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Tumor biomarkers contribute to the diagnosis and clinical management of the O-RADS MRI risk stratification system for epithelial ovarian tumors

Shengjie Xu^{1†}, Weijian Gong^{1†}, Xiyi Chen¹, Jiatong Wang¹, Yuan Zhu¹, Tao Zhang², Yun Gu³, Jinxia Zheng^{2*} and Juan Xu^{1,4*}

Abstract

Background To assess the effectiveness of tumor biomarkers in distinguishing epithelial ovarian tumors (EOTs) and guiding clinical decisions across each Ovarian-Adnexal Reporting and Data System (O-RADS) MRI risk category, the aim is to prevent unnecessary surgeries for benign lesions, avoid delays in treating malignancies, and benefit individuals requiring fertility preservation or those intolerant to over-extensive surgery.

Methods A total of 54 benign, 104 borderline, and 203 malignant EOTs (BeEOTs, BEOTs and MEOTs) were enrolled and retrospectively assigned risk scores. The role of tumor biomarkers in diagnosing and managing EOTs within each risk category was evaluated by combining receiver operating characteristic (ROC) curves with clinicopathological characteristics.

Results A score of 3 was assigned to 66.67% of BeEOTs, 50.96% of BEOTs, and 13.80% of MEOTs, whereas cancer antigen 125 (CA125) ≥ 60.39 U/ml helped identify MEOTs with a low-risk time-intensity curve (TIC) for prompt surgical assessment. Only 3.7% of the BeEOTs were classified as O-RADS MRI 4/5, whereas 48.08% and 86.2% of the BEOTs and MEOTs were classified, respectively. Overall, EOTs with a score of 4/5 are candidates for semi-elective surgery owing to the low probability of benign lesions. For EOTs with a ROMA index less than 20.14% (premenopausal) or 29.9% (postmenopausal), minimally invasive surgery is recommended for diagnostic and therapeutic purposes. Comprehensive staging or cytoreductive surgery is recommended for the remaining patients, especially when fertility preservation is not a priority.

Conclusions The O-RADS MRI primarily differentiates BeEOTs with risk scores of 2/4/5 from BEOTs/MEOTs, while tumor biomarkers further enhance the diagnosis and clinical management of EOTs with scores of 3/4/5. Future

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studies should focus on multi-center, prospective studies with larger sample sizes to validate and refine the integration of O-RADS MRI with tumor biomarkers.

Keywords ROMA index, Cancer antigen 125, O-RADS MRI, Epithelial ovarian tumor, Clinical management

Introduction

Epithelial ovarian tumors (EOTs) are categorized as benign, borderline, or malignant. Malignant epithelial ovarian tumors (MEOTs), which constitute 90% of all ovarian cancer cases, are recognized as the most lethal gynecological malignancies [1]. Women of reproductive age account for approximately 12% of patients with ovarian cancer [2]. With the continuous progress of diagnosis and treatment, the mortality rate of ovarian cancer has been decreasing nowadays [1]. Therefore, in addition to treatment outcomes, maintaining quality of life and preserving fertility are also crucial considerations.

Borderline epithelial ovarian tumors (BEOTs), accounting for 15-20% of EOTs, present a relatively low risk of malignancy and occur mainly in women of reproductive age. Most BEOTs can be cured entirely, and some young women can even opt for fertility-sparing surgery [3]. However, a small percentage of BEOTs are still at risk of secondary malignant lesions. Moreover, accurately distinguishing BEOTs from benign and malignant EOTs in terms of clinical symptoms, tumor biomarkers, and imaging examinations is difficult, which may lead to incorrect clinical management. Therefore, in clinical practice, the diagnosis and treatment of BEOTs have always been a thorny problem, and clinicians often fall into the trap of excessive intervention or malignant transformation.

Ultrasound (US) is the preferred imaging method for ovarian tumors and has high sensitivity and specificity for excluding malignancy when the lesions show classic benign features [4–6]. However, malignancy remains difficult to confirm in the absence of such signs. MRI assesses the risk of malignancy primarily based on the presence of enhancing solid components in adnexal lesions. When adnexal lesions cannot be definitively characterized by the US, the use of MRI to exclude malignant tumors can reduce the misdiagnosis rate, thereby improving the prognosis of malignant lesions and reducing the surgical rate of benign lesions. The Ovarian-Adnexal Reporting and Data System (O-RADS), established and released in 2018 by the American College of Radiology, was initially designed for the US and was extended to MRI in 2022 [7]. However, lacking prospective cohort studies and further peer-reviewed evidence, the O-RADS MRI system, notably for O-RADS categories 3/4/5, currently has no specific management guidelines [7].

