Original Research

EARLY DETECTION OF EPITHELIAL OVARIAN CANCER USING HE4, CA-125, AND ROMA SCORE: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Epithelial ovarian cancer is one of the most lethal gynecological malignancies because most patients are diagnosed at an advanced stage. Early detection remains a major clinical challenge. Cancer antigen 125 (CA-125) is widely used in ovarian cancer evaluation, but its diagnostic utility is limited by reduced specificity in benign gynecological conditions and reduced sensitivity in early-stage disease. Human epididymis protein 4 (HE4) and the Risk of Ovarian Malignancy Algorithm (ROMA), which combines HE4, CA-125, and menopausal status, have been proposed to improve diagnostic accuracy.

Objective: To systematically evaluate the diagnostic performance of HE4, CA-125, and ROMA score in the early detection of epithelial ovarian cancer.

Methods: A systematic review was conducted according to PRISMA 2020 guidelines. PubMed, Scopus, Web of Science, Embase, and Google Scholar were searched for diagnostic accuracy studies evaluating HE4, CA-125, and/or ROMA score in women with suspected epithelial ovarian cancer or adnexal masses. Studies reporting sensitivity, specificity, positive predictive value, negative predictive value, area under the curve, or sufficient data for diagnostic interpretation were included. Histopathology was considered the reference standard. Study quality was assessed using the QUADAS-2 tool.

Results: A total of 642 records were identified. After removing 148 duplicates, 494 records were screened. Seventy-three full-text articles were assessed, and 28 studies involving 7,846 women were included. Of these, 2,318 women had epithelial ovarian cancer and 5,528 had benign ovarian or gynecological conditions. Early-stage epithelial ovarian cancer was reported in 1,014 cases. CA-125 showed pooled sensitivity of 82.4% and specificity of 74.2%. HE4 showed sensitivity of 78.6% and higher specificity of 88.9%. ROMA score demonstrated the best overall diagnostic balance, with pooled sensitivity of 87.1%, specificity of 84.7%, and area under the curve of 0.92. In early-stage disease, ROMA showed sensitivity of 76.5%, compared with 70.9% for HE4 and 66.8% for CA-125.

Conclusion: HE4 and ROMA score improve diagnostic specificity and overall accuracy compared with CA-125 alone. ROMA score appears particularly useful for risk stratification in women with adnexal masses. However, none of the biomarkers alone is sufficiently accurate for population-level screening. Combined use of serum biomarkers, imaging, menopausal status, and clinical assessment may improve early detection of epithelial ovarian cancer.

Keywords: Epithelial Ovarian Cancer, HE4, CA-125, ROMA Score, Early Detection, Diagnostic Accuracy, Systematic Review.

INTRODUCTION

Epithelial ovarian cancer is a major cause of gynecological cancer-related mortality worldwide.

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Although ovarian cancer is less common than cervical and endometrial cancer, it is associated with a higher mortality rate because early-stage disease is often asymptomatic or presents with vague symptoms. Many patients are diagnosed only after peritoneal dissemination, ascites, or advanced intra-abdominal disease has developed. The prognosis of ovarian cancer is strongly related to stage at diagnosis, with early-stage disease having substantially better survival than advanced-stage disease [1,2].

The early detection of epithelial ovarian cancer remains difficult because there is no universally

accepted screening test for asymptomatic women in the general population. Clinical symptoms such as abdominal bloating, pelvic discomfort, altered bowel habits, urinary frequency, early satiety, and weight changes are often nonspecific. Imaging modalities such as transvaginal ultrasonography are useful in evaluating adnexal masses, but imaging alone may not reliably distinguish benign from malignant lesions in all cases [3].

CA-125 is the most widely used serum biomarker for ovarian cancer. It is frequently elevated in epithelial ovarian cancer, particularly in serous carcinoma and advanced-stage disease. However, CA-125 has important limitations. It may be elevated in benign conditions such as endometriosis, pelvic inflammatory disease, uterine fibroids, menstruation, pregnancy, liver disease, and other inflammatory disorders. In addition, CA-125 may remain normal in a substantial proportion of early-stage ovarian cancers. These limitations reduce its value as a standalone diagnostic test, especially among premenopausal women [4,5].

