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# The predictive value of nomogram for adnexal cystic-solid masses based on O-RADS US, clinical and laboratory indicators

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## Abstract

**Background** Ovarian cancer remains a leading cause of death among women, largely due to its asymptomatic early stages and high mortality when diagnosed late. Early detection significantly improves survival rates, and the Ovarian-Adnexal Reporting and Data System Ultrasound (O-RADS US) is currently the most commonly used method, but has limitations in specificity and accuracy. While O-RADS US has standardized reporting, its sensitivity can lead to the misdiagnosis of benign masses as malignant, resulting in overtreatment. This study aimed to construct a nomogram model based on the O-RADS US and clinical and laboratory indicators to predict the malignancy risk of adnexal cystic-solid masses.

**Methods** This retrospective study collected data from patients with adnexal cystic-solid masses who underwent ultrasonography and were pathologically confirmed between January 2021 and December 2023 at the First Affiliated Hospital of Shenzhen University. They were categorized into benign and malignant groups according to pathological findings. Least absolute shrinkage and selection operator (LASSO) regression analysis was used to select the most relevant predictors of ovarian cancer. A nomogram model was constructed, and its diagnostic performance was calculated. We bootstrapped the data 500 times to perform internal verification, drew a calibration curve to verify the prediction ability, and performed a decision curve analysis to assess clinical usefulness.

**Results** A total of 399 patients with adnexal cystic-solid masses were included in this study: 327 in the benign group and 72 in the malignant group. Five predictors associated with the risk of malignancy of adnexal cystic-solid masses were selected using LASSO regression: O-RADS, acoustic shadowing, postmenopausal status, CA125, and HE4. The area under the curve, sensitivity, specificity, accuracy, positive and negative predictive values of the nomogram were 0.909, 83.3%, 82.9%, 83.0%, 51.7%, and 95.8%, respectively. The calibration curve of the nomogram showed good consistency between the predicted and actual probabilities, and the decision curve showed good clinical usefulness.

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**Conclusion** The nomogram model based on O-RADS US and clinical and laboratory indicators can be used to predict the risk of malignancy in adnexal cystic-solid masses, with high predictive performance, good calibration, and clinical usefulness.

**Keywords** Ultrasound, Adnexal masses, Ovarian-adnexal reporting and Data System, O-RADS, Nomogram, HE4, CA125

## Introduction

Due to its high aggressiveness and fatality rate, ovarian cancer poses a serious threat to women's lives and health. Ovarian cancer ranks second in incidence among malignant tumors of the female reproductive system; however, it ranks first in mortality rate [1]. Due to the lack of early symptoms and a high degree of concealment, ovarian cancer often progresses to advanced stages before being diagnosed, resulting in a 5-year survival rate of less than 30–50% for advanced ovarian cancer [2–4]. However, it is reported that if early diagnosis and treatment are implemented for ovarian cancer, the 5-year survival rate of patients can reach 80% or more [5]. Therefore, early diagnosis of ovarian cancer is crucial [6].

Conventional ultrasonography (US), with its advantages of economic feasibility, non-invasiveness, and repeatability, is the first line imaging technique that can characterize up to 80% of adnexal masses [7]. US can be used to determine the benign or malignant nature of a mass by describing its location, morphology, size, internal echogenicity, blood flow, and other characteristics. However, due to the complexity of the pathological types of adnexal masses, ultrasound images have a wide variety of presentations [8]. Furthermore, it is important to note that ultrasound diagnostic results can vary significantly depending on the country, region, and expertise of the sonographers involved. In 2020, the American College of Radiology published the Ovarian-Adnexal Reporting and Data System (O-RADS) US risk stratification and management consensus guidelines [9]. These guidelines standardized and made the descriptions of masses more uniform and objective, reducing ambiguities in reporting, stratifying the risks of masses, and providing appropriate management recommendations, thereby improving the accuracy of diagnosing benign or malignant nature of ovarian masses. However, Lee's [10] meta-analysis showed that the sensitivity and specificity of the O-RADS were 95.6% and 76.6%, respectively. He considered that the O-RADS sacrifices specificity to maximize sensitivity, to avoid missing malignant masses that are low in prevalence but high in lethality. This means that O-RADS may misdiagnose some benign masses as malignant, leading to overtreatment.

CA125 is the most widely used serological marker for epithelial ovarian cancer [11]. HE4 is a novel biomarker found at high levels in ovarian cancer, while benign tumors and normal tissues show significantly lower levels [12]. HE4 has also been evaluated for the diagnosis of ovarian cancer. Studies have shown that CA125 and HE4 together can improve the specificity of diagnosing ovarian masses and serve as a complement to O-RADS in distinguishing between benign and malignant adnexal masses [13, 14]. Nevertheless, relatively few studies have combined O-RADS with clinical and laboratory indicators.

A nomogram is a user-friendly, reproducible, and relatively objective statistical model for individualized risk assessment that provides clinicians with a tool to quantitatively predict ovarian cancer risk [15]. Therefore, this study proposes to integrate O-RADS with clinical and laboratory indicators to develop a model that can predict the malignant risk of adnexal cystic-solid masses. The model will provide a visual imaging basis to help clinicians individualize and precisely treat patients early to reduce overtreatment and the associated social burden.

## Materials and methods

### Patients

Data were retrospectively collected from patients with adnexal cystic-solid masses who underwent US with pathological findings between January 2021 and December 2023 at the First Affiliated Hospital of Shenzhen University. Patients were categorized into benign and malignant groups based on pathological findings.

The exclusion criteria were as follows: (1) pregnancy; (2) patients without a complete tumor marker series; (3) unclear ultrasound images that could not be interpreted; (4) all O-RADS category 1 findings; (5) a unilocular cyst without solid component; and (6) surgery performed > 30 days after ultrasound.

This retrospective study was approved by the Ethics Committee of the First Affiliated Hospital of Shenzhen University (2024-097-01PJ). The requirement for written informed consent was waived.

### Clinical and laboratory acquisition

The clinical data included age, postmenopausal status, reproductive history, family history of ovarian cancer, and history of HPV infection.

Laboratory data included serological concentrations of CA125, HE4, CA199, and the ROMA index.

Postmenopausal women were defined as those with amenorrhea for more than one year; women aged 50 years or older who had undergone a hysterectomy or

lacked a record of their menopausal status were also included [16].

Serum concentrations of CA125, HE4, and CA199 were measured using Roche chemiluminescence. All tests were performed strictly according to the operating instructions, and the operators were specially trained. According to the manufacturer's instructions, the normal levels of CA125, HE4, and CA199 are 0–35 U/mL, 0-74.3 pmol/L, and 0–27 U/mL, respectively. Specific values were categorized into normal, 1-fold elevated, 2-fold elevated, and 3-fold or more elevated.