Tumor biomarkers are essential indicators for the initial screening and differentiation of benign EOTs (BeEOTs) and MEOTs and have specific reference values

for diagnosing BEOTs. Cancer antigen 125 (CA125) is the most common tumor biomarker for epithelial ovarian cancer, but it exhibits limited sensitivity when diagnosing early ovarian cancer and poor specificity due to physiological and pathological factors [8]. Human epididymis protein 4 (HE4) offers higher diagnostic specificity for ovarian cancer than CA125 [9]. The ROMA index, which combines CA125 and HE4 levels with menopausal status, is superior to a single tumor biomarker for evaluating the malignant risk of pelvic masses and has been widely used in clinical practice [9]. However, there is insufficient evidence that the combination of tumor biomarkers and the O-RADS MRI risk stratification system helps diagnose EOTs, especially BEOTs.

While prior studies have evaluated the diagnostic accuracy of the O-RADS MRI system, its role in distinguishing BEOTs from BeEOTs and MEOTs remains relatively underexplored. This study explored the potential of integrating tumor biomarkers, such as CA125 and the ROMA index, with O-RADS MRI risk stratification to enhance diagnostic accuracy. Additionally, by retrospectively analyzing a substantial patient cohort across multiple risk categories, we provide preliminary insights into refining management strategies by combining imaging features with serum biomarkers. These findings contribute to the refinement of the diagnostic utility of the O-RADS MRI system and offer insights that may help guide more individualized and efficient management of EOTs, potentially improving patient outcomes and optimizing resource utilization.

Materials and methods

Criteria of inclusion and exclusion

This retrospective analysis included 942 patients at Nanjing Women and Children's Healthcare Hospital, who were diagnosed with primary BeEOTs, BEOTs, or MEOTs from January 2017 to December 2023. All patients were initially diagnosed with ovarian tumors via US, and subsequent 1.5 or 3.0 T dynamic contrast-enhanced MRI scans were conducted within two weeks before surgery either due to challenges in accurate assessment with the US or when malignancy was suspected. Utilizing the postoperative pathological outcomes assessed by two pathologists (with 5/10 years of experience), the participants were categorized into three groups, including 182 BeEOTs, 110 BEOTs, and 650 MEOTs. A total of 60 BeEOTs and 216 MEOTs were randomly sampled in proportion to the initial numbers. All 110 BEOTs were enrolled to reduce data bias and statistical difficulties

due to the small sample size. The study excluded patients who underwent chemotherapy before surgery, those with residual or recurrent EOTs, those with a history of other malignant tumors, and those who were pregnant. Finally, 54 BeEOTs, 104 BEOTs and 203 MEOTs were included in this study. The flow chart in Fig. 1 illustrates the criteria for inclusion and exclusion.

Collection of clinical and laboratory data

The collected clinical and laboratory data included age, menopausal status, tumor biomarkers, pathological type, and FIGO stage. Serum CA125 and HE4 levels were measured utilizing the chemiluminescent assay kit provided

by Roche, with testing performed within one week before surgery. The malignancy probability was retrospectively assigned by two radiologists (with 6/8 years of experience) in accordance with the standards of the O-RADS MRI risk stratification system. Data collection was sanctioned by the Ethics Committee at Nanjing Women and Children’s Healthcare Hospital, adhering to the principles of the Declaration of Helsinki (2023KY-037).

Statistical analysis

Data analysis was conducted with the Statistical Package for Social Sciences (SPSS) for Windows, version 19.0. Continuous variables are depicted as mean±standard