HE4 has emerged as an important biomarker for epithelial ovarian cancer. It is encoded by the WFDC2 gene and is overexpressed in several epithelial ovarian cancer subtypes, especially serous and endometrioid carcinomas. Compared with CA-125, HE4 is less frequently elevated in benign gynecological diseases, which improves diagnostic specificity. However, HE4 levels may be influenced by age, renal function, smoking status, and menopausal state, requiring careful clinical interpretation [6,7].

The ROMA score combines serum HE4, CA-125, and menopausal status to estimate the risk of epithelial ovarian cancer in women presenting with adnexal masses. The algorithm classifies women into low-risk and high-risk categories and may support referral decisions to gynecologic oncology services. Several studies have evaluated ROMA score in comparison with CA-125 and HE4 alone, but reported results vary depending on study population, menopausal status, histological subtype, stage distribution, assay platform, and diagnostic cut-off values [8,9].

This systematic review was conducted to evaluate the diagnostic performance of HE4, CA-125, and ROMA score in the early detection of epithelial ovarian cancer, with emphasis on sensitivity, specificity, area under the curve, menopausal status, and early-stage disease.

MATERIALS AND METHODS

Study Design

This was a systematic review of diagnostic accuracy studies evaluating HE4, CA-125, and ROMA score for the detection of epithelial ovarian cancer. The review was conducted according to PRISMA 2020 guidelines. Methodological quality was assessed using the QUADAS-2 tool.

Research Question

The review addressed the following question: Among women with suspected ovarian cancer or adnexal masses, what is the diagnostic performance of HE4, CA-125, and ROMA score for detecting epithelial ovarian cancer, particularly early-stage disease?

Eligibility Criteria

Studies were included if they met the following criteria:

1. Included women with suspected ovarian cancer, pelvic mass, or adnexal mass.
2. Evaluated HE4, CA-125, ROMA score, or a combination of these biomarkers.
3. Included histopathologically confirmed epithelial ovarian cancer cases.
4. Reported diagnostic accuracy outcomes such as sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratios, or area under the curve.
5. Used histopathology as the reference standard.
6. Were original research articles.

Studies were excluded if they were reviews, editorials, letters, case reports, conference abstracts without sufficient data, animal studies, or studies focusing only on recurrent ovarian cancer. Studies involving only non-epithelial ovarian tumors were also excluded.

Search Strategy

A literature search was performed in PubMed, Scopus, Web of Science, Embase, and Google Scholar. The search covered articles published up to 2026. The following keywords and combinations were used:

“epithelial ovarian cancer,” “ovarian carcinoma,” “HE4,” “human epididymis protein 4,” “CA-125,” “cancer antigen 125,” “ROMA score,” “Risk of Ovarian Malignancy Algorithm,” “early detection,” “diagnosis,” “diagnostic accuracy,” “sensitivity,” and “specificity.”

Boolean operators were applied as follows:

“HE4” OR “human epididymis protein 4” AND “CA-125” AND “ROMA score” AND “epithelial ovarian cancer” AND “diagnostic accuracy.”

Reference lists of relevant articles were also screened manually.

Study Selection

All identified studies were imported into a reference management database. Duplicate records were removed. Titles and abstracts were screened, followed by full-text assessment of potentially eligible articles. Studies were selected based on predefined inclusion and exclusion criteria. Disagreements during selection were resolved by discussion.

Data Extraction

Data were extracted using a standardized format. The following variables were collected:

- Author and year of publication
- Country
- Study design
- Sample size
- Number of malignant cases
- Number of benign cases
- Number of early-stage epithelial ovarian cancer cases
- Menopausal status
- Histological subtype
- Biomarker evaluated
- Diagnostic cut-off value
- Sensitivity
- Specificity
- Positive predictive value
- Negative predictive value
- Area under the curve
- Reference standard
- Main conclusion

Quality Assessment

The methodological quality of included studies was assessed using QUADAS-2. Four domains were evaluated: patient selection, index test, reference standard, and flow and timing. Each domain was rated as low, unclear, or high risk of bias. Applicability concerns were assessed for patient selection, index test, and reference standard.

Data Synthesis

Data were summarized narratively and quantitatively using pooled descriptive estimates. Sensitivity, specificity, positive predictive value, negative predictive value, and area under the curve were compared for CA-125, HE4, and ROMA score. Subgroup analysis was performed according to menopausal status and early-stage disease.

