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CLINICAL ARTICLE

Comparative diagnostic performance of the early-stage ovarian malignancy score versus other risk prediction models in early-stage ovarian cancer: A Vietnamese prospective cohort study

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Abstract

Objective: This study compares the diagnostic performance of the early-stage ovarian malignancy (EOM) score against other risk prediction models for identifying early-stage ovarian cancer.

Methods: This prospective cohort study involved 925 cases from the obstetrics and gynecology departments of two tertiary hospitals from May 2018 to December 2023. The data included gynecologic examination and/or ultrasound findings, menopausal status, ultrasonography features, serum CA125, and HE4 values, which were used to calculate the EOM score and compare it with other algorithms. Preoperative predictions were validated against postoperative histopathological data.

Results: In total, 792 cases (85.62%) were benign tumors, 74 cases (8.00%) were identified as early-stage ovarian cancer, and 59 cases (6.38%) were classified as advanced-stage ovarian cancer. With a cut-off of ≥13, the EOM score achieved an area under the curve (AUC) value of 0.908 for distinguishing between cancer and non-cancer, demonstrating sensitivity of 83.46% and specificity of 82.90%. For early-stage cancer, the EOM score had an AUC value of 0.843. The EOM score outperformed the risk of malignancy index, the risk of ovarian malignancy algorithm, CPH-I, CA125, and HE4 ($P < 0.05$).

Conclusion: The EOM score is a straightforward and effective tool for predicting early-stage ovarian cancer, yielded performance similar to the IOTA Simple Rules combined with CA125.

KEYWORDS
CA-125, early-stage cancer, IOTA, ovarian neoplasms, predictive value of tests, ultrasonography

1 | INTRODUCTION

Ovarian cancer is among the deadliest gynecological cancers, surpassed only by breast and cervical cancers in terms of mortality rates.[1] The risk of ovarian cancer rises with age, and unfortunately, the early stages often show no symptoms, leading to over 75% of cases being diagnosed at an advanced stage.[2] Diagnosing ovarian cancer is challenging due to its silent progression and limited symptoms. Symptoms of ovarian cancer, such as bloating, pelvic or abdominal pain, difficulty eating, or urinary issues, are often overlooked until after a diagnosis has been made.[3,4]

While various tests aim to improve ovarian cancer prediction, a multimodal approach is recommended due to certain limitations. However, there is currently no definitive preoperative test to distinguish between benign and malignant pelvic tumors. The risk of ovarian malignancy algorithm (ROMA) and the risk of malignancy index (RMI) utilize biomarkers, ultrasound, and age for risk assessment. Therefore, an accurate preoperative diagnosis is crucial for optimal treatment and prognosis.[5–7] Ovarian cancer currently lacks recommended screening tests. There is an urgent need for new diagnostic methods for early-stage detection, when treatment is most effective.[8]

The early-stage ovarian malignancy (EOM) score, which integrates ultrasound, size, menopausal status, and CA125 level, effectively predicted EOM preoperatively.[9] External validity studies confirmed its predictive power in advanced-stage patients.[10] Thus, this study aimed to validate the EOM score for predicting early-stage ovarian cancer and compare its efficacy with other malignancy risk indices.

2 | MATERIALS AND METHODS

2.1 | Design and setting

This prospective cohort study was conducted at the Obstetrics and Gynecology Units of Hue University of Medicine and Pharmacy Hospital and Hue Central Hospital from May 2018 to December 2023. The Ethical Committee for Biomedical Research at Hue University of Medicine and Pharmacy granted ethical approval for the study (Decision No. H2022/048). All participants provided written informed consent.

Inclusion criteria: The study included women diagnosed with ovarian tumors who were scheduled for surgery. Participants underwent preoperative ultrasounds, and their postoperative pathology was examined.

Exclusion criteria: Patients were excluded if they had pseudocysts, hydrosalpinx, para-ovarian cysts, uterine fibroids, pregnancy-related ovarian tumors, or a history of malignancy treatment. We also did not include patients diagnosed with endometrial cancer showing metastasis to the adnexa or presenting other types of secondary ovarian cancer in the study.

2.2 | Sample size

The sample size for the development set was determined using a formula from Hanley et al. to estimate the necessary sample size for achieving an area under the receiver operating characteristic curve[11]:

$$n=\left(\frac{Z_{1-\alpha/2}}{\Delta}\right)^2 \times \frac{\mathrm{AUC}(1-\mathrm{AUC})+(n\times p-1)\left(Q_1-\mathrm{AUC}^2\right)+(n\times(1-p)-1)\left(Q_2-\mathrm{AUC}^2\right)}{(n\times p)\times(n\times(1-p))}$$

with:

$$Q_1=\frac{\mathrm{AUC}}{2-\mathrm{AUC}}$$

$$Q_2=\frac{2\times\mathrm{AUC}^2}{1+\mathrm{AUC}}$$

Here, Z is the "Z" value for $a=1.96$, with $\alpha=0.05$; AUC (area under the curve) refers to the expected AUC of 85%; Δ represents the desired width of the confidence interval, which is 0.1; p indicates the prevalence of ovarian cancer at 10.8%.[12] We calculated that the minimum sample size needed was 864, which was adjusted to 925 subjects to account for the dropout rate. The STROBE flow diagram illustrates participant enrollment and exclusion (Figure 1).