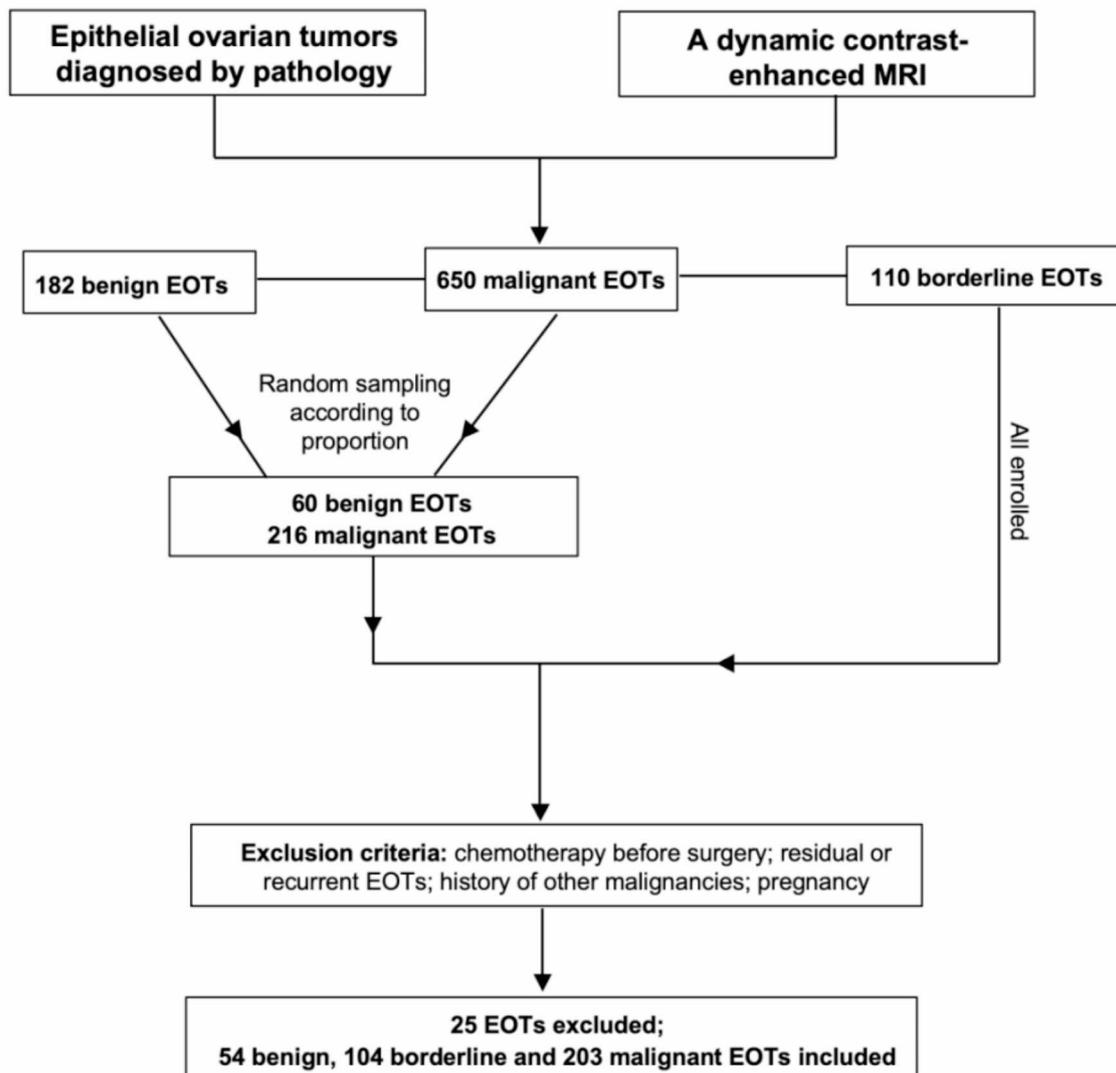


Fig. 1 Flowchart of inclusion and exclusion

deviations. Normality of data was tested using the Kolmogorov-Smirnov test. Based on the results of the normality test, characteristic differences across the three and two groups were evaluated by either a one-way ANOVA or Kruskal-Wallis test and a t-test or Mann-Whitney test, respectively. Differences in the proportions of time-intensity curves (TICs) among EOTs were analyzed employing Fisher's exact test. The cut-off value, sensitivity, and specificity were defined by the maximum Youden index of receiver operating characteristic (ROC) curves, and differences in the area under the curve (AUC) were detected via DeLong's test. A *P* value < 0.05 was considered statistically significant.

Results

External validation of the O-RADS MRI risk stratification system and the clinicopathological characteristics of EOTs

The distributions of O-RADS MRI risk scores and clinicopathological characteristics among BeEOTs, BEOTs and MEOTs are shown in Table 1. Among 54 BeEOTs, a higher proportion were classified as O-RADS MRI 3 compared to O-RADS MRI 2 (66.67% vs. 29.63%), and O-RADS MRI scores of 4 and 5 each accounted for 1.85% (1/54). The risk stratification of BEOTs also ranged from O-RADS MRI 2 to 5. Of 104 BEOTs, 1 (0.96%), 53 (50.96%), 40 (38.46%), and 10 (9.62%) were classified as O-RADS MRI 2/3/4/5, respectively. 86.2% (175/203) MEOTs scored 4/5, whereas 13.8% (28/203) scored 3. No risk score of 2 was assigned to any of the MEOTs.

68.52% (37/54) of BeEOTs and 82.69% (86/104) of BEOTs enrolled were premenopausal, whereas postmenopausal patients accounted for the majority of MEOTs (53.2%, 108/203). Serous, mucinous, serous-mucinous, and relatively rare endometrioid types were enrolled in BeEOTs and BEOTs. Serous (60.1%, 122/203), mucinous (7.39%, 15/203), endometrioid (13.79%, 28/203), clear cell (16.26%, 33/203), serous-mucinous (1.48%, 3/203) types were the main components of MEOTs. In addition, 1 malignant ovarian Brenner tumor and 1 ovarian carcinosarcoma were also enrolled into the MEOT group.

Of 203 MEOTs, 102 (50.25%) were in the early group (FIGO stage I-II), and 101 (49.75%) were in the advanced group (FIGO stage III-IV); the proportions of the two groups were nearly equal. Among MEOTs, the risk score of O-RADS MRI 5 was more prevalent in the advanced group (62.38%) whereas O-RADS MRI 4 was more prevalent in early group (61.76%), and the proportion of O-RADS MRI 3 in the early group was slightly higher than that in the advanced group (15.69% vs. 11.88%). Of 104 BEOTs, 87 (83.65%) were diagnosed at an early stage (FIGO stage I), whereas 17 (16.35%) were diagnosed at an advanced stage (FIGO stage II-IV).

