Clinical utility of R-OPS score in the preoperative diagnosis of ovarian cancer: a prospective cohort study

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Abstract

Objective: This study aimed to validate the diagnostic utility of the Rajavithi-Ovarian Cancer Predictive Score (R-OPS) in preoperative ovarian cancer diagnosis and compare its efficacy with that of the Risk of Ovarian Malignancy Algorithm (ROMA). **Methods:** A prospective cohort study was conducted at two hospitals in Vietnam from January 2024 to January 2025, involving 215 patients with adnexal masses (69 malignant, 146 benign) who underwent surgery. R-OPS was calculated using menopausal status, ultrasound findings, and serum cancer antigen 125 (CA125) and human epididymal protein 4 (HE4) levels. ***Results:*** R-OPS achieved an AUC of 91.4% (95% CI: 87.0 - 95.7%). At a cut-off of > 330, it displayed a specificity of 95.2% and a sensitivity of 71.0%, with positive and negative predictive values of 86.0% and 87.3%. R-OPS outperformed ROMA by 5.9% in AUC (P<0.001). **Conclusion:** R-OPS is an effective tool for preoperative differentiation between benign and malignant ovarian masses, demonstrating superior performance compared to ROMA.

Keywords: *Ovarian cancer, R-OPS, ROMA, diagnostic accuracy, predictive score, biomarkers.*

1. INTRODUCTION

Ovarian cancer (OC) is the seventh most commonly diagnosed cancer among women worldwide and ranks as the eighth leading cause of cancer-related deaths [1-3]. The five-year survival rate is generally below 45%. While age-standardized rates are stable or declining in high-income countries, the opposite trend is observed in many low and middle-income countries due to rising life expectancy and other factors [1]. Epithelial ovarian cancer is the most prevalent subtype, with various histotypes that differ in origin, pathogenesis, and prognosis [2].

Ovarian cancer is often diagnosed at advanced stages, contributing to its high mortality rate [4, 5]. Despite available screening methods such as blood tests and transvaginal ultrasound, no approaches have been found to demonstrate definitive mortality benefits. The diagnostic process combines multiple approaches, including serum biomarkers, including serum cancer antigen 125 (CA125) and human epididymal protein 4 (HE4), and imaging studies. For preoperative risk stratification, clinicians utilize the four versions of the Risk Malignancy Index and the Risk of Ovarian Malignancy Algorithm (ROMA). These assessment tools have demonstrated good discriminatory performance in differentiating between benign and malignant ovarian masses, enabling more informed clinical decision-making [6, 7].

The Rajavithi-Ovarian Cancer Predictive Score (R-OPS) was developed using data from women with pelvic or adnexal masses, incorporating menopausal status, serum CA 125, HE4, and ultrasound findings of solid lesions as significant predictors of ovarian cancer. The scoring system demonstrated good calibration and discrimination, with an area under the receiver operating characteristic curve (ROC-AUC) of 92.8% in the development set and 94.9% in the validation set. A cutoff value of R-OPS > 330 showed high sensitivity (93.9%) and specificity (79.9%) [8]. In comparison with other algorithms like the Risk of Malignancy Index (RMI) and the Risk of Ovarian Malignancy Algorithm (ROMA), R-OPS showed superior performance in postmenopausal women. It was found to be more accurate when combining ultrasound imaging with serum markers CA125 and HE4 for predicting malignancy in ovarian masses [9].

While the R-OPS has shown promising results, further prospective studies in different settings are necessary to confirm its effectiveness. The need for such studies is emphasized to ensure the reliability and generalizability of the R-OPS across diverse populations. Therefore, we conducted the study with two main objectives: to evaluate the diagnostic value of the R-OPS scoring system in preoperative

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ovarian cancer diagnosis and to compare the diagnostic performance between the R-OPS score and ROMA algorithm in preoperative ovarian cancer diagnosis.

2. METHODOLOGY

Design and setting

This prospective cohort investigation was conducted at two tertiary healthcare institutions in Vietnam - Hue University of Medicine and Pharmacy Hospital and Hue Central Hospital. Data collection occurred from January 2024 to January 2025.

Inclusion criteria: Eligible participants were patients presenting with ovarian tumors who required one of the following interventions: surgical interventions, tumor biopsy or cytological analysis of abdominal fluid. All cases underwent postoperative pathological examination. Preoperative assessment included an ultrasound examination of the ovarian masses. Informed consent was obtained from all study participants.

