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Accurate prediction of benign and malignant adnexal tumors in surgical resection and conservative treatment: construction and external validation of a diagnostic model based on CEUS, HE4, and O-RADS US v2022 evaluation

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Abstract

Purpose To establish a diagnostic model combining contrast-enhanced ultrasound (CEUS), human epididymis protein 4 (HE4), and Ovarian-Adnexal Reporting and Data Systems (O-RADS) US v2022, verify its diagnostic efficacy, and compare it with subjective evaluation.

Methods From January 2018 to August 2021 (the test group) and from September 2021 to September 2022 (the validation group), the data of patients classified as O-RADS US v2022 categories 2 to 5 who underwent adnexal ultrasound examinations were prospectively and continuously collected. In the test group, univariate and multivariate analyses were used to explore the relationship between age, body mass index (BMI), maximum diameter of the lesion, menopausal status, HE4, cancer antigen 125 (CA125), and the characteristics of CEUS and malignant lesions. Selecting independent influencing factors to construct diagnostic model, which was validated in the external validation group and compared with subjective evaluation.

Results The test group included 563 patients (mean age, 48.7 ± 13.2), and the validation group included 246 patients (mean age, 47.6 ± 12.9). Univariate and multivariate analyses showed that enhancement time, enhancement intensity, dynamic changes, and HE4 were independent influencing factors for predicting adnexal malignant tumors. In the validation group, the sensitivities and specificities of O-RADS US v2022, O-RADS US v2022 + CEUS, O-RADS US v2022 + CEUS + HE4, and subjective assessment were 88.89% and 70.69%, 94.44% and 79.31%, 91.67% and 92.53%, and 93.09% and 89.66% respectively. In addition, the combined diagnostic performance of O-RADS US v2022, CEUS and HE4 (AUC = 0.980) was higher than that of O-RADS US v2022 alone (AUC = 0.876, $P < 0.001$) and the combination

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of O-RADS US v2022 + CEUS (AUC = 0.908, $P < 0.001$), and was comparable to the subjective evaluation (AUC = 0.963, $P = 0.192$).

Conclusions The combined diagnostic model of O-RADS US v2022, CEUS and HE4 can improve the specificity of adnexal ultrasound diagnosis without sacrificing sensitivity, and it has high reliability.

Keywords O-RADS US v2022, CEUS, HE4, Ovarian tumor

Introduction

Ovarian cancer is a gynecological malignant tumor with a high mortality rate. Due to its complex and diverse pathological types, insidious onset, and lack of specific clinical symptoms, most patients are often diagnosed in the late stage [1], and the 5-year survival rate is relatively low [2, 3]. Malignant tumors require referral to gynecologic oncologists for precise treatment and high-quality care. For benign tumors, conservative treatment or laparoscopic surgery is the preferred option, and efforts should be made to preserve fertility [4]. Therefore, early and accurate diagnosis of benign and malignant ovarian lesions not only helps to improve the prognosis of patients, but also effectively avoids unnecessary surgical treatment.

Ultrasound examination is the preferred imaging method for evaluating adnexal lesions, providing valuable information for distinguishing the nature of adnexal lesions [5, 6]. Currently, it is widely believed that the subjective evaluation of experienced radiologists is the most accurate and effective method for distinguishing between benign and malignant adnexal masses [7, 8]. However, experienced radiologists are not universally available in clinical practice. To address these limitations, various predictive models and scoring systems based on ultrasound or serum tumor markers have been developed to assist inexperienced radiologists in diagnosing adnexal masses [9–12]. The Ovarian-Adnexal Reporting and Data System (O-RADS) US v2020 released by the American College of Radiology (ACR) in 2020 stratifies the malignant risk of adnexal masses and puts forward management recommendations for each O-RADS risk category. It shows high reliability among radiologists with different levels of experience [13, 14]. Despite having many strengths, O-RADS US v2020 exhibits relatively low specificity, which may lead to overtreatment [15–17]. The ACR released O-RADS US v2022 in November 2022, which adjusted some of the risk categories and management recommendations in the O-RADS US v2020 to improve the diagnostic accuracy and specificity of this categorization system [18].

The O-RADS ultrasound dictionary includes the color Doppler blood flow scores of the mass, which are subjectively evaluated by radiologists based on the color Doppler blood flow characteristics of the mass and rated from 1 to 4 points [19]. Traditional color Doppler ultrasound has its limitations, such as poor sensitivity to slow blood flow and deep blood vessels. Contrast-enhanced ultrasound (CEUS) is a method for imaging tissue microcirculation perfusion. By injecting microbubble contrast agents into the peripheral veins, the differences in microvascular perfusion between different lesions are significantly increased, making malignant tumors present more obvious and intuitive manifestations, thus improving the diagnostic accuracy [20].

Human epididymis protein 4 (HE4) and cancer antigen 125 (CA125) are commonly used tumor markers for evaluating ovarian malignant tumors. CA125 exhibits limited diagnostic sensitivity in early-stage ovarian carcinoma while concurrently showing elevation in benign gynecological conditions such as menstrual cycles, endometriosis, pelvic inflammatory disease, and gestational states [21, 22]. Therefore, it is insufficient to diagnose ovarian cancer using only CA125 [23]. HE4 is another very important detection indicator. Compared with CA125, it has similar sensitivity and higher specificity. It can not only be used for early diagnosis, but also play an important role in the follow-up period after treatment, remission monitoring, and treatment response [24, 25]. HE4 can identify benign lesions more accurately, thus avoiding overtreatment. Therefore, in order to improve the diagnostic specificity, HE4 detection can be considered for differential diagnosis [26].

Early and accurate preoperative diagnosis of adnexal masses should combine clinical features, tumor marker testing, and imaging examinations, which are crucial for reducing risks. Currently, the classification of adnexal masses by O-RADS US v2022 mainly relies on morphological features, and there is a shortage of more indicators sufficient to distinguish between benign and malignant adnexal lesions. The aim of this study is to establish a diagnostic model that combines O-RADS US v2022, CEUS and HE4, verify its diagnostic efficacy, and compare it with the subjective evaluation of experts.