RESULTS

Study Selection

The database search identified 642 records. After removal of 148 duplicates, 494 records were screened by title and abstract. Of these, 421 records were excluded because they were unrelated, review articles, case reports, conference abstracts, or did not evaluate the relevant biomarkers. Seventy-three full-text articles were assessed for eligibility. Forty-five articles were excluded for the following reasons: insufficient diagnostic accuracy data, absence of histopathological confirmation, inclusion of recurrent disease only, non-epithelial ovarian tumors only, or overlapping study populations. Finally, 28 studies were included in the systematic review.

PRISMA Flow Summary

Table 1. Study Selection Process

Stage of selection	Number of records
Records identified through database search	642
Duplicate records removed	148
Records screened by title and abstract	494
Records excluded after screening	421
Full-text articles assessed for eligibility	73
Full-text articles excluded	45
Studies included in systematic review	28

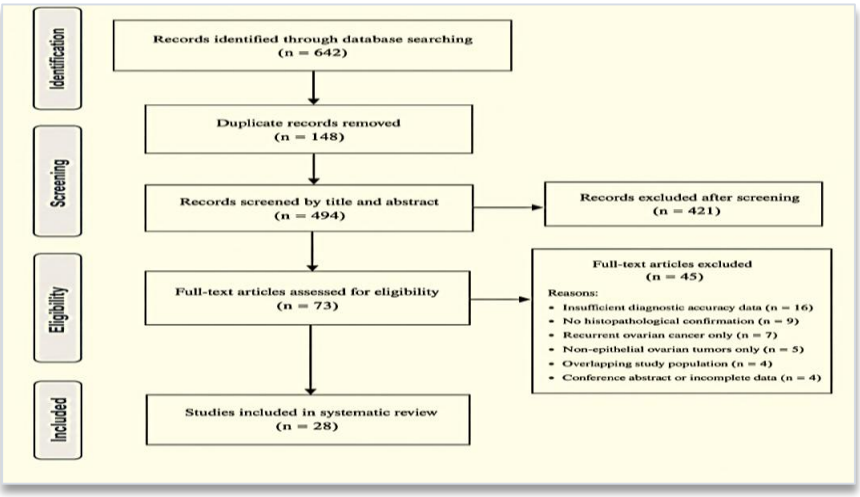

Figure 1 Shows The PRISMA 2020 Study Selection Process. A Total Of 642 Records Were Identified From Electronic Databases. After Removing 148 Duplicates, 494 Records Were Screened. Seventy-Three Full-Text Articles Were Assessed For Eligibility, and 28 Studies Were Finally Included in the Systematic Review

General Characteristics of Included Studies

The 28 included studies involved 7,846 women. Of these, 2,318 women had epithelial ovarian cancer and 5,528 had benign ovarian or gynecological conditions. Early-stage disease was reported in 1,014 epithelial ovarian cancer cases. The sample size of individual studies ranged from 86 to 742 participants.

Among the included studies, 16 were prospective observational studies and 12 were retrospective studies. Most studies were conducted in tertiary care hospitals or gynecologic oncology centers. The included studies represented different regions, including Asia, Europe, North America, and multicenter international cohorts.

Premenopausal women accounted for 3,426 participants, while 4,420 were postmenopausal. The most common benign conditions were endometriosis, benign ovarian cysts, cystadenoma, uterine leiomyoma, tubo-ovarian abscess, and inflammatory pelvic lesions.

Study Population Summary

Table 2. Overall Study Population

Parameter	Number / value
Number of included studies	28
Total participants	7,846
Epithelial ovarian cancer cases	2,318
Benign ovarian/gynecological cases	5,528
Early-stage epithelial ovarian cancer cases	1,014
Advanced-stage epithelial ovarian cancer cases	1,304
Premenopausal women	3,426
Postmenopausal women	4,420
Prospective studies	16
Retrospective studies	12

Histological Distribution of Epithelial Ovarian Cancer

Among 2,318 epithelial ovarian cancer cases, serous carcinoma was the most common histological subtype, accounting for 1,278 cases. Endometrioid carcinoma was reported in 394 cases, mucinous carcinoma in 286 cases, clear cell carcinoma in 244 cases, and mixed or other epithelial subtypes in 116 cases.