Exclusion criteria: Patients were excluded from the study if they fall under any of the following conditions:

- Postoperative diagnosis was pseudocysts, hydrosalpinx, para-ovarian cysts, or uterine fibroids.
- Concurrent pregnancy with ovarian tumor
- Prior history of:
+ Chemotherapy for ovarian malignancy
+ Surgical intervention for ovarian cancer
+ Any known malignant conditions
- Secondary ovarian cancer
- Presence of concurrent malignancies (e.g., endometrial or thyroid cancer)
- Incomplete diagnostic data (ultrasound findings and/or biomarker results)

Sample size

The sample size for the development set was determined using the formula proposed by Hanley et al. to estimate the sample size required to achieve an Area Under the Receiver Operating Characteristic Curve (ROC-AUC) [10].

We set an expected AUC of 90%, the width of the confidence interval of 0.15, and a confidence level of 95%. The calculation was informed by the ROC-AUC data from an estimated ovarian cancer (OC) prevalence of 13% among women presenting with a pelvic mass [6]. Consequently, a minimum of 191 subjects was indicated, with adjustments for an anticipated 10% dropout rate leading to a final requirement of 215 subjects. The sample size for the validation cohort was established to be equivalent to that of the development cohort.

Study protocols

Transabdominal and transvaginal ultrasonography were employed to identify an ovarian tumor in a patient presenting with a pelvic mass during a gynecological examination after administrative interviews, comprehensive medical history compilation, and physical assessment. The morphologic features assessed included multilocularity, presence of solid components, bilaterality, ascites, and intra-abdominal metastases by the consensus established by the International Ovarian Tumor Analysis (IOTA) group [11]. Serum samples were obtained for CA-125 and HE4 assays prior to the surgical excision of the ovarian tumors. A thorough histopathological evaluation was performed based on the criteria and classification the World Health Organization (WHO) defined in 2014 [12].

Preoperative blood samples were collected and processed within three hours, subjected to centrifugation, and stored as serum at -80 °C until assay. Analyses of serum biomarkers were conducted in strict compliance with clinical operational protocols, utilizing a Cobas 6000 analyzer series with Elecsys HE4 and Elecsys CA125 II reagent kits (Roche Diagnostics, Indianapolis, IN, USA), following the manufacturers' instructions for determining concentrations.

The patient was scheduled for surgery via an appropriate approach following a departmental consultation. During the surgical intervention, the surgeon conducted an initial assessment of the tumor's characteristics and assigned a cancer stage according to the FIGO classification (2014) based on the visual assessment of the tumor [13].

The newly developed R-OPS (Rajavithi Ovarian Cancer Predictive Score) scoring system integrates menopausal status with specific ultrasound characteristics and serum CA125 and HE4 levels into a predictive scoring formula designed to assess ovarian cancer risk:

R-OPS = M × U × (CA125 × HE4)$^{1/2}$ [8]

The values for CA125 and HE4 were recorded in U/mL and pM/L, respectively. The variable M was assigned a code of 1 for premenopausal women and 3 for postmenopausal women. Additionally, the variable U was coded as 1 in the absence of a solid lesion and 6 in the presence of a solid lesion.

The ROMA algorithm was developed utilizing serum levels of CA125 (U/mL) and HE4 (pM/L), in conjunction with the patient's menopausal status. The predictive index (PI) was computed following the methodology outlined by Moore.et al [6]:

ROMA (%) = exp(PI) / [1 + exp(PI)] * 100

PI (Predictive Index) is calculated as:

Pre-menopausal women: PI = -12.0 + 2.38 * Ln(HE4) + 0.0626 * Ln(CA125)

Post-menopausal women: PI = -8.09 + 1.04 * Ln(HE4) + 0.732 * Ln(CA125)

Statistical analysis

The statistical analysis was conducted utilizing SPSS version 27.0. We represented continuous data using mean and standard deviation (SD) or median and interquartile range (IQR) based on their distribution. Continuous variables were compared using the Student's T-test and Mann-Whitney U test, as appropriate, based on data distribution. Categorical variables were analyzed using the chi-squared or Fisher's exact test, depending on the sample size and distribution characteristics. The predictive performance was assessed by calculating the ROC-AUC and the corresponding 95% confidence interval (CI). Additionally, we computed key metrics, including sensitivity (Sn), specificity (Sp), and both positive (PPV) and negative predictive values (NPV). The diagnostic efficacy of the R-OPS was evaluated in comparison to the ROMA diagnostic tests through the analysis of the areas under the receiver operating characteristic (ROC) curves [14].