Materials and methods

Study design and setting

This single-center, diagnostic study used prospectively continuously collected data from January 2018 to September 2022. Selected patients with O-RADS US v2022 categories 2 to 5 detected by ultrasound examination at our hospital from January 2018 to August 2021 were used

to establish a diagnostic model for evaluating adnexal masses based on O-RADS US v2022, CEUS, and HE4 (the test group). Patients classified as O-RADS US v2022 categories 2 to 5 collected from September 2021 to September 2022 for external validation of diagnostic models (the validation group). Collection of patient data including age, body mass index (BMI), reproductive history, menopausal status, serum HE4 and CA125 levels, and renal function status. Patients aged 50 and above who have previously undergone hysterectomy or lack records related to menopause, as well as those who have been amenorrheic for more than one year, are defined as being in the postmenopausal state. The inclusion criteria were as follows: (1) All patients underwent ultrasound and CEUS examinations; (2) Obtained the surgical pathology or final follow-up results. Exclusion criteria were as follows: (1) The lesion and myometrium could not be displayed on the same ultrasound imaging plane; (2) The quality of the ultrasound images was poor; (3) Patients without detection of CA125, HE4 or without a clear menopausal status; (4) Patients who had received chemotherapy or radiotherapy in the past; (5) SonoVue allergy. Figure 1 depicts the participant flowchart.

Ultrasound and CEUS examinations

All Ultrasound and CEUS examinations were carried out using two US instruments (Samsung RS80A, and Philips Epiq 5) with 5.0–9.0 MHz, and 3.0–10.0 MHz transvaginal probes, and 1.0–7.0 MHz, and 1.0-5.0 MHz transabdominal probes.

Transvaginal ultrasound was the main scanning method. When the patient cannot tolerate vaginal ultrasound examination or the lesions are too large to be evaluated solely by transvaginal ultrasound, the abdominal ultrasound examination should be carried out in combination. For patients with multiple adnexal masses, the mass with the most complex morphological structure or the largest volume should be selected for evaluation [12]. Firstly, ultrasound evaluation was carried out to record the location, size, contour (regular/irregular), presence or absence of acoustic shadow, presence or absence of solid components, size of solid components, presence or absence of papillary nodules, number and size of the papillary nodules, septation, ascites, peritoneal nodules, and color Doppler flow characteristics of the lesion. The cross-sectional plane demonstrating the most abundant blood flow in the cyst wall, septa, or solid components of the lesion on color Doppler ultrasound was selected as the CEUS imaging plane. In this section, the adjacent normal myometrium tissue could be observed simultaneously. Because the synchronized visualization of adnexal masses and the myometrium is crucial for real-time evaluation contrast-enhanced time, enhancement intensity, and washout mode parameters. The ultrasound contrast agent was SonoVue (Bracco SpA, Milan, Italy). Add 5 ml of 0.9% saline to prepare the SonoVue suspension, and then draw 2.4 ml of the suspension and inject it into the cubital vein. Continuously and dynamically observed the perfusion and washout of the contrast agent in the lesion and the surrounding tissues until the contrast agent in the lesion was completely washed out, and stored the dynamic images for 300 s. Ultrasound examination was performed by a radiologist with 15 years of experience in pelvic ultrasound and 10 years of experience in CEUS of adnexal lesions, who was not involved in the later evaluation of ultrasound images. All images were stored in the Picture Archiving and Communication System (PACS) of the hospital.

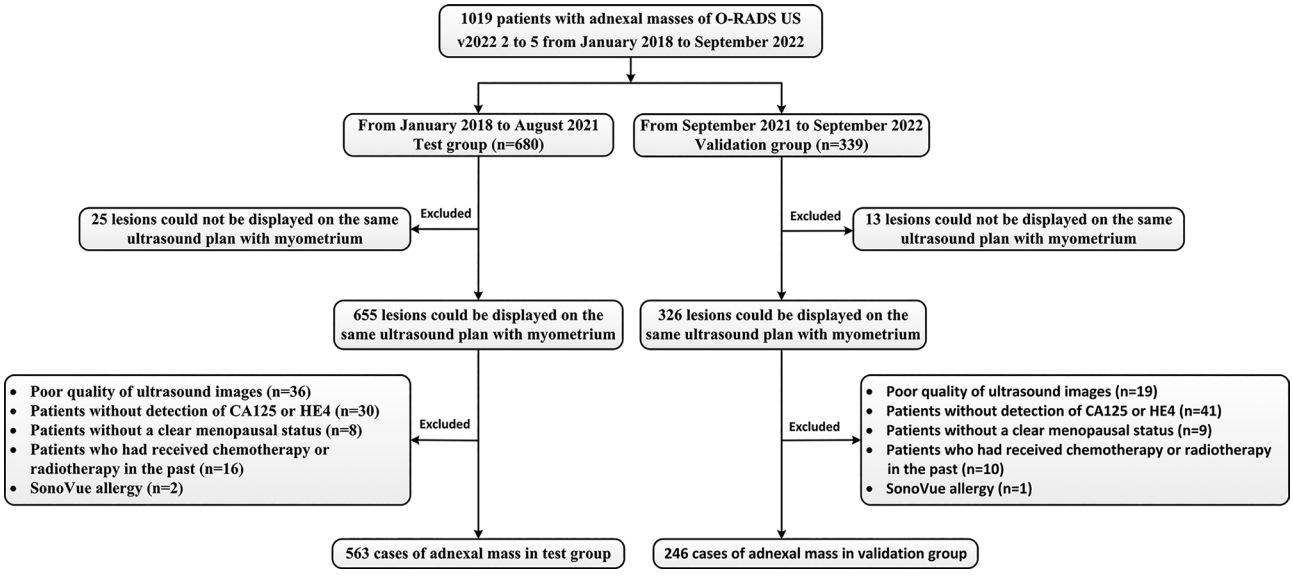

Fig. 1 Flowchart of the study. O-RADS = Ovarian-Adnexal Reporting and Data System; HE4: Human epididymis protein 4; CA125: Cancer antigen 125

Retrospective image analysis

Two radiologists (with 10 years and 20 years of experience in interpreting gynecological ultrasound images respectively) analyzed and summarized the features of the ultrasound images without knowing clinical data and final diagnosis results. Before the start of image analysis, the researchers had received the theoretical and practical training on the O-RADS US v2022 system. Subsequently, they retrospectively analyzed the morphological features of each lesion, and then independently classified the masses based on the O-RADS US v2022 system published by the ACR [18]. If there were disagreements among the radiologists, a final consensus would be reached through detailed discussions. The final classification results were used to calculate the diagnostic performance of the O-RADS US v2022 classification system. Two radiologists analyzed the CEUS video to determine the enhanced features of the solid components or irregular inner walls within the mass. In case of disagreement, consensus was reached through discussion. The evaluation indicators include [27, 28]: ① Enhancement intensity, which was described as hyperenhancement, isoenhancement, hypoenhancement, or no enhancement compared with the myometrium at the same plane; ② Enhancement time, the initial enhancement time of the lesion was early, synchronous, or later than the enhancement of myometrium; ③ Enhancement distribution patterns was classified as uniform or non-uniform; ④ Washout time: the start of the washout time of mass was earlier than, synchronous with, or later than that of myometrium; ⑤ Dynamic change of enhancement: in the washout phase, the dynamic change of lesion from hyper- or isoenhancement to hypoenhancement.