The ROMA index was calculated by a predictive index (PI) based on CA125 and HE4 levels and menopause status [17].

Premenopausal PI = -12.0 + 2.38 × LN [HE4] + 0.0626 × LN [CA125];

Postmenopausal PI = -8.09 + 1.04 × LN [HE4] + 0.0732 × LN [CA125];

ROMA (%) = Exp (PI/[1 + Exp (PI)]) × 100, It was considered positive when ROMA ≥ 11.4% of premenopausal and ≥ 29.9% of postmenopausal patients [13].

### Ultrasound image acquisition

GE Volusion E8/E10, Logic E9 (GE, USA), and EPIQ 7 (Philips, The Netherlands) were used, with an abdominal probe frequency of 3–5 MHz and a transvaginal probe frequency of 5–9 MHz. Transvaginal ultrasound is routinely performed in patients, while transrectal ultrasound is performed in patients in whom transvaginal ultrasound is not feasible. Transabdominal ultrasound can be combined with transvaginal ultrasound when the mass is large, and exploration is incomplete. According to the O-RADS guidelines [9], the ultrasound features of adnexal masses include morphology, size, borders, internal echogenicity, blood flow, presence or absence of septation, presence or absence of solid components and their size, presence or absence of papillary projections, presence or absence of ascites/peritoneal nodules, and presence or absence of acoustic shadows. Blood flow signals were evaluated according to the color score criteria developed by the IOTA [18] as follows: 1, no blood flow; 2, minimal blood flow; 3, moderate blood flow; and 4, significant blood flow. In cases of multiple adnexal masses, the mass with the highest O-RADS category was included in this study. If the O-RADS categories were equal, the mass with the largest diameter was selected.

All ultrasound images were independently interpreted by an experienced sonographer who was unaware of the pathological findings. Before analyzing the images, the sonographer received theoretical training on O-RADS risk stratification.

### Pathologic assessment

According to the World Health Organization guidelines [19], the gold standard for diagnosing the benign or malignant nature of adnexal masses is postoperative histopathology.

### Development and validation of nomogram

Least absolute shrinkage and selection operator (LASSO) regression is a reduction method used for linear regression. It adds a penalty function to the commonly used multiple linear regression, continuously compressing the coefficients to simplify the model, thereby avoiding collinearity and overfitting. It can provide simple, interpretable models while effectively addressing multicollinearity issues and offers multiple advantages, such as automatic feature selection and prevention of overfitting [20]. This study used LASSO regression to select the most significant features among the ultrasound, clinical, and laboratory indicators. A nomogram was constructed from the selected indicators and used to predict the risk of malignancy in adnexal cystic-solid masses.

The diagnostic performance of the nomogram was evaluated by plotting receiver operating characteristic (ROC) curves and calculating the area under the curve (AUC). Internal verification was performed by bootstrapping the data 500 times. A calibration curve was plotted to assess the model consistency. A decision curve analysis (DCA) was performed to evaluate the clinical usefulness of the nomogram by quantifying its net benefits.

### Statistical analysis

Empower (R) (X&Y Solutions, Inc., Boston, MA, USA) and R software version 3.4.3 (http://www.r-project.org) were used for all statistical analyses. The comparison of O-RADS categories and clinical and laboratory characteristics between the benign and malignant groups of adnexal cystic-solid masses was conducted using the Mann-Whitney U test, $X^2$ test, or Fisher's test. Continuous data are described as median (25th, 75th percentile), and categorical variables as frequencies and percentages. LASSO regression was used to select the most relevant indicators of ovarian cancer. A nomogram was constructed to calculate the AUC, sensitivity, specificity, accuracy, and positive and negative predictive values. Internal validation was performed using 500 bootstrap samples to reduce the overfitting bias. A calibration curve was plotted to validate predictive ability. A decision curve was plotted to assess the clinical utility of the nomograms.

## Results

### Patient characteristics

A total of 399 patients with adnexal cystic-solid masses were included in this study. Among them, 327 (82%)

were benign and 72 (18%) were malignant (Fig. 1). Other ultrasound, clinical, and laboratory characteristics are presented in Table 1. Comparing the malignant group with the benign group, the malignant group had an older median age (38.5 vs. 33.0 years), a larger mass size (92.5 mm vs. 72.0 mm), and a larger maximum diameter of the largest solid component (43.0 mm vs. 31.0 mm), all of which were statistically significant ($P<0.05$). Postmenopausal women accounted for 26.4% of the malignant group, significantly higher than the 10.1% in the benign group ($P<0.001$). CA125 levels within the normal range were observed in 63.9% of the benign and 29.2% of the malignant group, while levels elevated by two times or more were observed in 18.0% and 40.2% of the benign and malignant groups, respectively. Normal HE4 levels were found in 97.2% of the benign group and 68.1% of the malignant group, while levels elevated by two times or more were observed in 0.6% and 16.7% of the benign and malignant groups, respectively. Statistically significant differences were observed between the two groups