2.3 | Study protocol

Initial assessment

All participants thoroughly evaluated their medical histories and clinical assessments to determine eligibility and identify exclusion criteria. In the ultrasound examination, all women underwent thorough ultrasonography of the uterus and adnexa utilizing the Samsung-Medison UGEO WS80A, Siemens Acuson NX2 Elite, and Toshiba Aplio 400. Both transabdominal and transvaginal methods were used for patients presenting with a pelvic mass during gynecological evaluations, aiding in the diagnosis of ovarian tumors. The abdominal probe functioned at a frequency of 1–6 MHz, while the transvaginal probe operated at 6 MHz. The machines provided comprehensive capabilities, encompassing TM, 2D, 3D, and 4D modes and color Doppler and power Doppler functionalities. Ultrasound examinations were performed by an experienced gynecologist/radiologist with at least 5 years of experience in gynecological ultrasonography and ultrasound certification. The characterization of these tumors followed the consensus guidelines set by the International Ovarian Tumor Analysis (IOTA) group.[13] Key morphologic parameters were meticulously assessed and documented, including multilocularity (≥ two locules), solid component (tissue-like echogenicity), bilaterality (both ovaries), ascites (fluid beyond the Douglas pouch), and intra-abdominal metastases (extra-uterine masses). Vascularization was evaluated using a color score (1 = no flow to 4 = strong flow). If the bilateral adnexal mass was

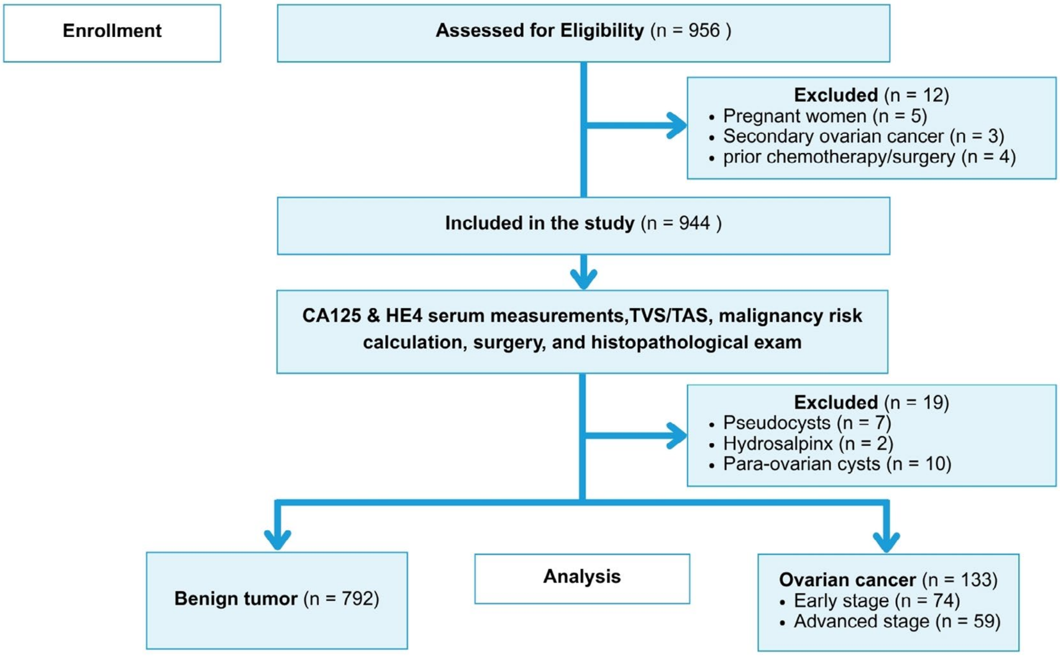

FIGURE 1 Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Flow Diagram. TVA, transabdominal ultrasonography; TVS, transvaginal ultrasonography.

presented, we selected the lesion with the most suspicious features for malignancy (index lesion) for risk stratification.[13]

Biomarker analysis

Blood samples were collected from all participants to analyze serum CA125 and HE4 levels, key biomarkers for ovarian cancer. To preserve the samples, the blood was centrifuged and fractionated into serum within 3h of collection, then stored at −80°C until testing. Testing for CA125 and HE4 was conducted at Hue University Hospital of Medicine and Pharmacy using a Luminescent Electrochemical Immunoassay on the COBAS 6000 system (Roche, Switzerland) and at Hue Central Hospital using a chemiluminescent microparticle immunoassay on the Architect i1000 system (Abbott Diagnostics, USA). An internal quality control system using RANDOX standard control samples was implemented to ensure the accuracy and reliability of the results.