O-RADS US v2022 combined with CEUS

The enhancement characteristics of lesions were analyzed to develop a CEUS-based scoring diagnostic model. This model was subsequently applied to adjust O-RADS US v2022 classifications according to predefined cut-off values.

O-RADS US v2022 + CEUS + HE4

According to the level of HE4, the category 4 lesions in the diagnostic model of O-RADS US v2022 + CEUS were stratified into subclasses 4a and 4b.

Subjective assessment

Experienced radiologists in pelvic ultrasound subjectively evaluated the nature of masses without knowledge of clinical data and final diagnostic results. The subjective evaluation system were as follows: (1) Definitely benign; (2) Probably benign; (3) Uncertain but most likely benign; (4) Uncertain but most likely malignant; (5) Probably malignant; (6) Definitely malignant.

Reference standards

The reference standard were postoperative pathological results or follow-up results under ultrasound monitoring. During the 2-year follow-up period, if the mass spontaneously regresses, decreases in size, or remains stable, it was considered a benign lesion. If the average linear dimension of mass (sum of length, height, and width divided by 3) increased by more than 10%, surgical treatment would be carried out. The postoperative pathological findings would be regarded as the gold standard. For the postoperative pathological examination, all specimens were examined by two pathologists who had rich experience in adnexal lesions and were unaware of the clinical data and the results of the ultrasound examination, in accordance with the guidelines of the World Health Organization [29]. In this study, borderline tumors were classified as malignant tumors.

Statistical analysis

Statistical analysis were performed using SPSS version 26.0 (SPSS, Chicago, III, USA) and MedCalc version 20.1 software. Continuous data with normal distribution were represented by ($\bar{x}$±s), while skewed data were represented by M (Q1, Q3). Categorical data were presented as cases (percentage). In the test group, the Mann-Whitney U test or t-test was used for continuous variables, and the chi-square test was used for categorical variables to compare the differences in clinical features, morphological features, and CEUS features between benign and malignant lesions. Multivariate logistic regression analysis was performed to obtain the independent risk factors for predicting malignant tumors. The receiver operating characteristic (ROC) curve was used to determine the cut-off value. The ROC curve was used to evaluate the diagnostic efficacy of O-RADS US v2022, O-RADS US v2022 + CEUS, O-RADS US v2022 + CEUS + HE4, and subjective evaluation. A P-value of less than 0.05 was considered statistically significant.

The inter-observer agreement of ultrasonic morphological features, CEUS features, and O-RADS US v2022 classification system were evaluated using kappa (κ) statistics. The interpretation of the κ value is as follows: 0.01 ~ 0.20 = poor agreement; 0.21 ~ 0.40 = fair agreement; 0.41 ~ 0.60 = moderate agreement; 0.61 ~ 0.80 = good agreement; 0.81 ~ 1.00 = excellent agreement.

Results

Patient and lesion characteristics

A total of 563 patients who met the inclusion criteria were enrolled in the test group. There were 422 benign cases (74.96%), 28 borderline cases (4.97%), and 113 malignant cases (20.07%). The validation group included a total of 246 patients who met the inclusion criteria. Among them, there were 174 benign lesions (70.73%),

16 borderline lesions (6.50%), and 56 malignant lesions (22.76%). The test group and the validation group were compared in terms of patient age, menopausal status, ascites, maximum diameter of the lesion, BMI, blood flow score, HE4, CA125, and O-RADS US v2022 classification ($P > 0.05$, Table 1). The correlation between the final diagnostic results of the test group and the validation group and each diagnostic model were shown in Tables 2 and 3, respectively. There were differences in the blood flow scores, menopausal status, HE4, CA125, CEUS score, and O-RADS US v2022 classification between the two groups of benign and malignant lesions ($P < 0.05$).

Univariate and multivariate analysis

Through univariate and multivariate Logistic regression analysis, the relationships between age, BMI, maximum diameter of the lesion, menopausal status, HE4, CA125, and characteristics of CEUS (enhancement time, enhancement intensity, enhancement morphology, washout time, and dynamic changes in enhancement) and malignant lesions were explored. Multivariate analysis showed that HE4(OR 1.006, 95% CI: 1.005–1.008, $P = 0.001$), enhancement time (OR 2.362, 95% CI: 1.362–4.097, $P = 0.002$), enhancement intensity (OR 4.640, 95% CI: 2.547–8.451, $P = 0.001$), and dynamic changes in enhancement (OR 2.228, 95% CI: 1.284–3.867, $P = 0.004$) were independent influencing factors for malignant tumors.

CEUS scoring criteria

The CEUS scoring criteria were as follows: compared with the myometrium, the enhancement intensity (2 = hyper- or isoenhancement; 1 = hypoenhancement; 0 = no enhancement), the enhancement time (2 = synchronous or early enhancement; 1 = late enhancement), the dynamic changes in enhancement (1 = hyper- or isoenhancement to hypoenhancement; 0 = hypoenhancement to hypoenhancement, isoenhancement to iso-or hyperenhancement, and hyperenhancement to hyperenhancement).

Cut-off value

In the test group, the ROC curve of CEUS score showed that the optimal cut-off value for predicting the benign and malignant of adnexal masses was 4 points. The AUC was 0.822, with a sensitivity of 75.89% and a specificity of 85.07%.