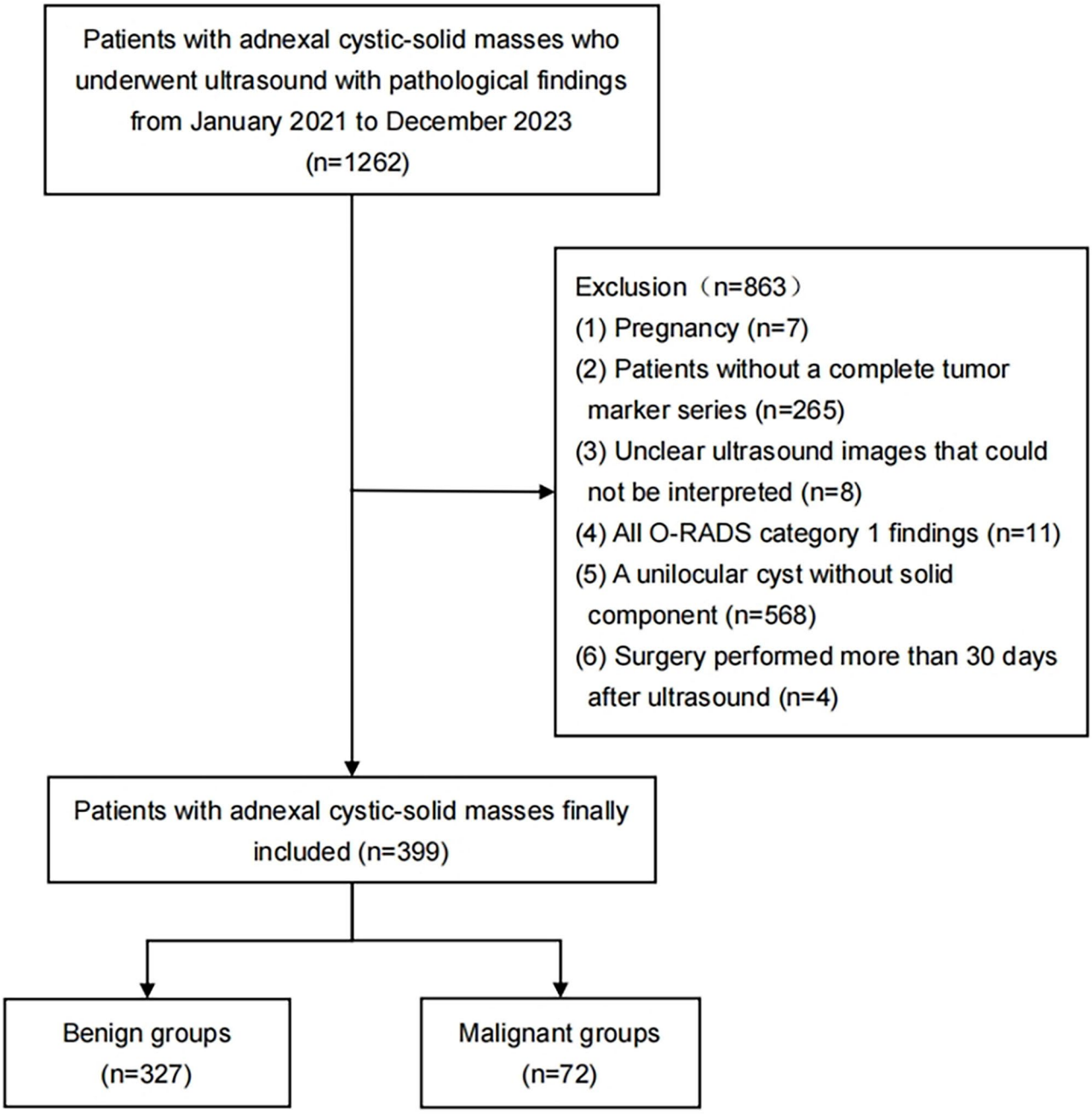


**Fig. 1** Flowchart of the study population

**Table 1** Ultrasound、clinical and laboratory characteristics of patients with adnexal cystic-solid masses

| Pathology | Benign (327) | Malignant (72) | *p* |
|---|---|---|---|
| Age (years, median (IQR)) | 33.0 (27.0–42.0) | 38.5 (29.0–48.0) | 0.018 |
| Postmenopausal | | | < 0.001 |
| No | 294 (89.9%) | 53 (73.6%) | |
| Yes | 33 (10.1%) | 19 (26.4%) | |
| Reproductive History | | | 0.147 |
| No | 158 (48.3%) | 28 (38.9%) | |
| Yes | 169 (51.7%) | 44 (61.1%) | |
| ROMA | | | < 0.001 |
| Negative | 286 (87.7%) | 39 (54.2%) | |
| Positive | 40 (12.3%) | 33 (45.8%) | |
| HPV Infection | | | 0.727 |
| No | 312 (95.4%) | 68 (94.4%) | |
| Yes | 15 (4.6%) | 4 (5.6%) | |
| Ca125 U/mL | | | < 0.001 |
| <1X | 209 (63.9%) | 21 (29.2%) | |
| 1X ~ 2X | 59 (18.0%) | 22 (30.6%) | |
| 2X ~ 3X | 19 (5.8%) | 5 (6.9%) | |
| ≥ 3X | 40 (12.2%) | 24 (33.3%) | |
| HE4 pmol/L | | | < 0.001 |
| <1X | 318 (97.2%) | 49 (68.1%) | |
| 1X ~ 2X | 7 (2.1%) | 11 (15.3%) | |
| 2X ~ 3X | 1 (0.3%) | 2 (2.8%) | |
| ≥ 3X | 1 (0.3%) | 10 (13.9%) | |
| Ca199 U/mL | | | 0.220 |
| <1X | 232 (70.9%) | 57 (79.2%) | |
| 1X ~ 2X | 54 (16.5%) | 5 (6.9%) | |
| 2X ~ 3X | 14 (4.3%) | 4 (5.6%) | |
| ≥ 3X | 27 (8.3%) | 6 (8.3%) | |
| Lesion category | | | < 0.001 |
| Unilocular cyst with solid component(s) | 75 (22.9%) | 21 (29.2%) | |
| Multilocular cyst, no solid elements | 155 (47.4%) | 6 (8.3%) | |
| Multilocular cyst with solid component(s) | 24 (7.3%) | 23 (31.9%) | |
| Solid | 73 (22.3%) | 22 (30.6%) | |
| Irregular external contour of solid lesions | | | 0.159 |
| No | 65 (89.0%) | 17 (77.3%) | |
| Yes | 8 (11.0%) | 5 (22.7%) | |
| Irregular inner wall | | | 0.065 |
| No | 207 (81.5%) | 35 (70.0%) | |
| Yes | 47 (18.5%) | 15 (30.0%) | |
| Number of papillary projection | | | 0.061 |
| 0 | 246 (96.9%) | 44 (88.0%) | |
| 1 | 4 (1.6%) | 3 (6.0%) | |
| 2 | 1 (0.4%) | 1 (2.0%) | |
| 3 | 2 (0.8%) | 2 (4.0%) | |
| >3 | 1 (0.4%) | 0 (0.0%) | |
| Papillary projection with color Doppler flow | | | 0.231 |
| No | 8 (100.0%) | 5 (83.3%) | |
| Yes | 0 (0.0%) | 1 (16.7%) | |
| Incomplete septations | | | 0.463 |
| No | 223 (87.8%) | 42 (84.0%) | |
| Yes | 31 (12.2%) | 8 (16.0%) | |

