	0.014	0.004	9.144	0.002	1.014	1.005–1.023

Note: RI, Resistance Index; PI, Perfusion Index; S/D, Systolic Peak Velocity/Ovarian Diastolic Low Velocity; CA125, Carbohydrate Antigen 125; HE4, Human Epididymis Protein 4; b, regression coefficient; S.E., Standard Error; OR, odds ratio; CI, Confidence Intervals.

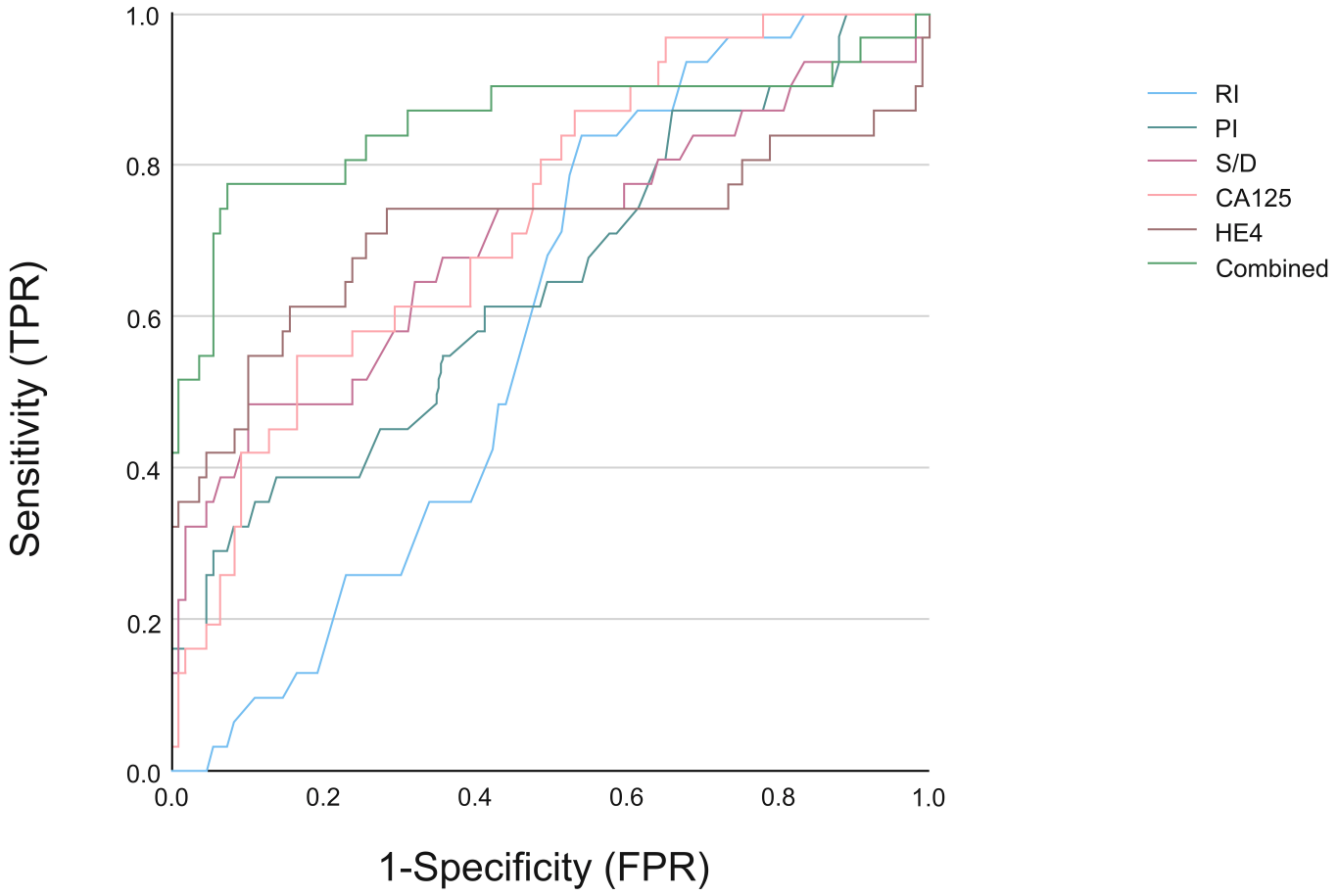

FIGURE 3. ROC curve analysis for the diagnosis of benign and malignant ovarian tumors using ultrasonic parameters and serum biomarkers. RI, Resistance Index; PI, Perfusion Index; S/D, Systolic Peak Velocity/Ovarian Diastolic Low Velocity; CA125, Carbohydrate Antigen 125; HE4, Human Epididymis Protein 4; TPR, True Positive Rate; FPR, False Positive Rate.