Surgical procedure and staging

After a multidisciplinary review, patients underwent surgery. Surgeons assessed and staged ovarian tumors intraoperatively following the FIGO 2014 guidelines. Early-stage cancer included FIGO stages I, II, and IIIA1 and borderline tumors.[14] In cases where ovarian cancer with metastasis to other organs was identified, we categorize ovarian tumors as either early or advanced stages exclusively based on their FIGO staging.

TABLE 1 Components of the early-stage ovarian malignancy score.

Components	EOM Score
Menopausal status	
Pre-menopause	0
Post-menopaus	7
Ultrasonographic features	
None	0
Solid component	3
Ascites	13
Size of tumor (cm)	
<9	0
9–12	10
>12	16
CA125 (U/mL)	
<30	0
30–200	1
>200	12

Abbreviations: CA125, cancer antigen 125; EOM, early-stage ovarian malignancy.

Histopathological assessment

All participants underwent a complete histopathological or immunohistochemical evaluation of the excised tissue after surgery.

The assessments were performed at the pathology departments of both hospitals using hematoxylin and eosin or immunohistochemical staining. Diagnosis and classification adhered to the criteria established by the World Health Organization in 2014, the gold standard for ovarian tumor diagnosis.[15] We excluded cases of secondary ovarian cancer based on pathological features and immunohistochemicals, where the tumor characteristics and histologic patterns were consistent with metastatic disease rather than independent primary ovarian malignancies.

Early-stage ovarian malignancy score

The EOM score was calculated for each participant based on five preoperative clinical predictors, as defined by Chirdchim et al.: menopausal status, tumor size (maximum tumor diameter), two ultrasonographic features (presence of solid component and ascites), and preoperative serum CA125 (refer to Table 1).[9] The maximum EOM score is 51, with established cut-off values of ≥15 and ≥30. An external validity study by Phinyo et al. demonstrated that the EOM score can effectively predict advanced stages of ovarian cancer in patients.[10]

Comparative analysis

Risk malignancy indices (I–IV): Four distinct versions of the RMI were calculated, each incorporating ultrasound findings, menopausal status, and serum CA125 levels, with variations in the weighting of these factors:

$$\text{RMI I} = \text{U} \times \text{M} \times \text{CA125}$$

(U: Ultrasound score (0=0, 1=1, ≥2=3); M: Menopausal status (premenopausal=1, postmenopausal=3); CA125).[16]

$$\text{RMI II} = \text{U} \times \text{M} \times \text{CA125}$$

(U: Ultrasound score (0 or 1=1, ≥2=4); M: Menopausal status (premenopausal=1, postmenopausal=4); CA-125).[17]

$$\text{RMI III} = \text{U} \times \text{M} \times \text{CA} - 125$$

(U: Ultrasound score (0 or 1=1, ≥2=3); M: Menopausal status (premenopausal=1, postmenopausal=3); CA125).[18]

$$\text{RMI IV} = \text{U} \times \text{M} \times \text{S} \times \text{CA} - 125$$

(U: Ultrasound score (0 or 1=1, ≥2=4); M: Menopausal status (premenopausal=1, postmenopausal=4); S: Tumor size (single greatest diameter) (<7 cm=1, ≥7 cm=2); CA125).[19]

Risk of ovarian malignancy algorithm: The ROMA algorithm combines serum CA125 and HE4 levels with menopausal status to calculate a risk probability.[6]

$$\text{ROMA}\,(\%) = \exp(\text{PI}) / \left[1 + \exp(\text{PI})\right]^{*} 100$$

PI (Predictive Index) is calculated as:

$$\text{Pre} - \text{menopausal women: PI} = -12.0 + 2.38^{*}\,\text{Ln(HE4)} + 0.0626^{*}\,\text{Ln(CA125)}$$

$$\text{Post} - \text{menopausal women: PI} = -8.09 + 1.04^{*}\,\text{Ln(HE4)} + 0.732^{*}\,\text{Ln(CA125)}$$

Copenhagen index: The CPH-I is another scoring system that utilizes HE4, CA125, and patient age to predict the risk of ovarian malignancy.[7]

$$\text{CPH} - \text{I} = -14.0647 + 1.0649 \times \log(\text{HE4}) + 0.6050 \times \log2(\text{CA125}) + 0.2672 \times (\text{age}/10),$$

with $\text{PP} = e^{(\text{CPH-I})}/(1 + e^{(\text{CPH-I})})$.