**Table 1** (continued)

| Pathology | Benign (327) | Malignant (72) | *p* |
|---|---|---|---|
| Complete septations | | | 0.067 |
| No | 78 (30.7%) | 22 (44.0%) | |
| Yes | 176 (69.3%) | 28 (56.0%) | |
| Irregular complete septations | | | 0.002 |
| No | 161 (91.5%) | 20 (71.4%) | |
| Yes | 15 (8.5%) | 8 (28.6%) | |
| Irregular external contour of largest solid component | | | < 0.001 |
| No | 73 (73.7%) | 18 (40.9%) | |
| Yes | 26 (26.3%) | 26 (59.1%) | |
| Color score | | | < 0.001 |
| 1 | 258 (78.9%) | 19 (26.4%) | |
| 2 | 38 (11.6%) | 17 (23.6%) | |
| 3 | 27 (8.3%) | 29 (40.3%) | |
| 4 | 4 (1.2%) | 7 (9.7%) | |
| Ascites/(Peritoneal nodules) | | | < 0.001 |
| No | 321 (98.2%) | 65 (90.3%) | |
| Yes | 6 (1.8%) | 7 (9.7%) | |
| Acoustic shadowing | | | < 0.001 |
| No | 131 (40.1%) | 67 (93.1%) | |
| Yes | 196 (59.9%) | 5 (6.9%) | |
| Cul-de-sac fluid | | | < 0.001 |
| No | 311 (95.1%) | 56 (77.8%) | |
| Yes | 16 (4.9%) | 16 (22.2%) | |
| O-RADS | | | < 0.001 |
| 2 | 104 (31.8%) | 0 (0.0%) | |
| 3 | 106 (32.4%) | 5 (6.9%) | |
| 4 | 101 (30.9%) | 47 (65.3%) | |
| 5 | 16 (4.9%) | 20 (27.8%) | |
| Maximum diameter of lesion(mm)(IQR) | 72.0 (60.0–92.0) | 92.5 (65.8-138.8) | 0.002 |
| Maximum diameter of largest solid component (mm)(IQR) | 31.0 (19.0-44.5) | 43.0 (27.0-68.5) | < 0.001 |

IQR: interquartile range, O-RADS: Ovarian Adnexal Reporting and Data System

($P<0.001$). The percentages of malignant masses in ultrasound O-RADS categories 2, 3, 4, and 5 were 0%, 4.5%, 31.8%, and 55.6%, respectively. The higher the O-RADS classification, the higher its percentage, and the difference was statistically significant ($P<0.001$).

#### Predictors selection and nomogram construction

Based on the LASSO regression, five predictors associated with adnexal malignant tumors were selected. The ultrasound indicators were the O-RADS and acoustic shadowing, and the clinical and laboratory indicators were postmenopausal status, CA125, and HE4 (Fig. 2). The formula is as follows:

**-0.99461 * Postmenopausal + 2.15159 * Acoustic shadowing + 0.35704*CA125 + 1.11635*HE4 + 1.10027 * O-RADS**.

A nomogram was constructed based on the above five predictors (Fig. 3). As shown in Fig. 4, the AUC of the nomogram model was 0.909, and the sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) were 83.3%, 82.9%, 83.0%, 51.7%, and 95.8%, respectively. Furthermore, the threshold corresponding to the linear predictor was −1.2628, and the total point was approximately 145.

The sensitivities and specificities of the five predictors are shown in Fig. 5.

#### Validation of the nomogram

The nomogram was verified internally using 500 bootstrap samples to reduce overfitting bias. The AUC, sensitivity, specificity, accuracy, PPV, and NPV of the internally validated nomogram were 0.921, 83.3%, 82.9%, 83.0%, 51.7%, and 95.8%, respectively. The blue shading in Fig. 6a indicates the AUC and 95% confidence interval (95% CI) for the bootstrap estimate after internal validation. The calibration curve of the model showed a good agreement between the predicted and actual probabilities (Fig. 6b). The DCA suggested that patients with adnexal masses can benefit from the constructed model over a considerable range of thresholds (Fig. 6c).

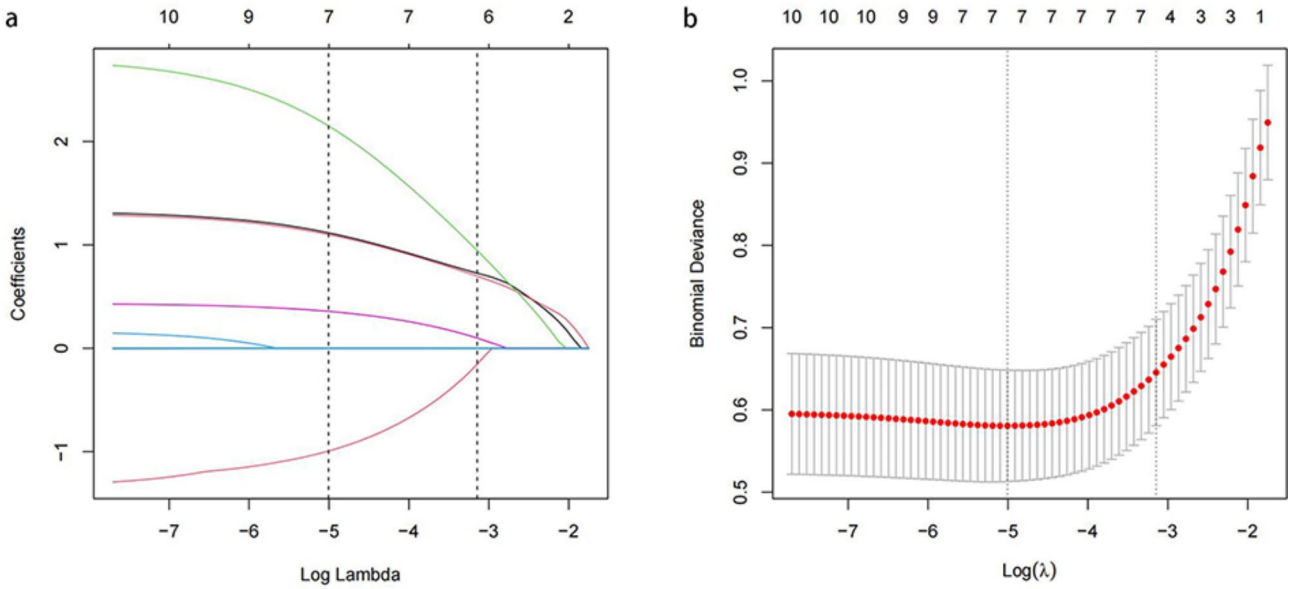


**Fig. 2** Ultrasound, clinical and laboratory feature selection using the LASSO regression. (**a**) The coefficient convergence graph of the feature selection process. The ordinate indicates the respective coefficients of the feature in the model, and the abscissa is log(λ). (**b**) The ordinate is the binomial deviation, and the abscissa is log(λ). A total of five predictors were selected in this study

### Comparison of the diagnostic efficacy of the nomogram with O-RADS

Analysis of the ROC curve of the O-RADS (Fig. 7a) showed that O-RADS>3 was the best threshold for predicting the risk of malignancy in adnexal cystic-solid masses, which indicated that adnexal masses were diagnosed as malignant on O-RADS 4–5 and benign on O-RADS 2–3. In our study, the AUC, sensitivity, and specificity of the O-RADS were 0.824 (95% CI, 0.786–0.823), 0.931, and 0.642, respectively. In comparison, the nomogram model demonstrated an AUC, sensitivity, and specificity values of 0.909 (95% CI, 0.881–0.938), 0.833, and 0.829, respectively. Compared with the O-RADS, the nomogram showed a significant improvement in both AUC and specificity. Figure 7b shows that the net benefit of the nomogram was higher than that of O-RADS. Thus, the nomogram showed higher efficacy in predicting the risk of malignancy in adnexal cystic-solid masses.