The HE4 level of 563 patients in the test group was 83.01 (47.83, 167.43) pmol/L. The HE4 level of patients with benign tumors was 68.01 (45.46, 98.72) pmol/L, and that of patients with malignant tumors was 432.61 (96.76, 685.41) pmol/L. The cut-off value of the patients' HE4 level calculated using the Youden index was 234.61

Table 1 Comparison of participant characteristics between the test group and the validation group

Characteristic	Test group ($n = 563$)		Validation group ($n = 246$)		
	Benign ($n = 422$)	Malignant ($n = 141$)	Benign ($n = 174$)	Malignant ($n = 72$)	*P* Value*
Age (years)#	48.89 ± 13.78	48.09 ± 11.18	45.98 ± 13.23	51.49 ± 11.37	0.28
Menopausal status					0.13
Yes	202(48)	49(35)	87(50)	26(36)	
No	220(52)	92(65)	87(50)	46(64)	
Lesion size (cm)#	8.04 ± 3.32	8.49 ± 2.70	6.70 ± 2.44	11.07 ± 2.39	0.47
Ascites	102(24)	62(44)	43(25)	38(53)	0.28
BMI (kg/m2)#	23.27 ± 8.79	22.45 ± 3.30	24.05 ± 3.74	23.23 ± 3.13	0.15
HE4 (pmol/ml)†	68.01(45.46,98.72)	432.61(96.76,685.41)	73.23(38.51,135.63)	521.38(136.71,905.95)	0.06
CA125 (U/ml)†	35.72(19.91,159.88)	99.94(46.70, 476.05)	56.66(29.45,87.76)	99.75(67.93,814.77)	0.06
Blood flow score					0.24
No flow, score 1	77(18)	7(5)	28(16)	5(7)	
Minimal flow, score 2	281(67)	51(36)	111(64)	28(39)	
Moderate flow, score 3	55(13)	20(14)	31(18)	7(10)	
Very strong flow, score 4	9(2)	63(45)	4(2)	32(44)	
O-RADS US v2022					0.19
2	173(41)	0(0)	49(28)	0(0)	
3	152(36)	12(9)	79(45)	7(10)	
4	81(19)	45(32)	38(22)	26(36)	
5	16(4)	84(59)	8(5)	39(54)	

Legend: O-RADS: Ovarian-Adnexal Reporting and Data System; HE4: Human epididymis protein 4; CA125:Cancer antigen 125; BMI: Body mass index

Unless otherwise specified, the data represent the number of participants, with the percentages shown in parentheses

*Compared between the test group and the validation group

#Data are means ± SDs

†Data are M (Q1, Q3)

Table 2 The correlations between subjective assessment, O-RADS US v2022, O-RADS US v2022 + CEUS, and O-RADS US v2022 + CEUS + HE4 and the final diagnosis of adnexal masses in test group

Final diagnosis	n	Subjective assessment		O-RADS US v2022		O-RADS US v2022 + CEUS		O-RADS US v2022 + CEUS + HE4	
		Benign	Malignant	2–3	4–5	2–3	4–5	2-4a	4b-5
Benign	422								
Serous cystadenoma	67	64	3	63	4	52	15	56	11
Mucinous cystadenoma	79	76	3	70	9	58	21	63	16
Mature teratoma	44	43	1	42	2	40	4	42	2
Endometriotic cyst	40	38	2	39	1	40	0	40	0
Fibroma	36	34	2	6	30	29	7	29	7
Thecoma	27	26	1	3	24	25	2	25	2
Struma ovarii	20	2	18	0	20	0	20	16	4
Hemorrhagic cyst	41	38	3	38	3	40	1	40	1
Corpus luteum cyst	39	37	2	35	4	37	2	39	0
Follicular cyst	29	29	0	29	0	29	0	29	0
Malignant	141								
Borderline serous cystadenoma	7	2	5	2	5	1	6	1	6
Borderline mucinous cystadenoma	5	1	4	2	3	1	4	1	4
Borderline endometrioid tumor	6	2	4	2	4	2	4	2	4
Borderline clear cell neoplasm	6	1	5	1	5	2	4	2	4
Borderline Brenner tumor	4	1	3	1	3	0	4	0	4
Serous cystadenocarcinoma	36	0	36	1	35	1	35	1	35
Mucinous cystadenocarcinoma	26	1	25	1	25	1	25	1	25
Endometrioid carcinoma	10	1	9	0	10	1	9	2	8
Clear cell carcinoma	16	1	15	1	15	0	16	1	15
Adult-type granulosa cell tumor	13	0	13	0	13	1	12	1	12
Yolk sac tumor	6	0	6	0	6	0	6	0	6
Immature teratoma	4	1	3	0	4	0	4	0	4
Ovarian squamous cell carcinoma	2	0	2	1	1	0	2	0	2

Legend: O-RADS: Ovarian-Adnexal Reporting and Data System; CEUS: Contrast-enhanced ultrasound; HE4: Human epididymis protein 4

pmol/L, with sensitivity of 68.09%, specificity of 91.47%, and AUC value of 0.812.

Inter-observer agreement

The inter-observer agreement for morphological features, CEUS features and O-RADS US v2022 categorization for diagnosis of adnexal masses were shown in Table 4. There was good inter-observer agreement in the O-RADS US v2022 classification (κ = 0.779). Regarding the description of the features of conventional ultrasound and CEUS of lesions, there were good agreement among observers in terms of the lesion category (κ = 0.640), papillary nodules (κ = 0.722), mass contour (κ = 0.791), dynamic changes in enhancement (κ = 0.777), enhancement time (κ = 0.698), and enhancement intensity (κ = 0.623). There were moderate agreement among observers in the blood flow scores (κ = 0.559) and washout time (κ = 0.435). The agreement between observers regarding the enhanced morphology (κ = 0.881) and acoustic shadow (κ = 0.857) of the mass were excellent. There were perfect agreement among observers regarding ascites (κ = 1) and the maximum diameter of lesion (κ = 1).

Compare the diagnostic efficacy of each diagnostic model and subjective assessment for adnexal masses

In the test group, O-RADS US v2022 + CEUS + HE4 was significantly better than O-RADS US v2022 and O-RADS US v2022 + CEUS ($P < 0.01$). The AUCs were 0.963 (95% CI, 0.944–0.977), 0.899 (95% CI, 0.871–0.923), and 0.929 (95% CI, 0.904–0.949), respectively. There was no significant difference between O-RADS US v2022 + CEUS + HE4 and subjective assessment (AUC, 0.972 [95% CI, 0.954–0.984]) ($P = 0.34$). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of the four groups in predicting the benign and malignant of adnexal masses were shown in Table 5.

In the test group, according to the CEUS score, 6 out of 45 malignant lesions classified as O-RADS 4 were correctly upgraded to category 5, while 21 out of 81 benign lesions were correctly downgraded to category 3. In addition, 20 out of 166 benign lesions classified as O-RADS category 3 were correctly downgraded to category 2, and 5 out of 12 malignant lesions were correctly upgraded to category 4. Five benign lesions classified as O-RADS class 5 were correctly downgraded. At the same time, incorrect upgrades and downgrades were found. Two benign O-RADS 4 lesions were incorrectly upgraded to category 5. Three malignant O-RADS 4 lesions were incorrectly downgraded to category 3. If the patients classified as O-RADS US v2022 + CEUS category 4 with HE4 < 234.6 pmol/L were stratified into subclass 4a, and those with HE4 ≥ 234.61 pmol/L were stratified into subclass 4b, their malignancy rates were 6.90% and 56.52% respectively, indicating excellent risk stratification ($P < 0.001$). After the sub-classification of category 4, the ROC curve showed that the optimal cut-off value for predicting the benign and malignant of adnexal masses was ≥ O-RADS 4b, with sensitivity of 91.49% and specificity of 89.81%.