The International Ovarian Tumor Analysis (IOTA) guidelines were employed for preoperative risk stratification, categorizing ovarian lesions as benign (B), malignant (M), or inconclusive (I). Benign lesions (B) were characterized by features such as unilocular cysts, solid components <7 mm, acoustic shadows, smooth multilocular tumors <100 mm, and absence of blood flow (color score 1). Malignant lesions (M) included irregular solid tumors, ascites, multiple papillary structures, irregular multilocular solid tumors ≥100 mm, and strong blood flow (color score 4). The classification was deemed benign if solely B features were present, malignant if solely M features were evident, and inconclusive if both sets of criteria were applicable or neither were.[20] We suggested combining CA125 levels with the IOTA SR to enhance diagnostic accuracy using multivariable logistic regression. This approach integrates ultrasound results and CA125 levels as independent variables to predict the probability of malignancy. The predictive probability formula is: $P\,(\%) = \frac{1}{1 + e^{-Z}}$.

$$Z = \beta_0 + \beta_1 \times \text{IOTA Simple Rules} + \beta_2 \times \log(\text{CA125}).$$

2.4 | Statistical analysis

Statistical analyses were performed using SPSS version 27.0 and R version 4.5.0. Variables were reported as *n* (%), mean ± standard deviation, or median (Q25%-Q75%), with a 95% confidence interval (CI). χ^2-tests assessed categorical associations, while ANOVA or Kruskal–Wallis tests compared groups. Differences in AUC values were evaluated through paired ROC area comparisons ($P < 0.05$).

3 | RESULTS

This study included 925 women with adnexal masses, and histopathological analysis revealed 792 benign neoplasms (85.62%), 74 early-stage ovarian carcinomas (8.00%), and 59 advanced-stage ovarian cancers (6.38%). Table 2 summarizes the characteristics of the participants.

Demographic analysis showed significant age differences among the groups. Patients with early-stage cancer had a higher average age (48.38) compared to the benign group (37.91, $P < 0.001$), while those with advanced-stage cancer were even older (57.73, $P < 0.001$). Postmenopausal status was more prevalent in both cancer groups than in the benign tumor group.

TABLE 2 Characteristics of women with adnexal masses.

Variables	Early stage ($n = 74$)		Advanced stage ($n = 59$)		Benign tumor ($n = 792$)		p
Group of age							
<20	3	4.05	0	0.00	56	7.07	<0.001
20–29	9	12.10	1	1.69	207	26.14	
30–39	9	12.16	2	3.39	212	26.77	
40–49	10	13.51	14	23.73	162	20.45	
50–59	25	33.78	18	30.51	82	10.35	
≥60	18	24.32	24	40.68	73	9.22	
Mean (SD)	48.38 (15.71)		57.73 (11.65)		37.91 (14.94)		<0.0001
Menopausal status							
Pre-menopause	36	48.65	16	27.12	649	81.94	<0.001
Post-menopause	38	51.35	43	72.88	143	18.06	
Characteristics of US							
Solid component	45	60.81	41	69.49	130	16.41	<0.0001
Multiloculation	10	13.51	7	11.86	61	7.70	0.141
Bilaterality	9	12.16	8	13.60	119	15.03	0.776
Ascites	22	29.73	43	72.88	13	1.64	<0.001
Intraabdominal metastasis	14	18.92	3	5.08	5	0.63	<0.001
Size of tumor (cm)							
<7	30	40.54	22	37.29	566	71.46	<0.001
7–12	20	27.03	17	28.81	145	18.31	
>12	24	32.43	20	33.90	81	10.23	
CA125 (Q25%–Q75%)	37.56 (19.96–144.10)		642.6 (239.7–1070)		19.03 (12.50–34.78)		<0.001
HE4 (Q25%–Q75%)	124.20 (60.36–202.70)		522.00 (282.8–913.5)		48.82 (35.27–105.2)		<0.001
Histopathology							
Epithelial-stromal tumor	66	89.19	52	88.14	472	59.60	<0.001
Germ cell tumor	6	8.11	6	10.17	288	36.36	
Sex cord-stromal tumor	2	2.70	1	1.69	32	4.04	
Stage of ovarian cancer							
Borderline	10	13.51	–	–	–	–	
I	37	50.00	–	–	–	–	
II	26	35.14	–	–	–	–	
IIIA1	1	1.35	–	–	–	–	
IIIA2-IIIC	–	–	47	79.66	–	–	
IV	–	–	12	20.34	–	–	

Note: Values are presented as number (%) or median (Q25%–75%) or mean (Standard Deviation).

Abbreviations: CA125, cancer antigen 125; cm, centimeter; HE4, human epididymal protein 4; US, Ultrasound.