### Case Presentation

Case 1 demonstrates a malignant mass (Fig. 8a), and Case 2 demonstrates a benign mass (Fig. 8b).

## Discussion

Despite improvements in the risk assessment of adnexal masses after the proposal of the O-RADS classification system, the complexity and variety of ultrasound presentations of adnexal masses have resulted in a wide range of malignancy rates assessed by the O-RADS, with high false positives and low specificity [8, 10].

To increase the diagnostic accuracy of malignant masses in the adnexal region and reduce unnecessary surgeries, it is necessary to further clarify the nature of the masses by combining clinical and laboratory indicators. Therefore, our study comprehensively analyzed the ultrasound, clinical, and laboratory information of the patients, incorporated more comprehensive indicators, and performed selection. A nomogram model was constructed based on the selected indicators and linearly weighted to obtain individualized predictive probabilities, allowing clinicians to more accurately assess the risk of ovarian cancer and select the appropriate treatment strategies.

Five predictors, including O-RADS, acoustic shadowing, postmenopausal status, CA125, and HE4, were selected using LASSO regression. A nomogram model was constructed, which was effective in predicting the malignant risk of adnexal cystic-solid masses.

Among the selected predictors, the O-RADS had a significant proportion in the nomogram model, indicating that it played an important role in the diagnosis of ovarian cancer. The proportion of malignant masses in adnexal cystic-solid masses categorized as O-RADS 2, 3, 4, and 5 in our study was 0%, 4.5%, 31.8%, and 55.6%, respectively, which aligned with the guideline malignancy rates [9]. Our findings suggest that O-RADS>3 is the best threshold for assessing the risk of malignancy in adnexal cystic-solid masses, with O-RADS 4 and 5 indicating malignancy. This result is consistent with that of Cao et al. [21]. Additionally, the sensitivity and specificity of the O-RADS in our study were 93.1% and 64.2%,

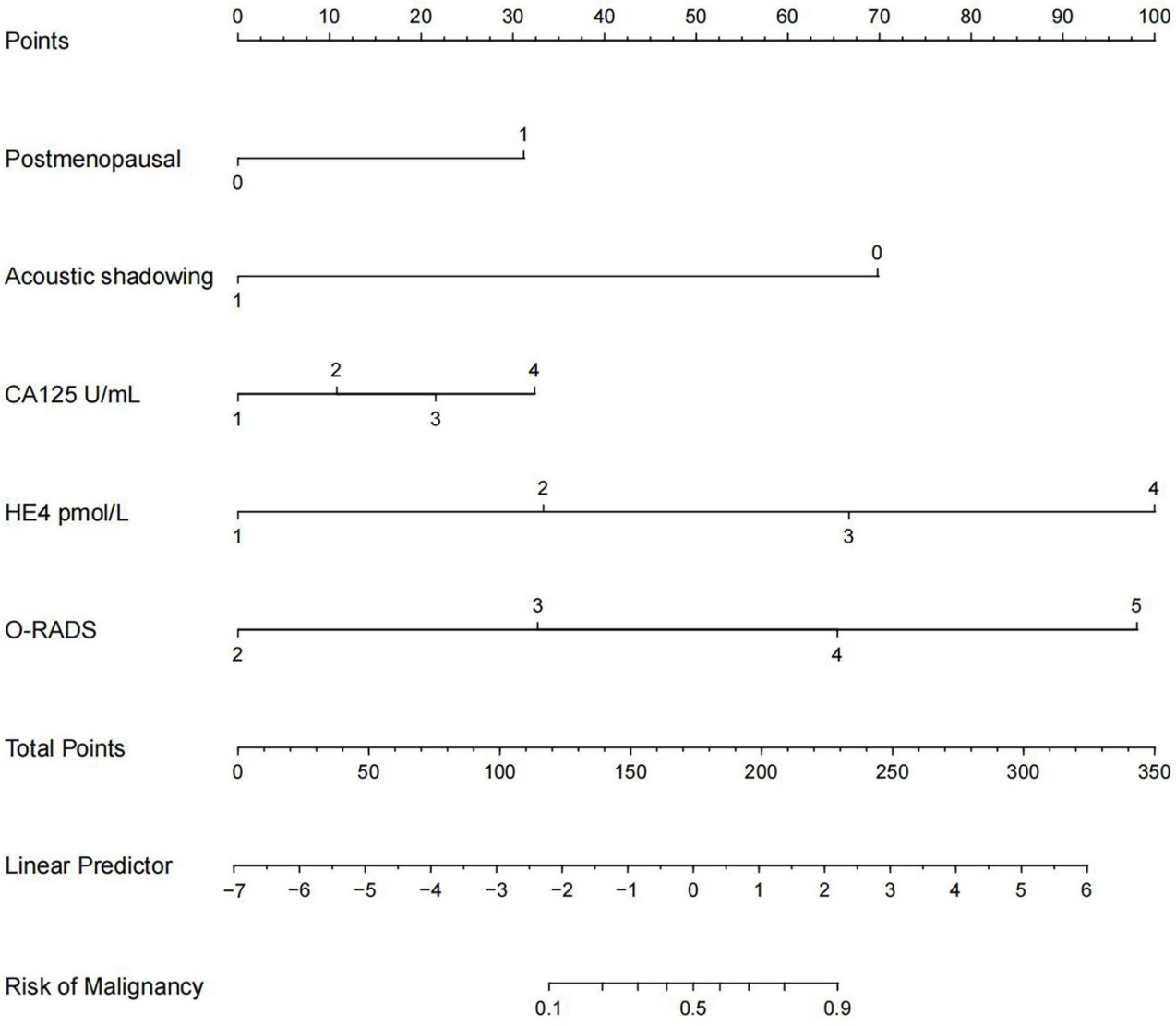


**Fig. 3** The nomogram was constructed using postmenopausal status, acoustic shadowing, CA125, HE4, and O-RADS. In Postmenopausal, 0 indicates non-postmenopausal, 1 indicates postmenopausal. In Acoustic shadowing, 0 indicates absent, 1 indicates present. CA125 (U/mL) and HE4 (pmol/L) use a four-point scale, where 1, 2, 3, 4 represent concentration ranges of normal, 1-fold elevated, 2-fold elevated, and 3-fold or more elevated. In O-RADS, 2-5 represent O-RADS categories 2-5

respectively. In a study that set the threshold at 10% and included only 150 patients, the sensitivity and specificity of O-RADS were 100% and 46.4% [22]. In a study by Hack et al. [16] which included 262 lesions, the sensitivity and specificity of the O-RADS were 99% and 70%, respectively, when O-RADS 4 was used as the threshold. Our study and the aforementioned studies demonstrated the high sensitivity but low specificity of the O-RADS in diagnosing malignant lesions of adnexal masses. We also found that the specificity of the O-RADS in Timmerman et al. [23] study was higher than that of our study, probably due to: first, the large age difference between our study subjects (us: 34 vs. Timmerman: 48 years); second, the difference in the selection of subjects for the O-RADS classification, with our study focusing on cystic-solid adnexal masses, which are usually more complex and difficult to diagnose, may have resulted in lower specificity. This suggests that the O-RADS alone has a limited ability to characterize cystic-solid adnexal masses.