TABLE 5. ROC analysis data of the individual and combined ultrasonic parameters and serum biomarkers.

Index	AUC	95% CI
RI	0.588	0.491–0.685
PI	0.643	0.527–0.759
S/D	0.698	0.578–0.818
CA125 (U/mL)	0.735	0.639–0.831
HE4 (pmol/L)	0.711	0.576–0.846
Combined	0.856	0.756–0.956

RI, Resistance Index; PI, Perfusion Index; S/D, Systolic Peak Velocity/Ovarian Diastolic Low Velocity; CA125, Carbohydrate Antigen 125; HE4, Human Epididymis Protein 4; AUC, areas under the curve; CI, confidence interval.

and treatment response in patients with ovarian tumors [9]. When combined with clinical symptoms and other diagnostic tools, serum biomarker analysis enhances the accuracy of tumor characterization. Non-invasive prenatal testing can provide accurate assessment of the fetal health status, and by collecting the peripheral blood of the pregnant woman, using advanced molecular biology techniques to isolate the free DNA fragments of the fetus from the maternal blood and conducting high-throughput sequencing and bioinformatics analysis, the risk of fetal chromosomal abnormalities such as Trisomy 21 (Down syndrome), Trisomy 18, and Trisomy 13 can be evaluated. These diseases may lead to severe intellectual disability and physical development retardation, and the birth of such infants could lead to a huge burden on families and society. Non-invasive prenatal testing has been shown to be effective and safe. Compared with traditional invasive testing methods such as amniocentesis or chorionic biopsy, non-invasive prenatal testing does not require puncture operations; instead, it only requires the extraction of the pregnant woman's peripheral blood, thereby significantly reducing the risks to the pregnant woman and the fetus. This is particularly important for pregnant women in the early stage of pregnancy, as the conditions of the fetus and the mother can easily become unstable, leading to unexpected complications. In addition, non-invasive prenatal testing can also reduce the anxiety and stress of pregnant women. As pregnancy may be considered an important stage in life, pregnant women often worry about the health of the fetus. Through non-invasive prenatal testing, pregnant women can better understand the health status of the fetus, thereby reducing unnecessary worries and stress and helping to maintain a good mental state and emotional state. However, it should be noted that despite its advantages, transvaginal ultrasound has some limitations in distinguishing benign from malignant ovarian masses, as its accuracy is largely dependent on the clinician's experience, which can contribute to false-positive and false-negative results. Similarly, CA125 has limited specificity and sensitivity in early ovarian cancer detection, as elevated levels can also be observed in various benign gynecological conditions, increasing the risk of misdiagnosis or missed diagnosis. On the other hand, HE4 has emerged as a novel biomarker for ovarian cancer, demonstrating significantly increased expression in both ovarian cancer tissues and serum. Compared to CA125, HE4 offers higher sensitivity and specificity. More importantly, the combined use of HE4 and CA125 has been shown to enhance diagnostic accuracy, reduce the likelihood of missed diagnoses, and improve the reliability of early ovarian cancer detection. Thus, integrating transvaginal ultrasound with CA125 and HE4 detection provides a comprehensive diagnostic strategy that maximizes the strengths of each modality. For instance, transvaginal ultrasound allows for clear visualization of ovarian structures and surrounding tissues, facilitating mass detection and preliminary classification, and the simultaneous assessment of serum levels of CA125 and HE4 provides additional information on tumor biology, which enhances the differentiation between benign and malignant tumors and improves the overall diagnostic accuracy and clinical utility of ovarian cancer screening.