Ultrasound findings showed that solid components were present in 60.81% of early-stage cancers and 69.49% of advanced-stage cancers, compared to only 16.41% in benign tumors ($P < 0.001$). Ascites was identified in 29.73% of early-stage cancers and 72.88% of advanced-stage cancers but only 1.64% of benign tumors ($P < 0.001$). Intra-abdominal metastasis was detected in 18.92% of early-stage cancers and 5.08% of advanced-stage cancers, while only 0.63% of benign cases exhibited such metastases ($P < 0.001$). Tumor size also varied significantly among the groups, with tumors ≥12 cm being more prevalent in the cancer groups (32.43% in early-stage and 33.90% in advanced-stage) compared to just 10.23% in the benign group ($P < 0.001$).

Serum CA125 and HE4 levels were significantly higher in the ovarian cancer groups compared to the benign group. The median CA125 levels for early-stage cancer were 37.56 U/mL (19.96–144.10), while for advanced-stage cancer, they were 642.6 U/mL (239.7–1070), and for benign tumors, 19.03 U/mL (12.50–34.78) ($P < 0.001$). The median HE4 levels were 124.20 pmol/mL for early-stage cancer (60.36–202.70), 522.00 pmol/mL for advanced-stage cancer, and 48.82 pmol/mL for benign tumors ($P < 0.001$).

TABLE 3 Diagnostic value and performance of various scoring models in ovarian cancer prognosis.

	Cut-off	AuROC	Se	Sp	PPV	NPV	LR
Cancer vs non-cancer							
EOM	≥13	0.908 (0.878–0.937)	83.46 (76.22–88.82)	82.95 (80.18–85.41)	45.12 (39.02–51.22)	96.76 (95.42–98.09)	4.12
CA125	≥34.5	0.816 (0.771–0.862)	75.94 (68.01–82.41)	74.75 (71.61–77.65)	33.55 (28.24–38.87)	94.87 (93.11–96.47)	3.00
HE4	≥184.5	0.840 (0.800–0.881)	60.15 (51.66–68.07)	93.81 (91.91–95.2)	62.02 (53.49–70.54)	93.34 (91.58–94.97)	9.72
RMI I	≥85.8	0.880 (0.841–0.919)	70.68 (62.45–77.75)	93.69 (91.77–95.18)	65.28 (57.64–72.92)	95.01 (93.47–96.41)	11.2
RMI II	≥114.4	0.871 (0.828–0.913)	78.20 (70.44–88.37)	89.77 (87.47–91.69)	56.22 (49.19–63.24)	96.08 (94.59–97.43)	7.65
RMI III	≥85.8	0.866 (0.823–0.909)	78.95 (71.26–85.01)	88.13 (85.69–90-20)	52.76 (45.73–59.80)	96.14 (94.63–97.52)	6.65
RMI IV	≥198.8	0.878 (0.838–0.918)	77.44 (69.63–83.72)	91.29 (89.12–93.06)	59.88 (52.33–66.86)	96.02 (94.55–97.34)	8.89
ROMA	≥28.1	0.861 (0.825–0.897)	79.70 (72.07–85.66)	74.24 (71.08–77.17)	34.19 (29.03–39.68)	95.61 (93.98–97.07)	3.09
CPH-I	≥6.7	0.886 (0.852–0.921)	78.82 (70.44–84.37)	84.60 (81.92–86.94)	46.02 (39.38–52.65)	95.85 (94.28–97.28)	5.08
IOTA SR+CA125	≥9.9	0.921 (0.892–0.951)	91.73 (85.80–95.32)	89.65 (87.33–91.58)	59.80 (52.94–66.67)	98.47 (97.50–99.31)	8.86
Early-stage cancer vs non-cancer							
EOM	≥13	0.843 (0.796–0.890)	70.27 (59.07–79.47)	82.95 (80.18–85.41)	27.81 (21.39–34. 22)	96.76 (95.43–98.09)	0.533
CA125	≥28.6	0.701 (0.633–0.769)	36.49 (26.44–47.87)	91.29 (89.12–93.06)	16.96 (12.80–21.45)	95.67 (93.93–97.22)	4.19
HE4	≥61.3	0.741 (0.683–0.798)	75.68 (64.79–84.02)	60.86 (57.41–64.20)	15.30 (11.75–19.13)	96.40 (94.60–98.00)	1.93
RMI I	≥37.2	0.790 (0.727–0.852)	60.81 (49.42–71.14)	84.09 (81.38–86.47)	26.74 (20.35–33.72)	95.97 (94.38–97.41)	3.82
RMI II	≥101.8	0.774 (0.705–0.843)	63.51 (52.13–73.56)	88.51 (86.10–90.55)	34.06 (26.09–42.03)	96.29 (94.92–97.66)	5.53
RMI III	≥85.8	0.767 (0.698–0.836)	62.16 (50.77–72.35)	88.13 (85.69–90.2)	32.86 (25.00–40.71)	96.07 (94.63–97.52)	5.24
RMI IV	≥162.4	0.785 (0.721–0.850)	62.16 (50.77–72.35)	88.89 (86.51–90.89)	34.33 (26.12–42.54)	96.17 (94.67–97.54)	5.60
ROMA	≥12.05	0.771 (0.720–0.823)	85.14 (75.31–91.49)	60.1 (56.65–63.45)	16.62 (12.93–20.58)	97.74 (96.30–98.97)	2.13
CPH-I	≥3.8	0.805 (0.924–0.923)	87.84 (78.47–93.47)	52.27 (48.79–55.73)	20.82 (15.99–25.65)	96.98 (95.48–98.33)	1.84
IOTA SR+CA125	≥9.8	0.874 (0.824–0.923)	85.14 (75.31–91.49)	89.65 (87.33–91.58)	43.45 (35.17–51.72)	98.47 (97.50–99.31)	8.22