In the validation group, CEUS score was used as an indicator to adjust O-RADS US v2022. Eight cases of O-RADS category 4 were upgraded to category 5, with final diagnosis of 1 benign and 7 malignant. After downgrading, 17 lesions were downgraded from O-RADS category 4 to category 3, and final diagnosis showed 15 benign and 2 malignant lesions. Four lesions were downgraded from O-RADS category 5 to category 4, and final diagnosis revealed 3 benign and 1 malignant lesions. Ten cases of O-RADS category 3 were upgraded to category 4, with final diagnosis of 4 benign and 6 malignant cases. Fifteen lesions of O-RADS category 3 were downgraded to category 2, and final diagnosis showed that they were all benign. The ROC curve showed that the O-RADS US v2022 + CEUS showed a slightly higher diagnostic performance than the use of O-RADS US v2022 alone (AUC = 0.908; 95% CI: 0.865, 0.941 vs. AUC = 0.876; 95% CI: 0.829, 0.915; $P = 0.17$). Based on the HE4 level, the lesions classified as O-RADS US v2022 + CEUS category 4 were sub-classified. The updated ROC curve AUC value (0.980; 95% CI: 0.953, 0.993) were significantly increased ($P < 0.001$), with sensitivity, specificity, PPV, NPV, and accuracy of 91.67%, 92.53%, 83.54%, 96.41%, and 92.28%, respectively (Table 6). The representative cases in this study are shown in Fig. 2、Figs. 3 and 4.

Discussion

O-RADS classifies adnexal masses and assesses their malignant risks based on morphological characteristics, which facilitates better patient management and communication with clinicians. Its effectiveness and reliability had been verified in multiple regions [6, 30–33]. However, its specificity is limited. The ACR issued the O-RADS US v2022, which updated some risk categories and management recommendations of O-RADS US v2020, aiming to improve the diagnostic specificity for low-risk lesions. Su [34] found that both O-RADS US v2020 and O-RADS US v2022 had a sensitivity of 100%, specificity of 79.5% and 86.1%, and accuracy of 84.4% and 89.4% in diagnosing benign and malignant adnexal masses. However, some study [35] had also shown that compared with O-RADS US v2020, O-RADS US v2022 had demonstrated comparable performance and specificity in predicting malignant ovarian lesions. This study evaluated the diagnostic performance of O-RADS US v2022 through a comprehensive retrospective analysis, and explored the inter-observer agreement among different physicians regarding the classification of O-RADS

Table 3 The correlations between subjective assessment, O-RADS US v2022, O-RADS US v2022 + CEUS, and O-RADS US v2022 + CEUS + HE4 and the final diagnosis of adnexal masses in validation group

Final diagnosis	n	Subjective assessment		O-RADS US v2022		O-RADS US v2022 + CEUS		O-RADS US v2022 + CEUS + HE4	
		Benign	Malignant	2–3	4–5	2–3	4–5	2-4a	4b-5
Benign	174								
Serous cystadenoma	38	37	1	29	9	30	8	33	5
Mucinous cystadenoma	31	29	2	20	11	17	14	25	6
Mature teratoma	40	38	2	38	2	40	0	40	0
Fibroma	11	8	3	3	8	11	0	11	0
Thecoma	8	7	1	4	4	8	0	8	0
Inflammatory lesion	6	4	2	1	5	0	6	6	0
Hydrosalpinx	3	3	0	3	0	3	0	3	0
Struma ovarii	8	3	5	2	6	1	7	6	2
Hemorrhagic cyst	7	6	1	6	1	7	0	7	0
Corpus luteum cyst	7	7	0	5	2	6	1	7	0
Endometriotic cyst	15	14	1	12	3	15	0	15	0
Malignant	72								
Borderline serous cystadenoma	5	2	3	2	3	1	4	1	4
Borderline mucinous cystadenoma	4	1	3	2	2	1	3	2	2
Borderline clear cell carcinoma	4	1	3	1	3	0	4	0	4
Borderline endometrioid carcinoma	3	1	2	1	2	1	2	1	2
Serous cystadenocarcinoma	13	0	13	1	12	1	12	1	12
Mucinous cystadenocarcinoma	21	0	21	1	20	0	21	0	21
Clear cell carcinoma	8	0	8	0	8	0	8	0	8
Immature teratoma	1	0	1	0	1	0	1	0	1
Metastatic carcinoma	2	0	2	0	2	0	2	1	1
Dysgerminoma	1	0	1	0	1	0	1	0	1
Undifferentiated carcinoma	1	0	1	0	1	0	1	0	1
Endometrioid carcinoma	8	0	8	0	8	0	8	0	8
Poorly differentiated neuroendocrine carcinoma	1	0	1	0	1	0	1	0	1

Legend: O-RADS: Ovarian-Adnexal Reporting and Data System; CEUS: Contrast-enhanced ultrasound; HE4: Human epididymis protein 4

Table 4 Inter-observer agreement for morphological features、CEUS features and O-RADS US v2022 categorization for diagnosis of adnexal masses

Feature	Inter-observer	
	κ coefficients	95% CI
Lesion category	0.640	0.590 to 0.691
O-RADS US v2022	0.779	0.738 to 0.817
Maximum diameter of lesion	1.000	1.000 to 1.000
Ascites	1.000	1.000 to 1.000
Acoustic shadow	0.857	0.781 to 0.918
Papillary nodules	0.722	0.672 to 0.770
Blood flow scores	0.559	0.510 to 0.609
Mass contour	0.791	0.733 to 0.849
Enhanced morphology	0.881	0.832 to 0.920
Dynamic changes in enhancement	0.777	0.717 to 0.829
Enhancement time	0.698	0.608 to 0.756
Enhancement intensity	0.623	0.566 to 0.673
Washout time	0.453	0.345 to 0.499

Legend: O-RADS: Ovarian-Adnexal Reporting and Data System; CI: Confidence interval; CEUS: Contrast-enhanced ultrasound

US v2022 and its key terms. The results showed that O-RADS US v2022 promoted effective risk stratification and had good reproducibility among different radiologists. However, in the validation group, the specificity of O-RADS US v2022 classification in predicting the benign and malignant of adnexal masses was only 70.69%, which was similar to the results of previous studies [32]. It can be seen that relying solely on the O-RADS US v2022 classification system to evaluate the benign and malignant of adnexal masses would result in a relatively high false positive rate. In order to reduce unnecessary surgeries, it is necessary to combine other diagnostic methods to improve the diagnostic accuracy.