Ultrasound examination is a non-invasive and repeatable imaging technique that allows for the direct visualization of ovarian morphology and structure by transvaginal access [10]. It enables the assessment of tumor-associated blood flow, providing essential diagnostic information for differentiating between benign and malignant ovarian tumors [11]. In this study, the RI, PI and S/D values were significantly lower in the benign group than in the malignant group ($p < 0.05$), with respective AUC for diagnosing ovarian malignancy of 0.588, 0.643 and 0.698. It has been previously reported that RI, PI and S/D values are significantly lower in patients with stage I–II ovarian malignancies than in those with stage III–IV disease, suggesting that vascular characteristics change as the tumor progresses [12]. Ultrasound can effectively show blood flow velocity and vascular distribution around ovarian tumors, as malignant tumors are characterized by the formation of new blood vessels, a dense vascular network in the peritumoral region, and vascular penetration into the tumor mass [13]. However, some studies have reported conflicting results, indicating that benign ovarian tumors may also present with irregular blood flow patterns, reducing the accuracy of ultrasound-based differentiation between benign and malignant tumors [14]. Additionally, the diagnostic reliability of ultrasound can be affected by factors such as ultrasound intensity and intestinal gas interference, which may obscure tumor imaging and lead to misdiagnosis or missed diagnosis [15]. Serum tumor markers also play a crucial role in distinguishing between benign and malignant ovarian tumors. CA125, a high-molecular-weight glycoprotein, is highly expressed in ovarian malignancies and has been widely used for clinical ovarian cancer screening. HE4, a secreted low-molecular-weight protein, is easily detected in peripheral blood and has been shown to improve the specificity of ovarian cancer diagnosis. CA125 is involved in cytokine-mediated cell proliferation and apoptosis, contributing to tumor progression [16]. In this study, CA125 and HE4 levels were found to be significantly higher in the malignant group than in the benign group ($p < 0.05$), with AUC values of 0.735 and 0.711, respectively, which might have been related to the abnormal proliferation, infiltration and metastasis of ovarian cancer cells, as these disrupt normal epithelial cell function and secretion, leading to increased secretion of CA125. Compared to benign tumors, malignant tumors exhibit rapid growth and increased vascularization, which is driven by tumor-secreted angiogenic factors that stimulate endothelial cell proliferation and differentiation. The formation of new blood vessels further reduces vascular resistance, contributing to changes in Doppler ultrasound indices. Overall, the variability of CA125, PI and RI levels is influenced by tumor-associated blood flow and vascular resistance, which can affect diagnostic interpretations [17].

The findings of this study indicate that combining transvaginal ultrasound with serum CA125 and HE4 significantly enhances the diagnostic accuracy of ovarian tumors, as the AUC of the combined approach was higher than that of each individual parameter. Although CA125 is a valuable biomarker for ovarian cancer, its clinical utility is limited by its elevation in non-malignant conditions such as pregnancy, lung cancer, pelvic inflammatory disease, and endometriosis. Similarly, the sensitivity of transvaginal ultrasound is affected by factors

such as intestinal gas, abdominal wall fat thickness, and the presence of pelvic masses, which may compromise its diagnostic accuracy. Therefore, the combined assessment of these diagnostic modalities maximizes their respective strengths, leading to improved detection efficiency and enhanced diagnostic reliability in differentiating benign from malignant ovarian tumors.

5. Conclusions

As an imaging examination method, transvaginal ultrasound can clearly show the size, shape, location and relationship with surrounding tissues of ovarian tumors. Benign tumors mostly appeared as cystic masses with clear boundaries and regular shapes under ultrasound, while malignant tumors may appear as cystic or solid masses with unclear boundaries and irregular shapes. However, transvaginal ultrasound still has some limitations in the diagnosis of benign and malignant tumors, and it needs to be combined with other examination methods for comprehensive judgment. As tumor markers, serum CA125 and HE4 are of great significance in the diagnosis of ovarian tumors. CA125 is often elevated in patients with ovarian cancer, but it may also be elevated in some benign diseases such as endometriosis and pelvic inflammatory disease. HE4 is a novel biomarker with high sensitivity and specificity for ovarian cancer. Combined detection of CA125 and HE4 can make up for the deficiency of single marker and improve the accuracy of diagnosis. The combination of transvaginal ultrasound with serum CA125 and HE4 can further improve the diagnostic accuracy of benign and malignant ovarian tumors. This combined detection method is able to integrate the information of imaging and tumor markers to more comprehensively evaluate the nature of the tumor. It is helpful for doctors to make more reasonable treatment plans and improve the survival rate and quality of life of patients.