Note: Values are presented as number (95% CI).

Abbreviations: AUC, area under the curve; CA125, cancer antigen 125; CI, confidence interval; CPH-I, Copenhagen index; EOM, early-stage ovarian malignancy; HE4, human epididymal protein 4; IOTA SR, international ovarian tumor analysis simple rule; NPV, negative predictive values; PPV, positive predictive values; RMI I, risk of malignancy index I; RMI II, risk of malignancy index II; RMI III, risk of malignancy index III; RMI IV, risk of malignancy index IV; ROC, receiver operating characteristic; ROMA, risk of ovarian malignancy algorithm; Se, sensitivity; Sp, specificity.

Epithelial-stromal tumors were prevalent in both early-stage (89.19%) and advanced-stage (88.14%) cancers and accounted for 59.60% of benign tumors. The distribution of ovarian cancer stages revealed that most early-stage cases were classified as Stage I (36.49%) and Stage II (35.14%). In advanced-stage cases, Stage IIIA2–IIIC represented the most significant percentage at 79.66%, while Stage IV accounted for 20.34%.

The EOM score effectively diagnosed preoperative ovarian cancer. At a threshold of ≥13, it achieved an AUC value of 0.908 (0.878–0.937), with 83.46% sensitivity and 82.95% specificity. Furthermore, applying the cut-off of ≥13 to early-stage cancer produced an AUC value of 0.843 (0.796–0.890), with 70.27% sensitivity and 82.95% specificity (Table 3).

The EOM score showed high sensitivity in detecting ovarian cancer, particularly in early-stage cases, compared to other diagnostic methods (Table 4, Figure 2). AUC analysis indicated that the EOM score outperformed CA125 ($P=0.000$), HE4 ($P=0.002$), all risk malignancy indices (RMI I–IV) ($P<0.05$), ROMA ($P=0.017$), and CPH-I ($P=0.041$) in distinguishing cancer from non-cancer cases and in identifying early-stage cancer ($P<0.05$). However, the IOTA Simple Rules in combination with CA125 levels showed similar efficacy to the EOM score, with no significant difference in AUC ($P=0.257$).

4 | DISCUSSION

This study compared the accuracy of the EOM score in predicting early-stage ovarian cancer in a Vietnamese cohort, highlighting its superiority over standard metrics. Incorporating demographic, ultrasound, and biochemical data emphasizes the importance of a multimodal approach. The EOM score is reliable for predicting preoperative malignancy, especially in early-stage disease.

In a study of postmenopausal patients, we found that benign tumors were present in 19.2% of cases. This finding is consistent with the studies conducted by Vo TQ (2024) and Huy NVQ (2018), both carried out in the exact location as our research. Their results indicate a notably significant prevalence of benign tumors in menopausal women, reported at 18.1% and 12.1%, respectively.[12,21] However, the rates of early and advanced-stage ovarian cancer in

TABLE 4 Pair-sample area difference under the receiver operating characteristic curves.

	z	p	AUC Difference
Cancer vs non cancer			
CA125 – EOM	−4.715	0.000	−0.091
HE4 – EOM	−3.139	0.002	−0.068
EOM – RMI I	1.646	0.038	0.032
EOM – RMI II	2.254	0.024	0.037
EOM – RMIIII	2.486	0.013	0.041
EOM – RMI IV	2.151	0.031	0.030
EOM – ROMA	2.377	0.017	0.046
EOM – CPH-I	1.311	0.041	0.029
EOM – IOTA SR+CA125	−0.877	0.390	−0.014
Early stage cancer vs non-cancer			
CA125 – EOM	−4.618	0.000	−0.136
HE4 – EOM	−2.970	0.003	−0.101
EOM – RMI I	1.939	0.024	0.055
EOM – RMI II	2.514	0.012	0.068
EOM – RMI III	2.749	0.006	0.074
EOM – RMI IV	2.521	0.012	0.057
EOM – ROMA	2.360	0.018	0.073
EOM – CPH-I	1.580	0.020	0.054
EOM – IOTA SR+CA125	−1.333	0.257	−0.031