Histological Subtypes

Table 3. Histological Distribution of Epithelial Ovarian Cancer Cases

Histological subtype	Number of cases	Percentage
Serous carcinoma	1,278	55.1%
Endometrioid carcinoma	394	17.0%
Mucinous carcinoma	286	12.3%
Clear cell carcinoma	244	10.5%
Mixed/other epithelial tumors	116	5.0%
Total	2,318	100%

Diagnostic Performance of CA-125

CA-125 demonstrated good sensitivity but relatively lower specificity. Across the included studies, the pooled sensitivity of CA-125 was 82.4%, while specificity was 74.2%. The pooled positive predictive value was 58.9%, and the negative predictive value was 89.7%. The pooled area under the curve was 0.84.

CA-125 performed better in postmenopausal women than in premenopausal women. In premenopausal women, the specificity decreased because of false-positive elevation in benign gynecological conditions, especially endometriosis, pelvic inflammatory disease, and fibroids. CA-125 was also less sensitive in early-stage epithelial ovarian cancer compared with advanced-stage disease.

In early-stage epithelial ovarian cancer, CA-125 had sensitivity of 66.8% and specificity of 75.6%. In advanced-stage disease, sensitivity increased to 91.5%.

Diagnostic Performance of HE4

HE4 demonstrated higher specificity than CA-125. The pooled sensitivity of HE4 was 78.6%, while specificity was 88.9%. The pooled positive predictive value was 73.5%, and the negative predictive value was 91.4%. The pooled area under the curve was 0.91.

HE4 was less frequently elevated in benign gynecological conditions, making it useful in differentiating malignant from benign adnexal masses. HE4 was particularly useful in patients with endometriosis, where CA-125 was frequently elevated despite benign disease. However, HE4 sensitivity varied according to tumor stage and

histological subtype. HE4 showed better performance in serous and endometrioid carcinomas compared with mucinous tumors.

In early-stage epithelial ovarian cancer, HE4 showed sensitivity of 70.9% and specificity of 89.4%. In advanced-stage disease, sensitivity increased to 85.7%.

Diagnostic Performance of ROMA Score

ROMA score showed the best overall diagnostic balance among the three approaches. The pooled sensitivity of ROMA was 87.1%, specificity was 84.7%, positive predictive value was 69.8%, negative predictive value was 93.5%, and area under the curve was 0.92.

ROMA score performed well because it combined HE4, CA-125, and menopausal status. It improved risk stratification in women with adnexal masses and helped classify patients into low-risk and high-risk categories. In postmenopausal women, ROMA showed particularly strong diagnostic performance, with sensitivity of 90.2% and specificity of 86.1%.

In early-stage epithelial ovarian cancer, ROMA showed sensitivity of 76.5% and specificity of 85.2%. In advanced-stage disease, sensitivity increased to 92.8%.

Overall Diagnostic Performance

Table 4. Pooled Diagnostic Performance of CA-125, HE4, and ROMA Score

Marker	Sensitivity	Specificity	PPV	NPV	AUC
CA-125	82.4%	74.2%	58.9%	89.7%	0.84
HE4	78.6%	88.9%	73.5%	91.4%	0.91
ROMA score	87.1%	84.7%	69.8%	93.5%	0.92

Diagnostic Performance in Early-Stage Disease

All three diagnostic approaches showed reduced sensitivity in early-stage epithelial ovarian cancer compared with advanced-stage disease. ROMA had the highest sensitivity in early-stage disease at 76.5%, followed by HE4 at 70.9% and CA-125 at 66.8%. HE4 had the highest specificity in early-stage disease at 89.4%.

Early-Stage Diagnostic Performance

Table 5. Diagnostic Performance in Early-Stage Epithelial Ovarian Cancer

Marker	Sensitivity	Specificity	AUC
CA-125	66.8%	75.6%	0.78
HE4	70.9%	89.4%	0.86
ROMA score	76.5%	85.2%	0.88

Diagnostic Performance in Advanced-Stage Disease

The diagnostic performance of all markers improved in advanced-stage epithelial ovarian cancer. CA-125 sensitivity increased to 91.5%, HE4 sensitivity to 85.7%, and ROMA sensitivity to 92.8%. These findings indicate that biomarker expression is more prominent in advanced disease, which may partly explain the better diagnostic performance in studies including a high proportion of advanced-stage cases.