This study and previous studies [28, 36] had shown that there were significant differences in the CEUS characteristics of benign and malignant adnexal lesions, which may be related to the different microcirculatory pathological foundations of benign and malignant lesions. In this study, the prediction results of the benign and malignant of adnexal masses by O-RADS US v2022 + CEUS were compared with the classification results of O-RADS US v2022 alone. The main differences in the diagnostic results between the two were mainly reflected in the category 3 and category 4 of lesions. After combining CEUS features, 17 O-RADS US v2022 category 4 masses were downgraded to category 3. These masses showed the enhancement features of benign lesions on CEUS, with a CEUS score of less than 4 points, so they were downgraded to category 3. Among them, 15 masses were finally diagnosed as benign lesions. After undergoing CEUS examination, 10 masses in category 3 had a CEUS score of ≥ 4 points, so they were upgraded to category 4. Among them, 6 masses were pathologically diagnosed as malignant lesions. Meanwhile, incorrect upgrading and downgrading occurred. The possible reasons were as follows: (1) The morphological characteristics and microcirculatory changes of borderline tumors and early-stage tumors were not significant, making it difficult to distinguish them from benign tumors; (2) Some benign lesions (such as struma ovarii, inflammatory lesions, etc.) had abundant neovascularization inside, local vascular dilation, or the presence of ascites, and their CEUS showed the enhancement characteristics of malignant tumors, resulting in misdiagnosis. Therefore, for patients with atypical ultrasound images, it is also necessary to combine their clinical characteristics and tumor markers to assist in diagnosis.

HE4 can provide valuable information for the evaluation of adnexal masses, especially in the identification of benign lesions. Previous studies [21, 35, 37] had combined O-RADS with CA125 or HE4 to improve the effectiveness of O-RADS in predicting the benign and

Table 5 In the test group, the efficacy of each diagnostic model in predicting the benign and malignant nature of adnexal masses

Method	Final diagnosis		AUC	Sensitivity	Specificity	PPV	NPV	Accuracy
	Benign (*n* = 422)	Malignant (*n* = 141)						
Subjective assessment			0.972	92.20	91.71	78.79	97.24	91.83
Benign	387	11						
Malignant	35	130						
O-RADS US v2022			0.899	91.49	77.01	57.08	96.44	80.64
Benign	325	12						
Malignant	97	129						
O-RADS US v2022 + CEUS			0.929	92.91	83.41	65.17	97.24	85.79
Benign	352	10						
Malignant	70	131						
O-RADS US v2022 + CEUS + HE4			0.963	91.49	89.81	75.00	96.93	90.23
Benign	379	12						
Malignant	43	129						

Legend: O-RADS: Ovarian-Adnexal Reporting and Data System; HE4: Human epididymis protein 4; CA125:Cancer antigen 125; HE4: Human epididymis protein 4; PPV: Positive predictive value; NPV: Negative predictive value; AUC: Area Under the Curve

Table 6 In the validation group, the efficacy of each diagnostic model in predicting the benign and malignant nature of adnexal masses

Method	Final diagnosis		AUC	Sensitivity	Specificity	PPV	NPV	Accuracy
	Benign ($n=174$)	Malignant ($n=72$)						
Subjective assessment			0.963	93.09	89.66	78.82	96.89	90.65
Benign	156	5						
Malignant	18	67						
O-RADS US v2022			0.876	88.89	70.69	55.65	93.89	76.60
Benign	123	8						
Malignant	51	64						
O-RADS US v2022 + CEUS			0.908	94.44	79.31	65.38	97.18	83.74
Benign	138	4						
Malignant	36	68						
O-RADS US v2022 + CEUS + HE4			0.980	91.67	92.53	83.54	96.41	92.28
Benign	161	4						
Malignant	13	68						

Legend: O-RADS: Ovarian-Adnexal Reporting and Data System; HE4: Human epididymis protein 4; CA125: Cancer antigen 125; PPV: Positive predictive value; NPV: Negative predictive value; AUC: Area Under the Curve