Ethical approval

The research obtained ethical approval from the Ethical Committee for Biomedical Research at the Hue University of Medicine and Pharmacy Hospital (Decision No. 17BV/24). All the study subjects were provided written informed consent.

3. RESULTS

In our research, we analyzed a cohort of 215 cases, revealing that 146 were identified with benign tumors, while 69 cases presented ovarian cancer. Detailed demographic and clinical characteristics of the participants are summarized in Table 1.

Table 1. Characteristics of women presenting with a pelvic or adnexal mass.

Variables		Ovarian cancer (n=69)		Benign (n=146)		P
		N	%	N	%	
Group of age	< 20	2	2.9	10	6.8	<0.001*
	20 - 29	3	4.3	35	24.0	
	30 - 39	4	5.8	38	26.0	
	40 - 49	16	23.2	34	23.3	
	50 - 59	22	31.9	13	8.9	
	≥ 60	22	31.9	16	11.0	
Age of patients mean (SD)		53.2 (140)		38.8 (154)		<0.001**
Menopausal status	Post-menopause	43	62.3	29	19.9	<0.001*
	Pre-menopause	26	37.7	117	80.1	
Clinical characteristics of ovarian tumors	Abdominal distension	10	14.5	8	5.5	0.026*
	Palpable mass	64	92.8	140	95.6	0.294*
	Easily mobile	25	36.2	129	88.4	<0.001*
	Well-defined margins	36	52.2	124	84.9	<0.001*
	Firm consistency	61	88.4	122	83.6	0.352*

*Pearson Chi-square ,** Independent sample T - Test

Ovarian cancer patients had a mean age of 53.2 years (SD=14.0), significantly older than the 38.8 years (SD=15.4) of benign cases (P<0.001). Most cancer patients were in the older age brackets: 31.9% (n=22) in both the 50 - 59 and ≥60 groups. In contrast, benign cases were more common in younger groups, with 26.0% (n=38) in the 30 - 39 age range and 24.0% (n=35) in the 20-29 range. Additionally, 62.3% (n=43) of cancer patients were postmenopausal, compared to only 19.9% (n=29) of benign cases (P<0.001). Furthermore, cancer patients experienced more abdominal distension

(14.5%) than benign cases (5.5%) with P=0.026. The rate of tumor mobility was significantly lower in cancer patients, with only 36.2% being easily mobile, compared to 88.4% in benign cases (P<0.001). Well-defined tumor margins were present in 52.2% of malignant tumors versus 84.9% of benign ones (P<0.001). However, no significant differences were found regarding palpable masses (92.8% vs 95.6%, P=0.294) or firm consistency (88.4% vs 83.6%, P=0.352).

The data presented in Table 3 highlighted the key differences between malignant and benign cases of ovarian tumors. Notably, there is a significantly higher prevalence of ascites in ovarian cancer cases (58.0% vs. 1.4%, P<0.001). Additionally, malignant tumors exhibit more solid components (49.3% vs. 23.3%, P<0.001) and a more considerable rate of intra-abdominal metastasis (20.3% vs. 0.7%, P<0.001). Furthermore, 34.8% of malignant cases involved large tumors (greater than 12 cm), compared to only 7.5% among benign cases (P<0.001). Tumor marker levels were found to be significantly higher in ovarian cancer cases. Specifically, the levels of CA125 in malignant cases had a median of 158.4 U/mL (IQR: 35.0-790.3), compared to 18.4 U/mL (IQR: 13.8-30.4) in benign cases. HE4 levels also showed significant elevation, with malignant cases having a median of 132.8 pmol/mL (IQR: 59.9-382.1) versus 41.0 pmol/mL (IQR: 34.1-51.5) in benign cases. Both of these differences were statistically significant (P<0.001). Another particularly noteworthy finding is the prevalence of epithelial-stromal tumors in ovarian cancer cases, which accounted for 94.2%. In contrast, benign cases displayed a more balanced distribution, with 52.1% epithelial-stromal tumors and 41.1% germ cell tumors. This difference is also statistically significant (P<0.001).