Table 1 O-RADS MRI scores and clinicopathological characteristics of 361 EOTs

Variable	Nature	BeEOT					BEOT					MEOT					Reference level
		O-RADS MRI	2	3	4	5	O-RADS MRI	2	3	4	5	O-RADS MRI	3	4	5		
	No. (%)	16 (29.63)	36 (66.67)	1 (1.85)	1 (1.85)	1 (1.85)	1 (0.96)	53 (50.96)	40 (38.46)	10 (9.62)	28 (13.80)	89 (43.84)	86 (42.36)	/			
Menopausal status		10	25	1	1	1	0	40	37	9	18	45	32	/			
		6	11	0	0	0	1	13	3	1	10	44	54				
Pathological type		10	9	1	0	0	0	36	27	4	17	40	65	/			
		4	25	0	0	0	1	10	9	4	5	9	1				
		0	0	0	1	1	0	1	0	1	2	20	6				
		0	0	0	0	0	0	0	0	0	3	19	11				
		2	2	0	0	0	0	6	4	1	1	1	1				
		0	0	0	0	0	0	0	0	0	0	0	2				
FIGO stage	I	/					1	47	31	8	13	40	14	I-IV			
	II						0	2	1	0	3	23	9				
	III-IV						0	4	8	2	12	26	63				

/: not applicable

Other pathological types of MEOTs included 1 ovarian Brenner tumor and 1 ovarian carcinosarcoma

Table 2 MRI features of EOTs classified as O-RADS MRI 3

Variable		BeEOT No. (%)	BEOT No. (%)	MEOT No. (%)
O-RADS MRI 3	No solid tissue	30 (83.33)	1 (1.89)	1 (3.57)
	Solid tissue with a low-risk TIC	6 (16.67)	52 (98.11)	27 (96.43)
	<i>P</i> value	ac		

Solid tissue is defined as a lesion component that enhances and conforms to one of the following morphologies: papillary projection, mural nodule, irregular septation/wall or other larger solid port

^a The difference between benign and borderline EOTs was statistically significant

^c The difference between benign and malignant EOTs was statistically significant

Table 3 Differences in tumor biomarkers of EOTs among the O-RADS MRI 3, 4, and 5 categories

Variable		O-RADS MRI 3	O-RADS MRI 4	O-RADS MRI 5	Reference level
CA125 (U/mL)	BeEOT	18.34±25.98	/	/	0–35
	BEOT	84.64±152.3	92.02±124.2	62.82±68.68	
	MEOT	321.1±397.3	496.1±780.8	703.9±867.1	
	<i>P</i> value	<0.0001 ^{abc}	<0.0001	0.0008	
ROMA index (%) Premenopausal	BeEOT	5.952±3.182	/	/	< 11.4
	BEOT	9.877±6.591	11.84±13.86	7.366±5.455	
	MEOT	25.92±17.32	43.45±29.52	74.71±31.24	
	<i>P</i> value	<0.0001 ^{abc}	<0.0001	<0.0001	
ROMA index (%) Postmenopausal	BeEOT	10.59±3.032	/	/	< 29.9
	BEOT	30.48±24.10	/	/	
	MEOT	40.78±26.39	61.10±31.22	73.06±29.75	
	<i>P</i> value	0.0102 ^{ac}	/	/	

/: not applicable

^a The difference between benign and borderline EOTs was statistically significant

^b The difference between borderline and malignant EOTs was statistically significant

^c The difference between benign and malignant EOTs was statistically significant

CA125 aids in screening MEOTs from EOTs with low-risk TICs in the O-RADS MRI 3 category

The MRI features of EOTs scored 3 and representative images of solid tissue with a low-risk TIC are shown in Table 2 and Supplementary Data 1, respectively. Only 1 (3.57%) of 28 MEOTs and 1 (1.89%) of 53 BEOTs assigned as O-RADS MRI 3 did not have solid tissue with a low-risk TIC. However, the prevalence of BeEOTs having solid tissue with a low-risk TIC in the O-RADS MRI 3 category was 16.67% (6/36), with a much lower rate than BEOTs and MEOTs (both $P < 0.0001$).

As shown in Table 3, among EOTs scored as O-RADS MRI 3, premenopausal MEOTs tended to have a higher ROMA index than premenopausal BEOTs did ($P = 0.0012$). However, no significant difference in the ROMA index was found between postmenopausal MEOTs and postmenopausal BEOTs ($P = 0.3403$). However, CA125 demonstrated a notable gradient variation among BeEOTs, BEOTs, and MEOTs classified as O-RADS MRI 3 ($P = 0.0001$). The AUC, cut-off value, sensitivity, and specificity of CA125 for distinguishing MEOTs from BeEOTs and BEOTs with a low-risk TIC were 0.7466, 60.39 U/ml, 70.37% and 80.7%, respectively (Supplementary Data 3).