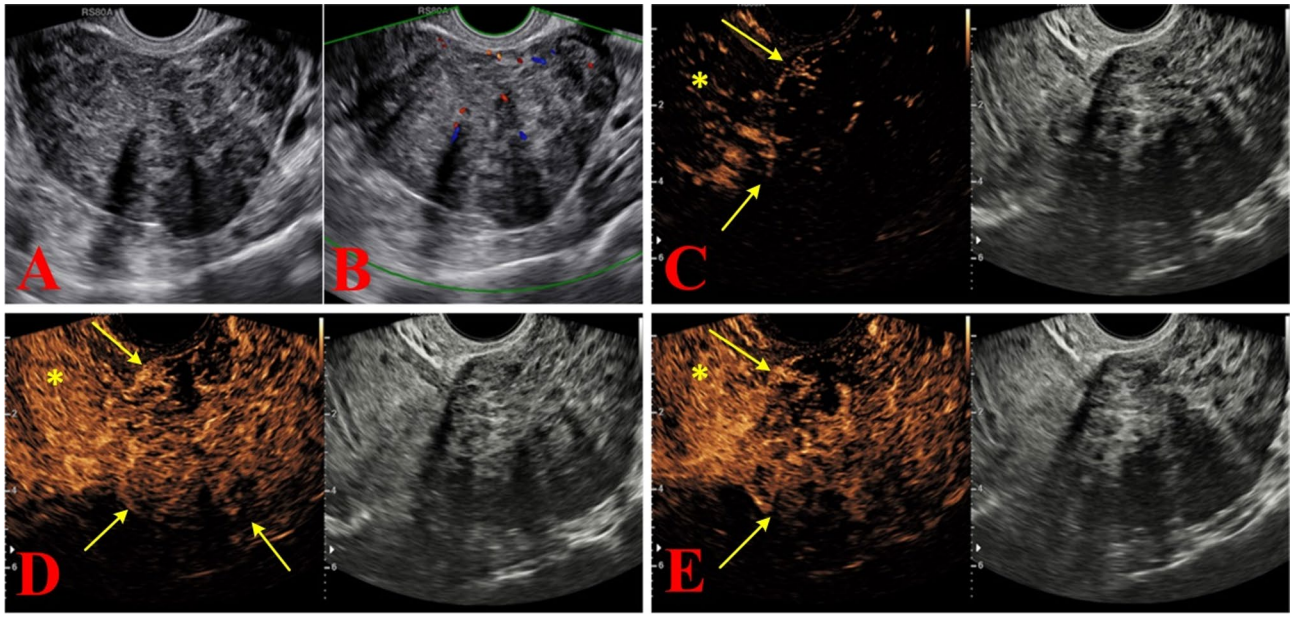

Fig. 2 Ultrasonographic images of the thecoma in a 52-year-old woman. The level of HE4 was 36.8 pmol/ml. (**A**) The ultrasound image shows an irregularly shaped solid mass in the right adnexal region, and (**B**) the color Doppler ultrasound reveals a small amount of blood flow signals within the lesion (color score = 2), which was classified as O-RADS US v2022 category 5. (**C**, **D**) CEUS images of the lesion show synchronous enhancement (arrows in C, score = 2) and hypoenhancement (arrows in D, score = 1) in comparison with myometrium (*). (**D**, **E**) Compared with the myometrium (*), the lesion shows a dynamic change in enhancement from hypoenhancement to hypoenhancement (score = 0). The CEUS score was 3, and this lesion was downgraded to O-RADS US v2022 category 4. With the combination of the HE4 level, it was sub-classified as category 4a

malignant of adnexal masses, especially in terms of specificity. However, these studies lack effective and unified diagnostic strategy as well as external validation. The malignant risk range of O-RADS US v2022 category 4 lesions is 10–50%, so there are difficulties in qualitative diagnosis. Some studies [30, 38] suggested that better sub-classification of O-RADS category 4 lesions could enhance risk stratification and improve diagnostic performance. Therefore, in this study, the category 4 lesions in O-RADS US v2022 + CEUS were sub-classified based on the HE4 level. In the test and validation groups, the diagnostic model considering HE4 showed a significant improvement in specificity compared to the diagnostic model not considering HE4 (89.81% vs. 83.41%, 92.53% vs. 79.31%; $P<0.05$), which could prevent a considerable number of benign masses from undergoing surgery. The validation group showed that combined diagnosis of the three had better diagnostic performance than using O-RADS US v2022 alone and O-RADS US v2022 + CEUS (AUC = 0.980 vs. 0.876, 0.908; $P<0.001$), while it had a

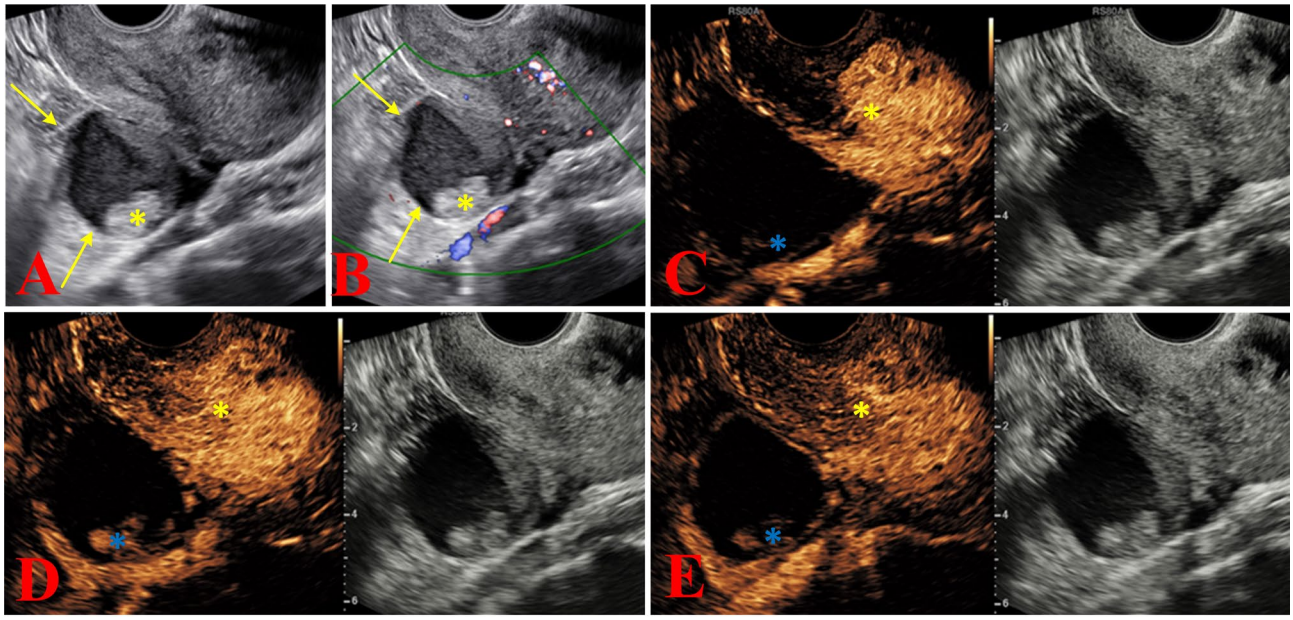

Fig. 3 Ultrasonographic images of a serous cystadenoma in a 46-year-old woman. (**A**) The ultrasonic image shows a unilocular cyst (arrows) with a papillary projection (*) in the right adnexal region. (**B**) Color Doppler ultrasound reveals that there were no blood flow signals in the cyst wall and the papillary nodules (*) of the lesion (color score = 1), which was classified as O-RADS US v2022 category 4. (**C**, **D**) CEUS images of the lesion show late enhancement (blue * in C, score = 1) and hypoenhancement (blue * in D, score = 1) in comparison with myometrium (yellow *). (**D**, **E**) Compared with the myometrium (yellow *), the lesion shows a dynamic change in enhancement from hypoenhancement to hypoenhancement (score = 0). The CEUS score was 2, and this lesion was downgraded to O-RADS US v2022 category 3