Table 3. Sonography characteristics, biomarker serums, and histopathological distribution in women with adnexal mass

Variables		Ovarian cancer (n=69)		Benign (n=146)		P
		N	%	N	%	
Characteristics of US findings	Solid component	34	49.3	34	23.3	<0.001*
	Multiloculation	10	14.5	28	19.2	0.400*
	Bilaterality	9	13.0	17	11.6	0.769*
	Ascites	40	58.0	2	1.4	<0.001**
	Intraabdominal metastasis	14	20.3	1	0.7	<0.001**
Size of tumor (cm)	<7	20	29.0	72	49.3	<0.001*
	7 - 12	25	36.2	63	43.2	
	>12	24	34.8	11	7.5	
CA125 (U/mL) (Q25% - Q75%)		158.4 (35.0 - 790.3)		18.4 (13.8 - 30.4)		<0.001***
HE4 (pmol/mL) (Q25% - Q75%)		132.8 (59.9 - 382.1)		41.0 (34.1 - 51.5)		<0.001***
Histopathology	Epithelial-stromal tumor	65	94.2	76	52.1	<0.001**
	Germ cell tumor	2	2.9	60	41.1	
	Sex cord-stromal tumor	2	2.9	10	6.8	

*Pearson Chi-square ,** Fisher's Exact test, ***Mann - Whitney U Test.

Table 3 and Figure 1 demonstrated that the R-OPS score was highly effective for predicting ovarian cancer. The analysis of the Receiver Operating Characteristic (ROC) curve showed an Area Under the Curve (AUC) of 91.4% (95% CI: 87.0 - 95.7%), indicating substantial diagnostic accuracy. With a cut-off value of >330, the test exhibited a specificity of 95.2% and a sensitivity of 71.0%. The positive predictive value (PPV) was 86.0%, while the negative predictive value (NPV) was 87.0%.

Table 3. Validity of R-OPS score for prediction ovarian cancer at standard cut-off.

	AUC (%) (95% CI)	Se (%)	Sp (%)	PPV (%)	NPV (%)
>330	91.4 (87.0 - 95.7)	71.0	95.2	86.0	87.3%

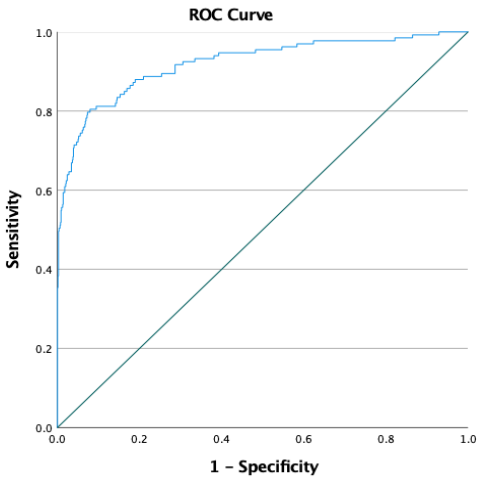

Figure 1. Receiver operating characteristic curve of R-OPS for prediction of ovarian cancer

The R-OPS score outperformed the ROMA score in distinguishing ovarian cancer from non-cancer cases, showing a 5.9% higher AUC (z=3.708, P<0.001). This difference was statistically significant, with a standard error of 0.183.

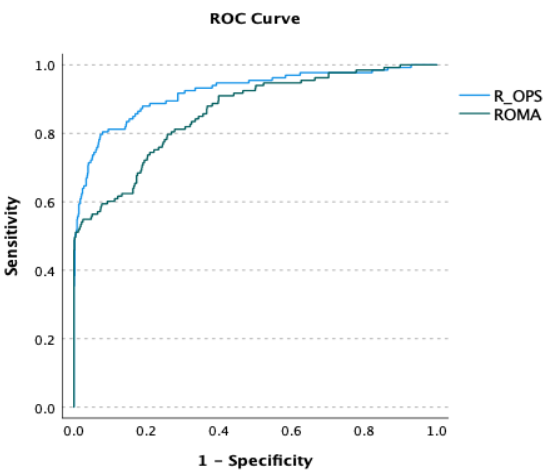

Figure 2. Comparative validation of the discriminative ability between the R-OPS and ROMA