Abbreviations: AUC, area under the curve; CA125, cancer antigen 125; CPH-I, Copenhagen index; EOM, early-stage ovarian malignancy; HE4, human epididymal protein 4; IOTA SR, international ovarian tumor analysis simple rule; RMI I, risk of malignancy index I; RMI II, risk of malignancy index II; RMI III, risk of malignancy index III; RMI IV, risk of malignancy index IV; ROMA, risk of ovarian malignancy algorithm.

postmenopausal women were significantly higher, at 51.35% and 72.88%, respectively ($P<0.001$). Another study by Koray Aslan in 2020 reported a 57.9% rate of ovarian cancer in the postmenopausal group, which was lower than our findings.[22]

Ultrasound findings confirmed that solid components, ascites, and tumor size were crucial differentiators between benign and malignant ovarian tumors, consistent with the results of Lam HL (2022).[23] Solid components strongly indicated ovarian malignancy, while ascites was common in malignant cases, especially in advanced stages. Suh–Burgmann E. reported adnexal masses with a median size of 9.6 cm, with no simple unilocular cysts present. Additionally, 97.4% of tumors had solid components (excluding septations), and 74.8% exhibited vascularity. The prevalence of ascites varied significantly by stage, with moderate-to-severe ascites present in 18% of stage II and 3.1% of stage I cases.[24]

While CA125 and HE4 are recognized ovarian cancer biomarkers, their effectiveness in early-stage detection is limited. CA125, which is elevated in 80–85% of ovarian cancer patients (consistent with our findings), exhibits lower sensitivity in early-stage and premenopausal cases. The standard CA125 thresholds are 35 U/mL for postmenopausal women and 200 U/mL for those of reproductive age, with higher values indicating an increased risk of cancer.[25] However, relying exclusively on CA125 for diagnosis is constrained by sensitivity and specificity, particularly in early-stage and premenopausal women. Consequently, incorporating biomarkers, ultrasound, and clinical data is essential for dependable preoperative risk stratification.[26] While most advanced-stage ovarian cancer cases in our study were observed in postmenopausal women, a small proportion (5.08%) occurred in women under 40. This aligns with global data showing that ovarian cancer, particularly in advanced stages, is most common in women over 60 years.[27,28] However, recent studies have reported a gradual

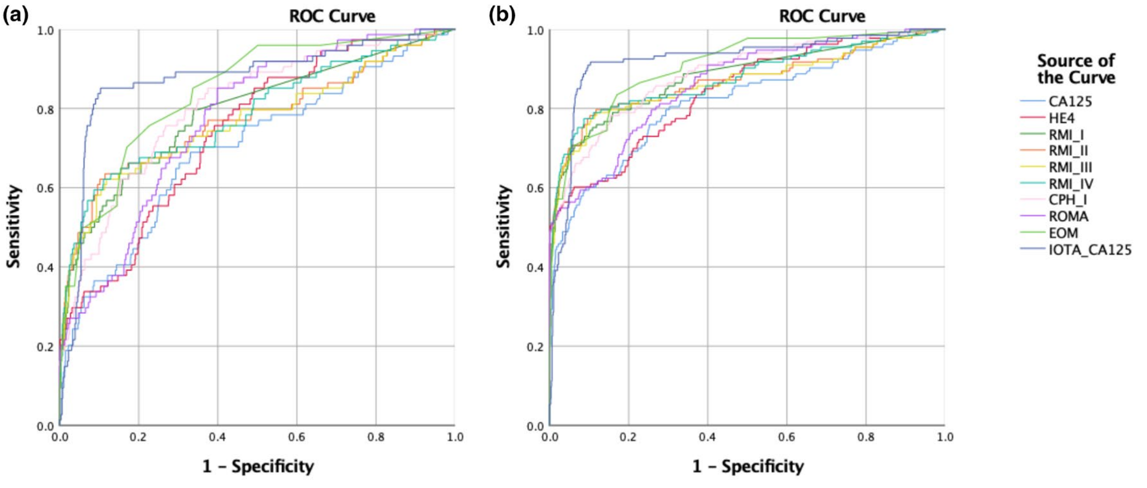

FIGURE 2 Comparative validation of the discriminative ability between the EOM scores and other algorithms using the receiver operating characteristic curve (A: Ovarian cancer; B: Early stage). CA125, cancer antigen 125; CPH-I, Copenhagen index; HE4, human epididymal protein 4; IOTA SR, international ovarian tumor analysis simple rule.; RMI I, risk of malignancy index I; RMI II, risk of malignancy index II; RMI III, risk of malignancy index III; RMI IV, risk of malignancy index IV; ROMA, risk of ovarian malignancy algorithm.

rise in the incidence and prevalence of ovarian cancer among younger women, with annual rates in those aged 20–39 years increasing by approximately 0.74% and 0.89%, respectively, from 1990 to 2019.[29] Although younger women typically present with early-stage disease and have better survival outcomes, advanced-stage ovarian cancer in this group remains a significant clinical challenge, affecting fertility and long-term prognosis.[28,30] These trends emphasize the importance of early detection and customized management strategies for younger women, alongside the conventional focus on postmenopausal patients.