Among EOTs with a low-risk TIC but a CA125 level lower than 60.39 U/ml (subgroup 1), 87.5% (7/8) MEOTs were at FIGO stage I, and 12.5% (1/8) MEOT was at FIGO stage II, 62.5% (5/8) had normal CA125, HE4, and ROMA index levels (Table 4, Supplementary Data 2). 95% (38/40) BEOTs were at FIGO stage I. Among EOTs with a low-risk TIC and $CA125 \geq 60.39$ U/ml in the O-RADS MRI 3 category (subgroup 2) (Table 4), no BeEOTs were included, 33.33% (4/12) BEOTs were at advanced FIGO stage (II-IV) and 63.16% (12/19) MEOTs were at advanced FIGO stage (III-IV).

The ROMA index facilitates distinguishing between BEOTs and MEOTs of O-RADS MRI 4/5

48.08% BEOTs and 86.2% MEOTs were assigned a risk score of 4/5, but it remains challenging to distinguish them using O-RADS MRI system alone. The premenopausal ROMA index and CA125 level were both significantly higher in MEOTs than in BEOTs within the O-RADS MRI 4 and 5 categories (Table 3). The premenopausal ROMA index had a better application value than CA125 in distinguishing BEOTs and MEOTs in terms of sensitivity and specificity, although no meaningful distinctions were observed in the AUC ($P = 0.2783$), and the optimal cut-off value was 20.14% (Supplementary Data

Table 4 The distribution of FIGO stages in six subgroups of EOTs, stratified by O-RADS MRI, CA125 levels, or the ROMA index

Variable	O-RADS MRI 3 with a low-risk TIC						O-RADS MRI 4/5 (Premenopausal)						O-RADS MRI 4/5 (Postmenopausal)						
	CA125 < 60.39 U/ml (subgroup 1)		CA125 ≥ 60.39 U/ml (subgroup 2)		ROMA index < 20.14% (subgroup 3)		ROMA index ≥ 20.14% (subgroup 4)		ROMA index < 29.9% (subgroup 5)		ROMA index ≥ 29.9% (subgroup 6)		ROMA index < 29.9% (subgroup 5)		ROMA index ≥ 29.9% (subgroup 6)				
	BeEOT	MEOT	BeEOT	MEOT	BeEOT	MEOT	BeEOT	MEOT	BeEOT	MEOT	BeEOT	MEOT	BeEOT	MEOT	BeEOT	MEOT			
Total	6	40	8	8	0	12	19	2	43	16	0	3	61	0	4	13	0	0	85
FIGO stage I	/	38	7	/	/	8	5	/	34	10	/	1	16	/	4	10	/	0	18
II	0	0	1	2	2	2	2	0	1	4	0	0	10	0	0	1	0	0	17
III	2	2	0	2	2	2	12	2	8	2	2	2	35	0	0	1	0	1	48
IV	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	2

/: not applicable

3). Among premenopausal EOTs classified as O-RADS MRI 4/5 with a ROMA index below 20.14% (subgroup 3), 62.5% (10/16) and 25.0% (4/16) MEOTs were at FIGO stage I and II, respectively. 81.4% (35/43) BEOTs were at FIGO stage I-II. Two BeEOTs were also included in subgroup 3 (Table 4, Supplementary Data 2). Among premenopausal EOTs classified as O-RADS MRI 4/5 with a ROMA index higher than 20.14% (subgroup 4), 57.38% (35/61) MEOTs and 66.67% (2/3) BEOTs were at FIGO stage III, respectively. No BeEOTs were included in subgroup 4 (Table 4, Supplementary Data 2).

Considering the low incidence of postmenopausal BEOTs with O-RADS MRI 4/5, a ROMA index ≥ 29.9% (postmenopausal), representing a high risk for ovarian cancer in clinical practice, was selected as the cut-off value; the corresponding sensitivity and specificity were 82.47% and 100%, respectively. Among postmenopausal EOTs scoring 4/5 with a ROMA index below 29.9% (subgroup 5), 76.92% (10/13) and 7.69% (1/13) MEOTs were at FIGO stage I and II, respectively. All 4 BEOTs were at FIGO stage I, and no BeEOTs were included (Table 4, Supplementary Data 2). Among postmenopausal EOTs scoring 4/5 with a ROMA index higher than 29.9% (subgroup 6), 58.82% (50/85) MEOTs were at FIGO stage III-IV. No BeEOTs or BEOTs were included (Table 4, Supplementary Data 2).

Discussion

The O-RADS MRI system has been proposed to assign malignancy probability to adnexal lesions indeterminate under the US. In general, it was demonstrated that this system was highly accurate in differentiating BeEOTs from MEOTs and BEOTs in the O-RADS MRI 2/4/5 categories. However, more management recommendations are needed for each risk category, particularly for the 3/4/5 categories. Moreover, distinguishing between BEOTs and MEOTs is crucial for young patients wishing to preserve fertility and elderly patients who cannot tolerate over-extensive surgery in the O-RADS MRI 4/5 category. Nevertheless, these challenges remain difficult to address using O-RADS MRI alone.