Table 4. Pair-Sample Area Difference Under the ROC Curves

Test Result Pair(s)	Asymptotic		AUC Difference (%)	Std. Error Difference
	z	p		
Cancer vs Non cancer				
R-OPS - ROMA	3.708	<0.001	5.9	0.183

4. DISCUSSION

A multimodal approach integrating demographic, morphological, and biochemical data proves to be an effective strategy for predicting ovarian cancer (OC) in women presenting with pelvic or adnexal masses. The results from this study demonstrate that menopausal status, specific morphological features observed via ultrasound, and serum levels of CA125 and HE4 are significant predictive biomarkers for distinguishing OC from benign masses. These variables have been incorporated into the newly developed R-OPS scoring system.

Our finding that 62.3% of ovarian cancer patients were postmenopausal underscores the significant role of menopausal status in risk assessment. Menopause and age-related hormonal changes have been linked to DNA damage and the risk of ovarian cancer. This connection is particularly significant as ovarian cancer is often diagnosed in postmenopausal women. Women who experience menopause at a younger age have a higher risk of developing ovarian cancer, suggesting that prolonged exposure to endogenous hormones may contribute to cancer risk [15]. Our results show that the incorporation of menopausal status in the R-OPS formula (with a threefold weight for postmenopausal status) appears well-justified. This weighting likely contributes to the improved diagnostic accuracy compared to other assessment tools that may undervalue this factor.

The R-OPS scoring system showed excellent diagnostic capability with an AUC of 91.4% (95% CI: 87.0 - 95.7%). At the standard cut-off value of >330, this system demonstrated high specificity (95.2%) while maintaining moderate sensitivity (71.0%), with strong positive and negative predictive values (86.0% and 87.3%, respectively). These results align with the original development study of R-OPS, though our sensitivity was relatively lower than their reported 93.9% [8]. This divergence might be attributed to differences in study populations and clinical settings.

A notable finding was the superior performance of R-OPS compared to the ROMA algorithm, with a statistically significant difference in AUC of 5.9% ($P<0.001$). This improvement in diagnostic accuracy suggests that integrating ultrasound findings with serum biomarkers and menopausal status in R-OPS provides a more comprehensive assessment tool than ROMA's reliance on serum markers alone.

Our findings revealed distinct patterns in the presentation of ovarian cancer versus benign cases. Malignant cases were significantly associated with older age (mean 53.2 years) and postmenopausal status (62.3%), consistent with established epidemiological patterns. The predominance of epithelial-stromal tumors (94.2%) in malignant cases further aligns with known histological distributions in ovarian cancer.

The study identified several key ultrasound features highly associated with malignancy: the presence of ascites (58.0%), solid components (49.3%), and intra-abdominal metastasis (20.3%). Combined with elevated serum biomarkers (CA125 and HE4), these findings underscore incorporating multiple diagnostic parameters in risk assessment.

Clinical Implications

The high specificity and PPV of R-OPS at the > 330 cut-offs suggest its particular utility in identifying high-risk cases requiring specialist referral. This could facilitate more appropriate triaging of patients and optimize the use of gynecologic oncology specialists services. However, the moderate sensitivity indicates that clinicians should continue to exercise clinical judgement and possibly employ additional diagnostic tools in cases with negative R-OPS scores but high clinical suspicion.

Study Limitations

While our study demonstrates the effectiveness of R-OPS, several limitations should be noted. The study was conducted at tertiary care centers, which might affect the generalizability of results to primary care settings. Additionally, the relatively small sample size in certain subgroups may limit the precision of estimates for specific patient populations.

Future Research Directions

Further research is warranted to validate these findings in diverse clinical settings and populations. Studies examining the cost-effectiveness of implementing R-OPS in routine clinical practice and its impact on patient outcomes would be valuable. Additionally, investigating potential modifications to improve sensitivity while maintaining high specificity could enhance the tool's clinical utility.

5. CONCLUSION

Rajavithi-Ovarian Cancer Predictive Score proves to be a highly effective tool for preoperatively distinguishing between benign and malignant ovarian masses, demonstrating significantly better performance than the ROMA.

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