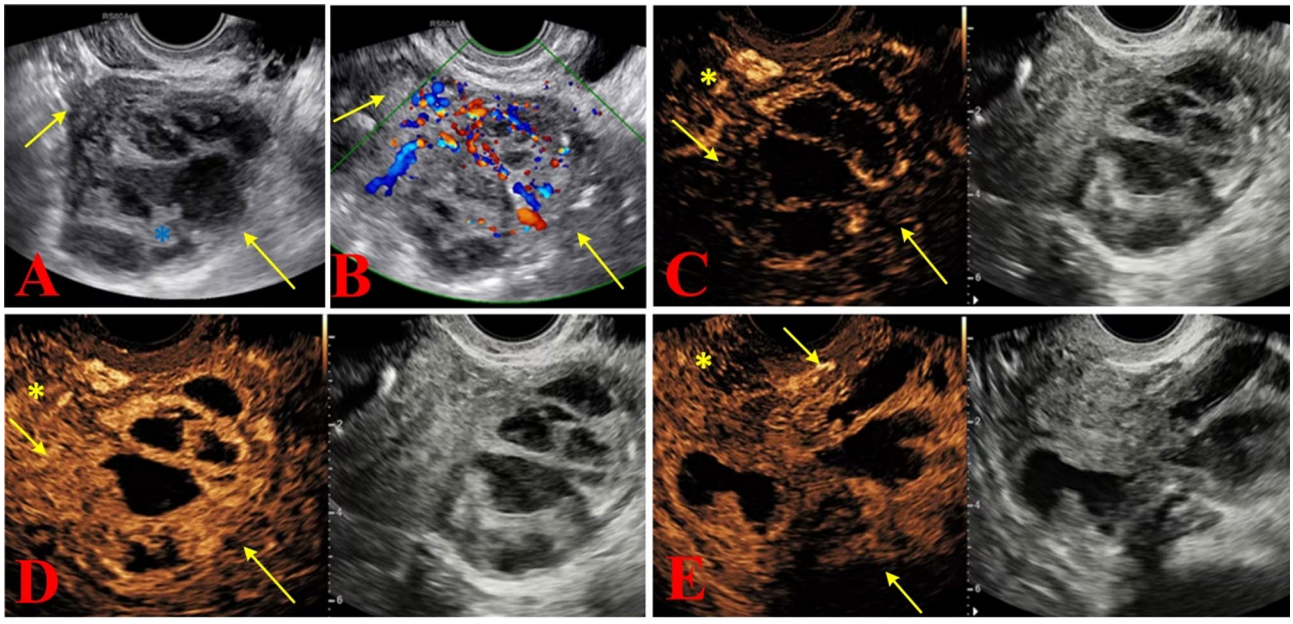

Fig. 4 Ultrasonographic images of the inflammatory lesion located in the left adnexa of a 49 - year - old female patient. The level of HE4 was 39.2 pmol/ml. (**A**) The ultrasonic image shows a multilocular cyst (arrows) in the left adnexal region, with solid components present (blue *). (**B**) Color Doppler ultrasound shows that the lesion had relatively abundant blood flow signals (color score = 4), and this lesion was classified as O-RADS US v2022 category 5. (**C**, **D**) CEUS images of the lesion show synchronous enhancement (arrows in C, score = 2) and hyperenhancement (arrows in D, score = 2) in comparison with myometrium (*). (**D**, **E**) Compared with the myometrium (*), the lesion shows a dynamic change in enhancement from hyperenhancement to hypoenhancement (score = 1). The CEUS score was 5

similar diagnostic performance to the subjective evaluation (AUC = 0.963, $P = 0.192$). A recent study showed that the combination of O-RADS US v2022 and HE4 had higher diagnostic efficacy in predicting benign and malignant of adnexal masses [35], which was consistent with the results of this study. This indicates that the combined diagnosis overcomes the limitations of a single examination. It can not only make judgments based on the morphological characteristics of mass and the microcirculatory perfusion, but also incorporate the level of serum tumor markers for the early screening of malignant adnexal lesions before the morphological and hemodynamic changes occur.

The detection of serum HE4 has the strengths of objectivity, easy accessibility, high cost-effectiveness and non-invasiveness, and can provide valuable information for the differential diagnosis of adnexal masses. However, its standalone predictive capacity is suboptimal. Multiple studies have shown that on the basis of traditional ultrasound, CEUS can effectively differentiate between benign and malignant adnexal masses through qualitative or quantitative analysis [20, 36, 38]. The results of this study show that the combined diagnostic model of O-RADS US v2022, CEUS and HE4 promotes effective risk stratification and improves the diagnostic efficiency. More accurate risk assessment not only reduces the need for costly imaging examinations, but also effectively avoids unnecessary surgical treatments, which contributes to lowering the overall medical costs. Based on this study and previous research [28, 35], it is recommended to use the O-RADS US v2022 classification for the initial screening of adnexal masses. For solid and solid-containing lesions, or lesions with uncertain findings in ultrasound examinations, it is essential to combine CEUS and HE4 detection to assist in the diagnosis.

This study had some limitations. Firstly, excluding patients with insufficient follow-up information and poor image quality could easily lead to selection bias. Secondly, this study used qualitative analysis for CEUS imaging, and the results may be subjectively influenced by radiologists. However, the use of myometrium as the reference standard in the study, along with the research results showed good consistency of CEUS features among radiologists, which had alleviated this concern. Thirdly, The data of this study were obtained from a single cancer center and did not include patients with renal impairment, which may limit the generalizability of the findings. Therefore, large-scale multicenter prospective studies are needed in the future, including patients with renal dysfunction, to further validate the efficacy of the O-RADS US v2022 + CEUS + HE4 combined diagnostic model, overcome existing limitations, and confirm its widespread application value in routine clinical practice.

Conclusions

This study verified the effectiveness and reliability of O-RADS US v2022 in predicting benign and malignant of adnexal masses. The O-RADS US v2022 classification adjusted based on the CEUS score had higher sensitivity, specificity, and accuracy than the O-RADS US v2022 alone in distinguishing between benign and malignant of adnexal masses. Subclassifying the category 4 lesions in the O-RADS US v2022 + CEUS according to the HE4 level had improved the specificity of some lesions with moderate malignant risk, promoted better risk stratification, and its diagnostic efficacy was comparable to subjective assessment.

Abbreviations

CEUS	Contrast enhanced ultrasound
HE4	Human epididymis protein 4
O-RADS	Ovarian-Adnexal Reporting and Data Systems
BMI	Body mass index
CA125	Cancer antigen 125
AUC	Area under the ROC curve
ACR	American College of Radiology
PACS	Picture Archiving and Communication System
ROC	Receiver operating characteristic
CI	Confidence interval
NPV	Negative predictive value
PPV	Positive predictive value

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Author contributions

YL and ML conceptualized and designed this study. CL was the major contributor to writing the manuscript. BT and KJD analyzed the images. The collection and organization of data were completed by CL, JL, RH, and HD. CL and YZ carried out the data analysis. All the authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study had obtained approval and consent from the participating hospital ethics review committee. All patients signed informed consent forms.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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