As demonstrated by the prospective study [10] and this retrospective study, three different types of EOTs accounted for a non-negligible proportion of the O-RADS MRI 3 category; thus, the primary goal is to avoid unnecessary or over-extensive surgeries of BeEOTs and BEOTs and to conduct timely surgical evaluations for MEOTs. Previous studies [11–14] indicate that the malignancy risk is nearly zero in the absence of solid tissue. We also observed an extremely low proportion of BEOTs and MEOTs without a low-risk TIC in the O-RADS MRI 3 category, and all of them had normal tumor biomarkers (Supplementary Data 2). Therefore, it is critical and efficient to screen for MEOTs among EOTs with a low-risk

TIC in the O-RADS MRI 3 category and a CA125 level higher than 60.39 U/ml could be highly beneficial. Specifically, EOTs in subgroup 2 should be promptly referred for surgical evaluation, avoiding delayed treatment of MEOTs, unnecessary surgery of BeEOTs and early FIGO stage BEOTs; In subgroup 1, 8 MEOTs were all at an early FIGO stage and most of them were difficult to diagnose even when tumor biomarkers were combined. Therefore, for EOTs in subgroup 1, elective surgery is recommended, and close follow-up is necessary if elective surgery is refused by patients; For EOTs without a low-risk TIC in the O-RADS MRI 3 category, elective surgery or routine follow-up is optional.

48.08% of BEOTs and 86.2% of MEOTs were classified as the O-RADS MRI 4/5 categories, while EOTs were only 3.7%. Therefore, EOTs with an O-RADS MRI score of 4/5 should receive semi-elective surgery because of the high probability of MEOTs and BEOTs. However, the surgical scope of BEOTs and MEOTs varies greatly, especially for those younger than 40 years with fertility preservation needs and elderly patients who cannot tolerate over-extensive surgery, which needs further exploration. The optimal cut-off values of the ROMA index for distinguishing between BEOTs and MEOTs with scores of 4/5 were 20.14% (premenopausal) and 29.9% (postmenopausal), respectively. For EOTs in subgroup 3, 87.5% MEOTs and 81.40% BEOTs were at FIGO stage I-II and 2 BeEOTs were included as well. Therefore, EOTs

in subgroup 3 are recommended to undergo diagnostic surgery to further identify their nature, followed by therapeutic surgery. Either diagnosis or therapy could be conducted with minimally invasive surgery for most of the patients in terms of FIGO stage. Furthermore, this subgroup was mainly composed of BEOTs and FIGO stage I MEOTs, and from the perspective of FIGO stages and age of onset, there is a substantial demand for fertility preservation and a high possibility of performing related surgery in subgroup 3 should be considered; For EOTs in subgroup 4, 57.38% MEOTs and 66.67% BEOTs were at FIGO stage III, respectively. No BeEOTs were included in subgroup 4. Therefore, premenopausal EOTs in subgroup 4 are recommended to undergo comprehensive staging or cytoreductive surgery when there is no need for fertility preservation; For EOTs in subgroup 5, 76.92% MEOTs were at FIGO stage I-II, while all BEOTs were at FIGO stage I, and no BeEOTs were included. Therefore, minimally invasive surgery is also recommended for diagnostic and subsequent therapeutic procedures in subgroup 5, thus benefiting elderly patients who cannot tolerate over-extensive surgery; For EOTs in subgroup 6, no BeEOTs and BEOTs were included, and 58.82% MEOTs were at FIGO stage III-IV. Therefore, comprehensive staging or cytoreductive surgery is recommended for patients of subgroup 6.

In addition, an O-RADS MRI score of 1 is given when the ovaries appear normal, indicating that no treatment is