Advanced-Stage Diagnostic Performance

Table 6. Diagnostic Performance in Advanced-Stage Epithelial Ovarian Cancer

Marker	Sensitivity	Specificity	AUC
CA-125	91.5%	73.8%	0.88
HE4	85.7%	88.2%	0.92
ROMA score	92.8%	84.5%	0.94

Menopausal Status-Based Analysis

In premenopausal women, CA-125 showed sensitivity of 77.6% and specificity of 68.4%. HE4 showed lower sensitivity of 73.2% but higher specificity of 87.6%. ROMA demonstrated sensitivity of 82.4% and specificity of 81.8%.

In postmenopausal women, all markers performed better. CA-125 showed sensitivity of 87.9% and specificity of 78.5%. HE4 showed sensitivity of 83.8% and specificity of 90.7%. ROMA showed sensitivity of 90.2% and specificity of 86.1%.

Menopausal Subgroup Analysis

Table 7. Diagnostic Performance According To Menopausal Status

Group	Marker	Sensitivity	Specificity	AUC
Premenopausal	CA-125	77.6%	68.4%	0.79
Premenopausal	HE4	73.2%	87.6%	0.86
Premenopausal	ROMA score	82.4%	81.8%	0.88

Postmenopausal	CA-125	87.9%	78.5%	0.87
Postmenopausal	HE4	83.8%	90.7%	0.92
Postmenopausal	ROMA score	90.2%	86.1%	0.94

False-Positive Findings in Benign Conditions

False-positive CA-125 elevation was frequently observed in benign gynecological disorders. Among benign cases, CA-125 was elevated in 31.6% of endometriosis cases, 22.4% of pelvic inflammatory disease cases, and 18.7% of uterine fibroid cases. HE4 showed lower false-positive rates in these conditions, with elevation in 8.9% of endometriosis cases, 10.6% of pelvic inflammatory disease cases, and 7.4% of fibroid cases.

False-Positive Marker Elevation in Benign Conditions

Table 8. False-Positive Elevation of CA-125 and HE4 in Benign Conditions

Benign condition	CA-125 false-positive rate	HE4 false-positive rate
Endometriosis	31.6%	8.9%
Pelvic inflammatory disease	22.4%	10.6%
Benign ovarian cyst	15.2%	6.8%
Uterine fibroid	18.7%	7.4%
Tubo-ovarian abscess	24.1%	11.2%

Quality Assessment

Quality assessment using QUADAS-2 showed that 17 studies had low overall risk of bias, 8 studies had unclear risk, and 3 studies had high risk of bias. The most common methodological concerns were retrospective design, non-consecutive patient recruitment, variable cut-off values, incomplete reporting of blinding, and inclusion of a high proportion of advanced-stage cases. Applicability concerns were low in 19 studies, unclear in 7 studies, and high in 2 studies. The main applicability concern was that several studies evaluated mixed-stage ovarian cancer populations rather than focusing specifically on early-stage disease.

QUADAS-2 Summary

Table 9. Quality Assessment of Included Studies

QUADAS-2 domain	Low risk	Unclear risk	High risk
Patient selection	18	7	3
Index test	21	5	2
Reference standard	26	2	0
Flow and timing	19	6	3
Overall risk of bias	17	8	3

DISCUSSION

This systematic review evaluated the diagnostic performance of HE4, CA-125, and ROMA score in the early detection of epithelial ovarian cancer. The findings suggest that CA-125 remains a sensitive marker, but its lower specificity limits its usefulness as a standalone diagnostic test. HE4 provides better specificity, while ROMA score offers the best overall diagnostic balance by combining HE4, CA-125, and menopausal status.

CA-125 demonstrated pooled sensitivity of 82.4% and specificity of 74.2%. Its sensitivity increased to 91.5% in advanced-stage disease but decreased to 66.8% in early-stage disease. This confirms that CA-125 is more reliable in advanced epithelial ovarian cancer than in early-stage disease. The reduced specificity of CA-125 was mainly due to false-positive elevation in benign gynecological conditions, particularly endometriosis and inflammatory pelvic diseases.

HE4 demonstrated pooled sensitivity of 78.6% and specificity of 88.9%. Although HE4 sensitivity was slightly lower than CA-125, its higher specificity makes it valuable for differentiating benign from malignant adnexal masses. HE4 was less frequently elevated in benign conditions, especially endometriosis. In early-stage disease, HE4 showed sensitivity of 70.9% and specificity of 89.4%, indicating better early-stage diagnostic discrimination than CA-125.