Acoustic shadowing was found to be a protective factor in this study. Research has shown that acoustic shadowing often appears in benign adnexal masses such as teratomas, cystic adenofibromas, and fibromas, increasing the likelihood of benignity [24]. Hack et al. [16] also showed that lesions with acoustic shadowing had a high likelihood of being benign, with improved sensitivity and specificity when acoustic shadowing was added to the O-RADS and an increase in AUC from 0.91 to 0.94. Thus,

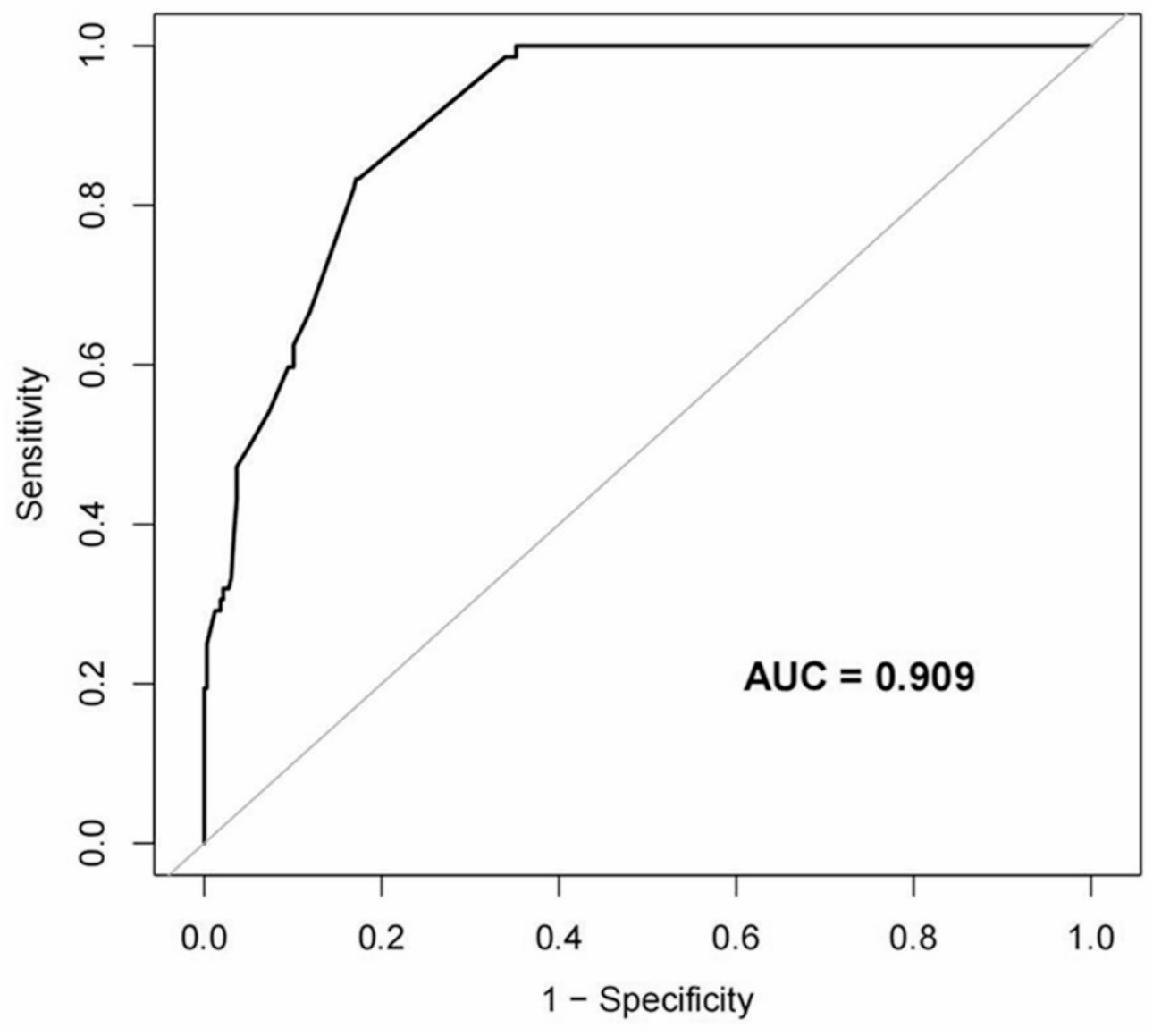


**Fig. 4** The receiver operating characteristic curve (ROC) of the nomogram

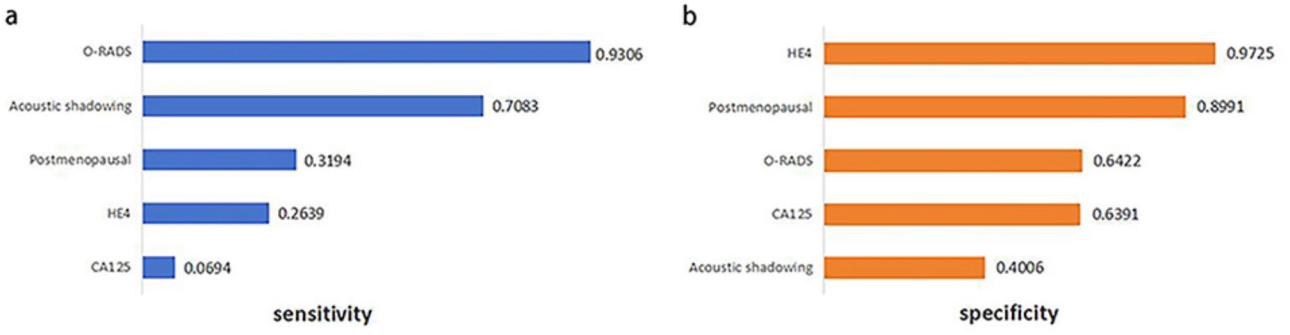


**Fig. 5** (**a**) Sensitivity ranking of the five predictors. (**b**) Specificity ranking of the predictors

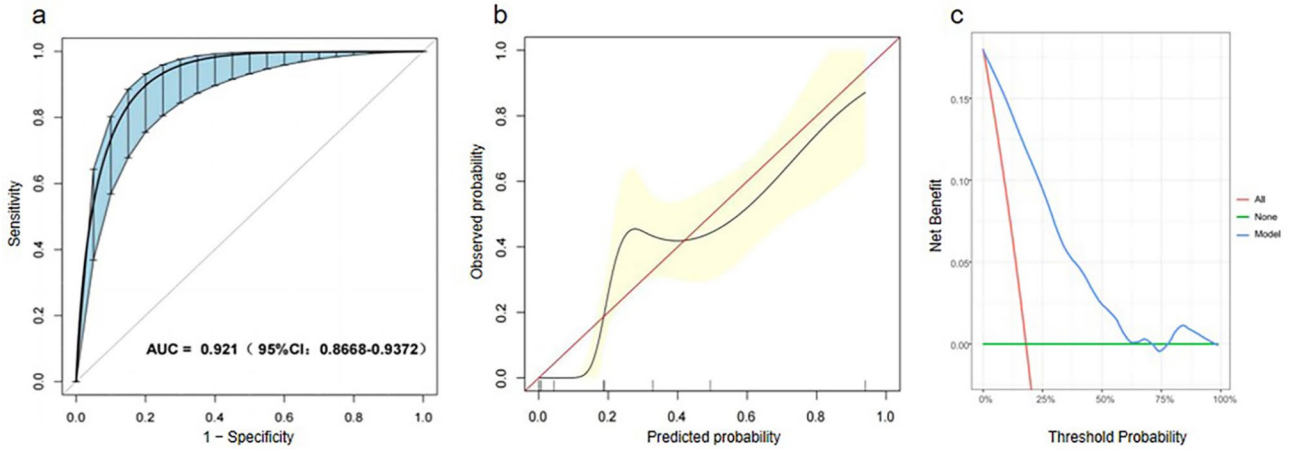


**Fig. 6** (**a**) The ROC of the nomogram after internal validation. Blue shading indicates the bootstrap estimated AUC and its 95% confidence interval. (**b**) The calibration curve of the nomogram shows good concordance between predicted and actual probability. (**c**) The DCA of the nomogram shows that our model can benefit patients with adnexal masses within a considerable threshold range

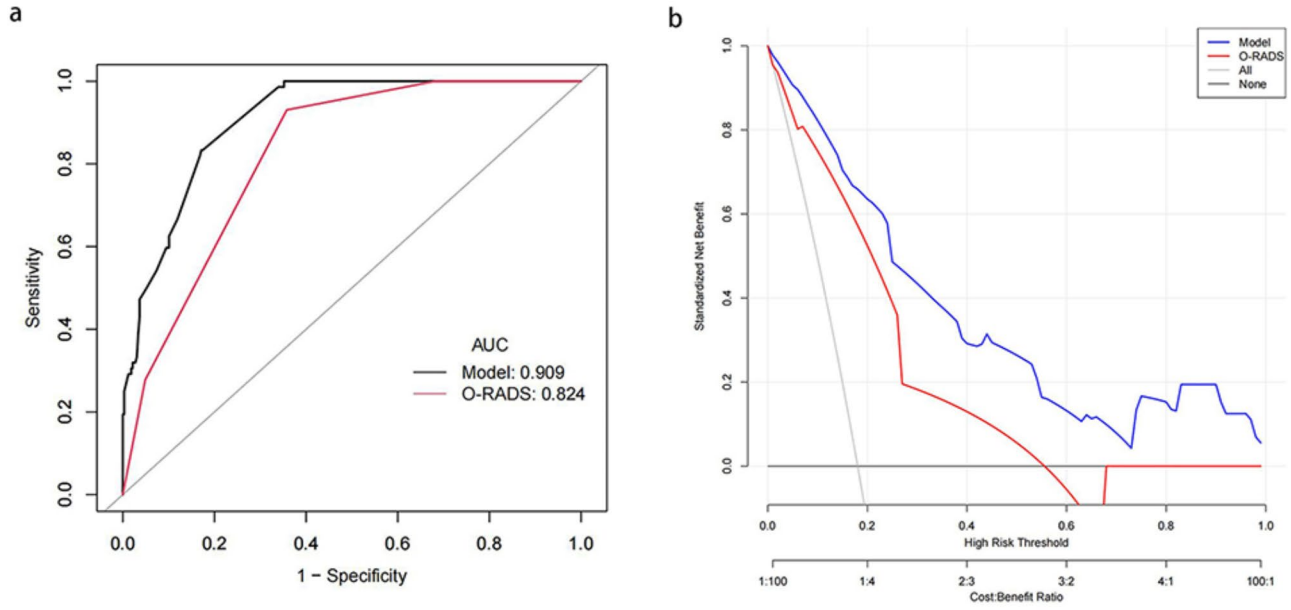


**Fig. 7** (**a**) The AUC of nomogram is higher than that of O-RASD. (**b**) The net benefit of nomogram is higher than that of O-RASD

acoustic shadowing can compensate for the low specificity of O-RADS and enhance the efficacy of differential diagnosis of adnexal cystic-solid masses.

Postmenopausal status was also identified as a predictor in this study. The results showed a higher proportion of postmenopausal women in the malignant group than in the benign group, which was statistically significant ($P<0.001$). Postmenopausal women have an increased risk of adnexal mass malignancy due to changes in hormone levels [25], suggesting that postmenopausal status plays an important role in distinguishing between the benign and malignant nature of adnexal masses.

Both CA125 and HE4 were significant predictors of malignancy risk in adnexal cystic solid masses. In a previous study, the diagnostic accuracy of CA125 was assessed by setting a specific threshold (usually≥35 U/mL) [26]. However, this dichotomy might result in the loss of important information, leading to misclassification of biomarker discriminatory ability [27]. Therefore, in this study, we used a four-category method for both CA125 and HE4 to further refine the correlation between different concentrations of CA125 and HE4 and the risk of malignancy in adnexal cystic-solid masses. Our results showed that the proportion of high concentrations of CA125 and HE4 was higher in the malignant group. HE4 was superior to CA125 in terms of specificity and nomogram model contribution, and the combination of CA125 and HE4 could help differentiate between benign