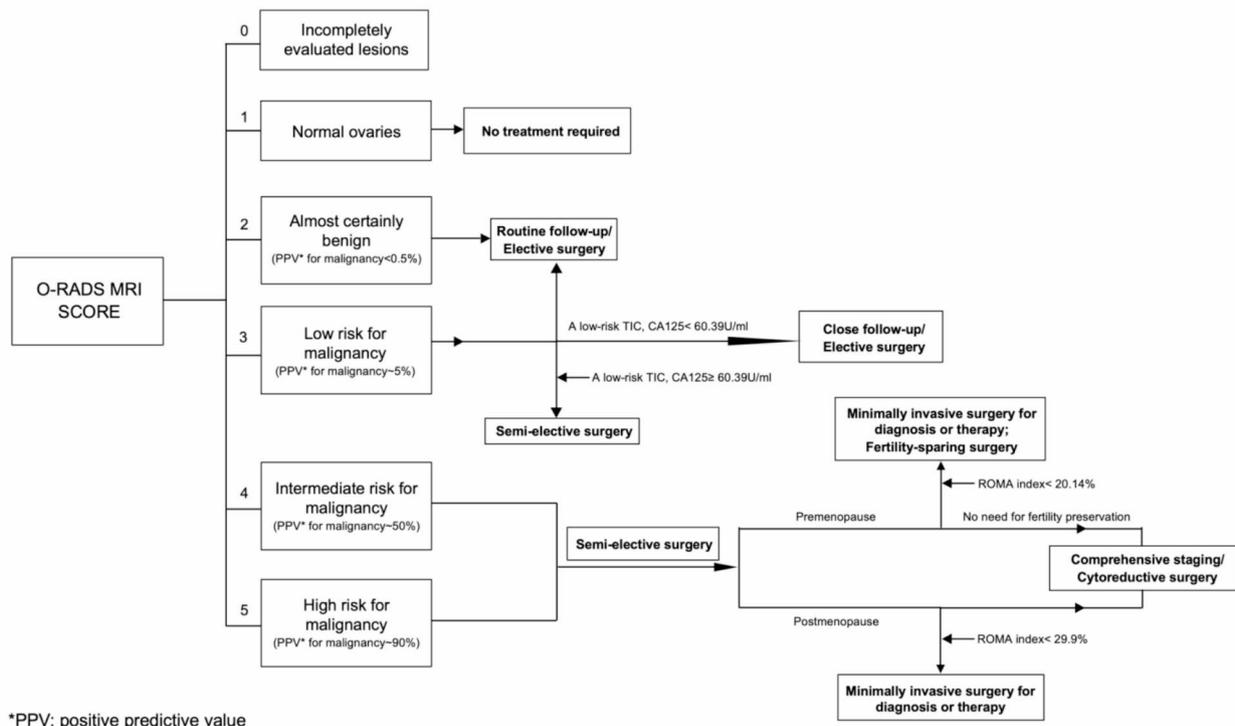


Fig. 2 Flowchart of the clinical management of EOTs combining O-RADS MRI risk scores and tumor biomarkers

needed. EOTs with a score of 2 are eligible for routine follow-up or elective surgery because of the low possibility of BEOTs and MEOTs. On the basis of the above analysis and referring to the clinical management recommendations from previous studies [10, 15], we propose the corresponding improvement measures in conjunction with tumor biomarkers, and the flowchart is as follows (Fig. 2).

There are also some restrictions that need to be addressed in upcoming studies. First, multi-center studies, larger sample sizes and even prospective studies are required to verify the diagnostic efficiency and identify the best cut-off values for the ROMA index and CA125 in determining the nature of EOTs. Second, although the clinical management recommendations for the O-RADS MRI risk stratification system, which integrates tumor biomarkers based on this retrospective study, seem useful and promising, it must be further validated and improved prospectively. Third, there is a need for specific biomarkers such as metabolic factors [16–18] for non-epithelial ovarian tumors or other serum markers that can effectively distinguish between benign, borderline, and malignant EOTs, to enhance the clinical utility of the O-RADS MRI risk stratification system. Fourth, while this study focused primarily on the role of tumor biomarkers in enhancing the clinical management within the O-RADS MRI risk stratification system for EOTs, it is crucial to recognize that additional imaging features from MRI and even PET-MRI [19] to differentiate between various types of EOTs, could also make a substantial contribution to the stratification of ovarian cancer.

Conclusions

The O-RADS MRI risk stratification system was highly accurate in differentiating benign from borderline and malignant EOTs within the O-RADS MRI 2/4/5 categories. The incorporation of tumor biomarkers significantly enhanced diagnostic precision and clinical management within the O-RADS MRI risk stratification system, particularly for highly suspected EOTs, especially those in the O-RADS MRI 3/4/5 categories.

Abbreviations

EOT	Epithelial ovarian tumor
O-RADS	Ovarian-Adnexal Reporting and Data System
BeEOT	Benign epithelial ovarian tumor
BEOT	Borderline epithelial ovarian tumor
MEOT	Malignant epithelial ovarian tumor
ROC	Receiver operating characteristic curve
CA125	Cancer antigen 125
TIC	Time-intensity curve
US	Ultrasound
HE4	Human epididymis protein 4
AUC	Area under the curve

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12957-024-03648-3>.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions

Shengjie Xu, Weijian Gong made substantial contributions to the analysis and interpretation of data and were involved in drafting the manuscript and revising it critically for important intellectual content. Xiyi Chen, Jiatong Wang and Yuan Zhu were responsible for data collection and management. Yun Gu made significant contributions to the analysis and interpretation of pathology reports. JinXia Zheng and Tao Zhang made significant contributions to the analysis and interpretation of image reports. Juan Xu provided financial support for the study. Jinxia Zheng and Juan Xu contributed substantially to the conception, design, and acquisition of data and gave final approval for the version to be published. All authors read and approved the final manuscript.

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Data availability

The data are not publicly accessible but are available upon reasonable request from the corresponding author.

Declarations

Ethics approval and consent to participate

Data collection was sanctioned by the Ethics Committee at Nanjing Women and Children's Healthcare Hospital, adhering to the principles of the Declaration of Helsinki (Approval Number: 2023KY-037). Given the retrospective study design, the informed consent was waived off by the institutional review board.

Competing interests

None.