In summary, the combination of transvaginal ultrasound and serum biomarkers significantly enhances the diagnostic accuracy for differentiating benign and malignant ovarian tumors.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

XXL, YH—designed the study and carried them out; analyzed the data; prepared the manuscript for publication and reviewed the draft of the manuscript. XXL—supervised the data collection; interpreted the data. Both authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of General Hospital of Northern Theater Command (Approval no. Y2024(164)). Written informed consent was obtained from a legally authorized representative for anonymized patient information to be published in this article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Castillo Simón AG, Martínez Ramos CV, Rodríguez Morales VV, Núñez Arana B, Dominguez Prado I, Muñoz Iglesias JL. Follicular thyroid carcinoma arising in a struma ovarii and femoral metastasis. Revista Española de Medicina Nuclear e Imagen Molecular. 2022; 41: 325–326.

[2] Cheng CC, Ting A, Chang, Yang WP. First case report of papillary thyroid carcinoma arising within a functional teratoma in Graves' disease patient. Gynecological Endocrinology. 2021; 37: 955–958.

[3] Donato S, Simões H, Leite V. Malignant struma ovarii with concurrent thyroid cancer: outcomes during and after pregnancy. European Thyroid Journal. 2021; 10: 523–527.

[4] Leite C, Rodrigues P, Oliveira SL, Martins NN, Martins FN. Struma ovarii in bilateral ovarian teratoma-case report and literature review. Journal of Surgical Case Reports. 2021; 2021: rjab028.

[5] Leuștean L, Ungureanu MC, Preda C, Bilha SC, Obrocea F, Dănilă R, *et al*. Management of malignant struma ovarii: is aggressive therapy justified? Case report and literature review. Thyroid Research. 2022; 15: 14.

[6] Prentice J, Panter K, Attygalle A, Ind T, Prentice M. Pure T3 thyrotoxicosis from a Struma Ovarii characterised by a paradoxical rise in thyroxine on treatment. Endocrinology, Diabetes & Metabolism Case Reports. 2020; 2020: 19-0097.

[7] Rahma A, Mardiyana L, Fauziah D. Malignant struma ovarii: case report of an unusual ovarian tumor with CT imaging. Radiology Case Reports. 2022; 17: 1705–1708.

[8] Tamura N, Murakami K, Ozaki R, Takeuchi S, Ochiai A, Kawasaki Y, *et al*. Current state of management of struma ovarii and preoperative imaging features: a retrospective case series study of 18 patients at a single institution. Journal of Obstetrics and Gynaecology Research. 2023; 49: 1007–1011.

[9] Terzic M, Aimagambetova G, Norton M, Della Corte L, Marín-Buck A, Lisón JF, *et al*. Scoring systems for the evaluation of adnexal masses nature: current knowledge and clinical applications. Journal of Obstetrics and Gynaecology Research. 2021; 41: 340–347.

[10] Ye AQ, Reyes MF, Lester F, Ye J, Umetsu S, Poder L, *et al*. Boba sign with a twist—a variant presentation of a mature cystic teratoma complicated by torsion and rupture. Clinical Imaging. 2022; 83: 28–32.

[11] Abera SA, Molla DK, Abera KA, Adisu GD, Worku MA, Molla YD. Struma ovarii with papillary thyroid carcinoma and metastasis to the appendix: a case report and literature review. International Medical Case Reports Journal. 2023; 16: 571–578.

[12] Dumachița-Șargu G, Socolov R, Balan TA, Gafițanu D, Akad M, Balan RA. Struma ovarii during pregnancy. Diagnostics. 2024; 14: 1172.

[13] Iavarone I, Padovano M, Pasanisi F, Della Corte L, La Mantia E, Ronsini C. Meigs syndrome and elevated CA-125: case report and literature review of an unusual presentation mimicking ovarian cancer. Medicina. 2023; 59: 1684.

[14] Li S, Hong R, Yang J. Malignant struma ovarii with synchronous primary

papillary thyroid cancer in the neck: a case report and literature review. Oncology Letters. 2024; 27: 174.

[15] Obeidat RA, Alshwayyat S, Alshwayyat TA, Rjoop A, Sharqiah QM. Presentation and treatment of two cases of malignant struma ovarii. BMC Womens Health. 2024; 24: 158.

[16] Qin H, Chen D, Jin S, Liu J, Gao B, Wang Y. Teratoma combined with struma ovarii and sarcomatoid carcinoma: a case report and review of the literature. BMC Womens Health. 2024; 24: 517.

[17] Stefanopol IA, Petecariu A, Baroiu L, Neagu AI, Bogdan-Goroftei RE, Nechifor A, *et al*. Giant benign struma ovarii with high-grade fever, elevated CA 125, and hormonal function in an adolescent patient. Children. 2023; 10: 856.

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