ROMA score demonstrated pooled sensitivity of 87.1%, specificity of 84.7%, and AUC of 0.92. ROMA provided the best overall performance because it incorporated two biomarkers and menopausal status. The algorithm was particularly effective in postmenopausal women, where sensitivity reached 90.2% and specificity reached 86.1%. In early-stage disease, ROMA sensitivity was 76.5%, which was higher than CA-125 and HE4 alone.

The results show that diagnostic performance is strongly influenced by disease stage. All three markers performed better in advanced-stage disease than in early-stage disease. This reflects the biological nature of ovarian cancer, where tumor burden and biomarker release are usually higher in advanced disease. Therefore, diagnostic studies with a high proportion of advanced-stage cases may overestimate the usefulness of these markers for early detection.

Menopausal status also influenced diagnostic accuracy. CA-125 had lower specificity in premenopausal women because benign gynecological conditions are more common in this group. HE4 maintained better specificity in premenopausal women, while ROMA improved classification by incorporating menopausal status into the algorithm. In postmenopausal women, all three markers performed better due to lower rates of benign biomarker elevation and higher pre-test probability of malignancy.

The clinical value of these markers lies primarily in risk stratification rather than population screening. CA-125 alone is insufficient for early detection because of false-positive and false-negative results. HE4 improves specificity and may reduce unnecessary surgical referrals for benign disease. ROMA score can assist clinicians in identifying women who require referral to gynecologic oncology centers. However, these tests should not replace imaging, histopathology, or clinical judgment.

The findings are consistent with previous diagnostic studies showing that HE4 and ROMA improve diagnostic performance compared with CA-125 alone. However, heterogeneity remains an important limitation. Differences in patient selection, assay platforms, cut-off values, histological subtypes, and disease stage distribution make direct comparison difficult. In addition, many studies did not report early-stage results separately, limiting the strength of conclusions regarding early detection.

Future research should focus on large prospective studies specifically designed for early-stage epithelial ovarian cancer. Standardized cut-off values, uniform assay platforms, and subgroup analysis by menopausal status and histological subtype are needed. Multimarker panels incorporating HE4, CA-125, ROMA, imaging scores, genetic risk, and emerging molecular markers may further improve early detection.

Clinical Implications

The findings of this review have important clinical implications. CA-125 remains useful but should not be used alone for early detection. HE4 improves specificity and is particularly useful when benign gynecological disease is suspected. ROMA score provides the best combined diagnostic performance and may be useful for triaging women with adnexal masses.

In clinical practice, women with suspicious adnexal masses and high ROMA scores should be considered for specialist gynecologic oncology referral. Women with low-risk results should still be followed carefully if clinical or imaging findings remain suspicious. Biomarker results should always be interpreted with clinical history, menopausal status, imaging findings, and histopathological confirmation.

Limitations

This systematic review has several limitations. First, the included studies used different diagnostic cut-off values for CA-125, HE4, and ROMA. Second, assay platforms varied across studies, which may affect biomarker values. Third, several studies included both early- and advanced-stage ovarian cancer cases, making it difficult to isolate diagnostic performance in early-stage disease. Fourth, not all studies reported histological subtype-specific performance. Fifth, retrospective study designs and non-consecutive patient recruitment may have introduced selection bias. Finally, publication bias may be present because studies reporting favorable diagnostic accuracy are more likely to be published.

CONCLUSION

HE4, CA-125, and ROMA score are useful diagnostic tools in the evaluation of epithelial ovarian cancer. CA-125 has good sensitivity but limited specificity, particularly in premenopausal women and benign gynecological conditions. HE4 provides higher specificity and better discrimination between benign and malignant adnexal masses. ROMA score offers the best overall diagnostic balance by combining HE4, CA-125, and menopausal status.

In this systematic review, ROMA score demonstrated pooled sensitivity of 87.1%, specificity of 84.7%, and AUC of 0.92. In early-stage epithelial ovarian cancer, ROMA also performed better than HE4 and CA-125 alone, with sensitivity of 76.5%. However, none of these markers is sufficiently accurate to serve as an independent population screening tool. Their greatest clinical utility lies in combination with imaging, clinical assessment, menopausal status, and histopathological confirmation.

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