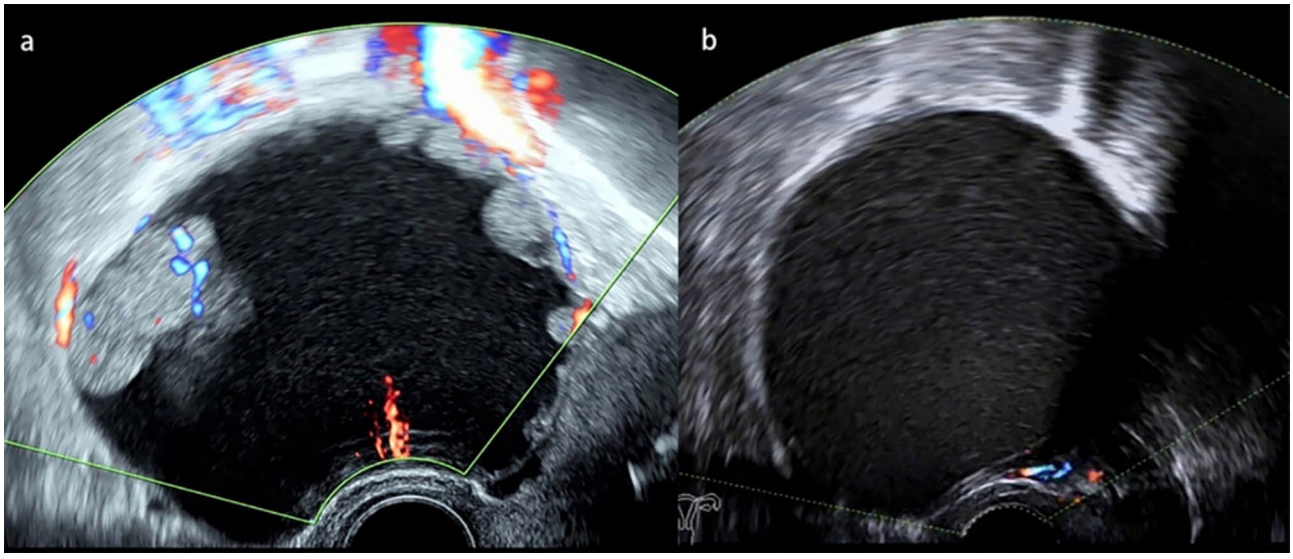


**Fig. 8** (**a**) Case 1: A post-menopausal patient. Transvaginal ultrasound showed a unilocular cyst with more than four papillary projections, and a blood flow score of 2. It was categorized as an O-RASD category 5 lesion. The pathological diagnosis was clear cell carcinoma. (**b**) Case 2: A pre-menopausal patient. Transvaginal ultrasound showed a unilocular cyst measuring 126 mm. The internal echoes were ground glass-like and a blood flow score of 1. Therefore, it was categorized as O-RASD category 3 lesion. The pathological diagnosis was endometrioma

and malignant adnexal cystic-solid masses. Yanaraop et al. [28] and Romagnolo et al. [29] also indicated that HE4 has a higher diagnostic efficacy than CA125 in the diagnosis of ovarian epithelial cancer. This may be due to the susceptibility of CA125 to factors such as menstruation, pregnancy, endometriosis, and inflammatory diseases of the peritoneum [11]. Similarly, Yang et al. [30] demonstrated that the combined detection of CA125 and HE4 improved the diagnostic efficacy of adnexal masses. This demonstrates the potential of the combination of the two in predicting the risk of malignancy in cystic-solid masses in the adnexal region.

The ROMA index is an assessment model that integrates CA125 and HE4 levels with the patient's menopausal status using a specific formula to obtain values that are used to evaluate the risk of ovarian cancer [17]. Our results showed that the proportion of patients with a positive ROMA index was significantly higher in the malignant group than in the benign group. Three predictors–CA125, HE4, and menopausal status–were selected in this study using LASSO regression. Given that ROMA is a model based on these three factors, the ROMA index was not included in the model for this study.

By incorporating these factors, a nomogram model was constructed to predict the benignity or malignancy of adnexal cystic-solid masses. Our results showed that although the sensitivity of the nomogram was lower than that of the O-RADS, AUC and specificity of the nomogram were significantly improved. The improvement in specificity and AUC helps to reduce the false-positive rate, which reduces unnecessary surgeries and overtreatment, lowers healthcare costs, and reduces the psychological burden on patients.

In addition, the effectiveness of the nomogram model constructed in our study is comparable to that of the models developed by Gong et al. [31] (training set AUC: 0.898, validation set AUC: 0.912) and Wu et al. [32] (training set AUC: 0.958, validation set AUC: 0.940). Our nomogram model incorporated CA125, HE4, and menopausal status, which comprehensively assessed for adnexal cystic-solid masses. Furthermore, the calibration curves in our study showed good consistency with the nomogram model, and the decision curves showed that it could benefit patients within a considerable threshold range.

In practical applications, clinicians can locate the corresponding scores on the nomogram based on various patient parameters (postmenopausal status, acoustic shadowing, CA125 level, HE4 level, and O-RADS), and sum these scores to obtain the total points. If the total score exceeds 145 points, further examination was advised due to the higher probability of malignancy. The nomogram provides an intuitive, individualized tool for clinical decision-making, helping clinicians better assess patients' malignancy risk and formulate appropriate diagnostic and treatment plans.

However, our study has certain limitations. (1) It was a retrospective study, and only patients who underwent gynecological surgery were included. Consequently, inherent selection bias was unavoidable. (2) This was a single-center study with a relatively small sample size, which limited the generalizability of the findings. (3) Despite performing 500 bootstrap samples for internal

validation, we lacked external validation, which has the following drawbacks: potential risk of overfitting, issues with result stability, and alteration of data distribution. Thus, future large-scale multicenter prospective studies are needed to further validate the model and enhance its reliability and applicability.

## Conclusion

The nomogram model constructed based on the O-RADS and clinical and laboratory indicators had high predictive efficacy, good calibration, and clinical usefulness. It effectively reduces the incidence of missed diagnoses and misdiagnoses, positioning itself as a potentially significant tool for personalized diagnosis of ovarian adnexal masses.

### Abbreviations

| | |
|---|---|
| CI | Confidence interval |
| AUC | Area under the curve |
| CA125 | Cancer antigen 125 |
| DCA | Decision curve analysis |
| HE4 | Human epididymis protein 4 |
| IOTA | International Ovarian Tumor Analysis |
| LASSO | Least absolute shrinkage and selection operator |
| NPV | Negative predictive value |
| O-RADS US | Ovarian-Adnexal Reporting and Data System Ultrasound |
| PI | Predictive index |
| PPV | Positive predictive value |
| ROC | Receiver operating characteristic |
| US | Ultrasonography |

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### Author contributions

CCJ and MFD contributed equally to this manuscript. CCJ and MFD was major contributors in writing the manuscript. SY, LHQ and XYL collected the patient data. YLB analyzed the images. CZ captures the images. QXC and SYW conceptualized the study and provided supervision, writing review, and editing. All authors read and approved the final manuscript.

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### Data availability

The authors will provide the original data without reservation if necessary, but the data will not be used for sharing purposes.

## Declarations

### Ethics approval and consent to participate

This retrospective study was approved by the Ethics Committee of The First Affiliated Hospital of Shenzhen University (2024-097-01PJ). The requirement to obtain written informed patient consent was waived.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

### Conflict of interest

All authors declared that they have no conflicts of interest in this work.

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