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References

1. Torre LA, Trabert B, DeSantis CE, Miller KD, Samimi G, Runowicz CD, et al. Ovarian cancer statistics, 2018. *Cancer J Clin*. 2018;68:284–96.
2. Crafton SM, Cohn DE, Llamocca EN, Loudon E, Rhoades J, Felix AS. Fertility-sparing surgery and survival among reproductive-age women with epithelial ovarian cancer in 2 cancer registries. *Cancer*. 2020;126:1217–24.
3. Raad J, Rolland L, Grynberg M, Courbiere B, Mathieu d'Argent E. [Borderline Ovarian tumours: CNGOF guidelines for clinical practice - fertility]. *Gynecol Obstet Fertil Senol*. 2020;48:330–6.

4. Andreotti RF, Timmerman D, Strachowski LM, Froyman W, Benacerraf BR, Bennett GL, et al. O-RADS US Risk Stratification and Management System: a Consensus Guideline from the ACR ovarian-adnexal reporting and Data System Committee. *Radiology*. 2020;294:168–85.
5. Levine D, Brown DL, Andreotti RF, Benacerraf B, Benson CB, Brewster WR, et al. Management of asymptomatic ovarian and other adnexal cysts imaged at US Society of Radiologists in Ultrasound consensus conference statement. *Ultrasound Q*. 2010;26:121–31.
6. Timmerman D, Van Calster B, Testa A, Savelli L, Fischerova D, Froyman W, et al. Predicting the risk of malignancy in adnexal masses based on the simple rules from the International Ovarian Tumor Analysis group. *Am J Obstet Gynecol*. 2016;214:424–37.
7. Sadowski EA, Thomassin-Naggara I, Rockall A, Maturen KE, Forstner R, Jha P, et al. O-RADS MRI risk stratification system: guide for assessing Adnexal lesions from the ACR O-RADS Committee. *Radiology*. 2022;303:35–47.
8. Bottoni P, Scatena R. The role of CA 125 as tumor marker: biochemical and clinical aspects. *Adv Exp Med Biol*. 2015;867:229–44.
9. Moore RG, Brown AK, Miller MC, Skates S, Allard WJ, Verch T, et al. The use of multiple novel tumor biomarkers for the detection of ovarian carcinoma in patients with a pelvic mass. *Gynecol Oncol*. 2008;108:402–8.
10. Thomassin-Naggara I, Poncelet E, Jalaguier-Coudray A, Guerra A, Fournier LS, Stojanovic S, et al. Ovarian-Adnexal Reporting Data System Magnetic Resonance Imaging (O-RADS MRI) score for risk stratification of Sonographically Indeterminate Adnexal masses. *JAMA Netw Open*. 2020;3:e1919896.
11. Kaijser J, Vandecaveye V, Deroose CM, Rockall A, Thomassin-Naggara I, Bourne T, et al. Imaging techniques for the pre-surgical diagnosis of adnexal tumours. *Best Pract Res Clin Obstet Gynaecol*. 2014;28:683–95.
12. Forstner R, Thomassin-Naggara I, Cunha TM, Kinkel K, Masselli G, Kubik-Huch R, et al. ESUR recommendations for MR imaging of the sonographically indeterminate adnexal mass: an update. *Eur Radiol*. 2017;27:2248–57.
13. Bernardin L, Dilks P, Liyanage S, Miquel ME, Sahdev A, Rockall A. Effectiveness of semi-quantitative multiphase dynamic contrast-enhanced MRI as a predictor of malignancy in complex adnexal masses: radiological and pathological correlation. *Eur Radiol*. 2012;22:880–90.
14. Thomassin-Naggara I, Aubert E, Rockall A, Jalaguier-Coudray A, Rouzier R, Daraï E, et al. Adnexal masses: development and preliminary validation of an MR imaging scoring system. *Radiology*. 2013;267:432–43.
15. Sasaguri K, Yamaguchi K, Nakazono T, Mizuguchi M, Aishima S, Yokoyama M, et al. External validation of ADNEX MR SCORING system: a single-centre retrospective study. *Clin Radiol*. 2019;74:131–9.
16. Lin J, Wang L, Huang M, Xu G, Yang M. Metabolic changes induced by heavy metal copper exposure in human ovarian granulosa cells. *Ecotoxicol Environ Saf*. 2024;285:117078.
17. Han L, Xu S, Zhou D, Chen R, Ding Y, Zhang M, et al. Unveiling the causal link between metabolic factors and ovarian cancer risk using mendelian randomization analysis. *Front Endocrinol (Lausanne)*. 2024;15:1401648.
18. Wu N, Zhang X, Fang C, Zhu M, Wang Z, Jian L et al. Progesterone enhances Niraparib Efficacy in Ovarian Cancer by promoting palmitoleic-acid-mediated ferroptosis. *Research (Wash D C)*. 2024; 7: 0371.
19. Zou Y, Zhu S, Kong Y, Feng C, Wang R, Lei L et al. Precision matters: the value of PET/CT and PET/MRI in the clinical management of cervical cancer. *Strahlenther Onkol*. 2024.

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