Ovarian tumors were mainly epithelial-stromal (88.7%), with a smaller proportion of germ cell (9.0%) and sex cord tumors (2.3%). This finding aligned with Gupta et al. (2019), who reported 71.7% epithelial, 22.2% germ cell, 3.8% sex cord, and 2.3% other tumor types. Tran DT et al. also supported this, identifying epithelial cells as the most common histotype of ovarian cancer.[31,32]

The EOM score, which combines menopausal status, tumor size, ultrasound features, and CA125 levels, demonstrates high sensitivity and specificity in predicting both cancerous and non-cancerous ovarian masses. The EOM score was validated primarily for epithelial ovarian malignancy, the most common type.[9] However, our initial findings indicate it might also be applicable for detecting other ovarian cancers, including rarer subtypes like germ cell and sex cord-stromal tumors. At the optimal cutoff of ≥13, the EOM score achieved an AUC of 0.908, with a sensitivity of 83.46% and specificity of 82.95%. Furthermore, the EOM score's ability to differentiate early-stage ovarian cancer from benign masses, with an AUC value of 0.843, highlights its importance in early detection, which is crucial for improving patient outcomes. These findings aligned with those reported by Chirdchim et al., who demonstrated the EOM score's predictive capability in early-stage ovarian cancer.[9]

The EOM score excelled in detecting early-stage ovarian cancer compared to other indices, following international guidelines. It contributes to global research, validating EOM's predictive value. The EOM score enhances preoperative identification, reducing reliance on CA125. At a ≥ 13 cutoff, it demonstrated superior sensitivity for early-stage cancer, outperforming previous algorithms in distinguishing benign conditions from early malignancy. Our results demonstrated that the diagnostic performance of the EOM score was essentially equivalent to that of the IOTA Simple Rules combined with CA125, as there was no significant difference in AUC between the two models in our cohort. This finding supports the robustness of the EOM score as a preoperative diagnostic tool. Furthermore, when compared with the results of Xie et al., our data showed high consistency: Xie et al. reported an AUC of 0.900 for the combined IOTA SR and CA125 model, with sensitivity and specificity of 92.19% and 76.09%, respectively, for distinguishing benign from malignant adnexal masses.[33]

This study's strength comes from a large, prospective cohort, which enhances the generalizability of its findings. It is the first to apply the EOM score in Vietnam, providing valuable insights into its diagnostic performance for distinguishing benign from malignant ovarian tumors, particularly in early-stage cancer. Combining clinical, ultrasound, and biomarker data increases accuracy and reliability. Our study primarily focused on the routine application of CA125 and HE4 for ovarian tumor evaluation, excluding other tumor markers such as CEA, hCG, CA19-9, AFP, and LDH. While these markers are widely used in clinical practice, they were not included in our analysis due to the specific clinical context of our cohort. A limitation of our study is its single-region, dual-center design, which may influence the generalizability of our findings. Our analysis emphasized the importance of integrating clinical, ultrasound, and biomarker data. However, incorporating comprehensive patient background information, such as reproductive history, family history, previous gynecological conditions, and relevant environmental exposures, would significantly enhance risk assessment.

Future multicenter studies, including a broader range of markers and diverse patient populations, will be crucial to validate the diagnostic effectiveness of the EOM score in broader clinical contexts. This initial finding encourages further exploration of the EOM score's broader applicability, and we plan to conduct larger studies to assess its potential for diagnosing various subtypes of ovarian cancer. Additionally, there is potential to develop a machine learning prediction model that could improve the accuracy and efficiency of diagnosing ovarian cancer.

5 | CONCLUSION

The EOM score effectively predicts ovarian cancer, particularly in the early stages, and it provides high sensitivity and specificity with an optimal cut-off of ≥13. The performance score is comparable to that of IOTA Simple Rules combined with CA125.

AUTHOR CONTRIBUTIONS

HLV, VQHN, and MTL were involved in conceptualizing the study. The methodology and investigation were carried out by HLV, VQHN, TNTN, MTL, and LHL. VQHN and MTL provided supervision for the research. HLV, VQHN, MTL, and LHL were responsible for drafting the original manuscript, while HLV, TDT, VQHN, TNTN, MTL, and LHL contributed to its review and editing. All authors have read and approved the final version of the manuscript and agree to take responsibility for all aspects of the work.

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DATA AVAILABILITY STATEMENT

All data supporting the conclusions of this study are available from the corresponding author upon reasonable request.

DISCLAIMER

The authors take full responsibility for the accuracy, integrity, and objectivity of the results and conclusions presented in this research.

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