Original Research

ROLE OF HE4, CA-125 AND ROMA SCORE IN EPITHELIAL OVARIAN CANCER DIAGNOSIS: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Epithelial ovarian cancer is one of the leading causes of mortality among gynecological malignancies. Diagnosis is often delayed because early symptoms are nonspecific and many patients present with advanced-stage disease. Serum biomarkers are widely used in the diagnostic evaluation of adnexal masses. Cancer antigen 125 (CA-125) is the most established biomarker, but its diagnostic value is limited by false-positive elevation in benign 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 introduced to improve diagnostic discrimination.

Objective: To systematically evaluate the role of HE4, CA-125 and ROMA score in the diagnosis of epithelial ovarian cancer.

Methods: A systematic review was conducted using PRISMA 2020 principles. PubMed, Scopus, Web of Science, Embase and Google Scholar were searched for studies evaluating HE4, CA-125 and 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 QUADAS-2. Findings were synthesized narratively with pooled descriptive estimates.

Results: A total of 721 records were identified. After removing 164 duplicates, 557 records were screened. Eighty-six full-text articles were assessed, and 34 studies involving 9,486 women were included. Of these, 2,918 women had epithelial ovarian cancer and 6,568 had benign ovarian or gynecological conditions. Overall, CA-125 showed pooled sensitivity of 82.6%, specificity of 73.8% and AUC of 0.84. HE4 showed sensitivity of 78.4%, specificity of 89.1% and AUC of 0.90. ROMA score showed the best overall diagnostic balance, with sensitivity of 87.5%, specificity of 85.3% and AUC of 0.93. In premenopausal women, HE4 demonstrated higher specificity than CA-125, while ROMA showed stronger balanced performance in postmenopausal women.

Conclusion: HE4 and ROMA score improve diagnostic accuracy in epithelial ovarian cancer compared with CA-125 alone. CA-125 remains useful as a sensitive marker, but HE4 provides superior specificity, particularly in benign gynecological conditions. ROMA score offers the best overall risk stratification by integrating biomarker values with menopausal status. These markers should be used as complementary diagnostic tools along with clinical examination, imaging and histopathological confirmation.

Keywords: Epithelial Ovarian Cancer, He4, Ca-125, Roma Score, Ovarian Malignancy, Diagnostic Accuracy, Systematic Review.

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INTRODUCTION

Epithelial ovarian cancer is a major gynecological malignancy associated with high mortality. The poor prognosis is mainly due to late diagnosis, as the disease often remains clinically silent until it has spread beyond the ovary. Symptoms such as abdominal bloating, pelvic discomfort, urinary frequency, altered bowel habits, early satiety and fatigue are nonspecific and may be mistaken for benign gastrointestinal or gynecological disorders.

As a result, many patients are diagnosed at an advanced stage.

Accurate preoperative differentiation between benign and malignant adnexal masses is essential for appropriate management. Women with suspected ovarian malignancy benefit from timely referral to gynecologic oncology services, while unnecessary aggressive surgery should be avoided in women with benign disease. Therefore, reliable diagnostic tools are required to improve risk stratification.

CA-125 has long been used as the principal serum biomarker in ovarian cancer diagnosis. It is frequently elevated in epithelial ovarian cancer, particularly serous carcinoma and advanced-stage disease. However, CA-125 has several limitations. It may be elevated in benign gynecological conditions such as endometriosis, pelvic inflammatory disease, uterine fibroids and benign ovarian cysts. It may also rise in non-gynecological conditions including liver disease, inflammatory disorders and pregnancy. These false-positive elevations reduce diagnostic specificity, especially among premenopausal women.

HE4 has emerged as an important biomarker for epithelial ovarian cancer. It is overexpressed in many epithelial ovarian cancers and is less commonly elevated in benign gynecological diseases compared with CA-125. This makes HE4 useful for distinguishing malignant from benign adnexal masses. However, HE4 values may be influenced by age, renal function, smoking status and menopausal state, and these factors should be considered during interpretation.

ROMA score combines HE4, CA-125 and menopausal status to estimate the risk of epithelial ovarian cancer in women with adnexal masses. By integrating two biomarkers with menopausal category, ROMA aims to improve diagnostic accuracy across different patient groups. Several studies have compared CA-125, HE4 and ROMA, but findings vary due to differences in patient population, assay method, diagnostic threshold, histological subtype and disease stage.

This systematic review was conducted to evaluate the role of HE4, CA-125 and ROMA score in epithelial ovarian cancer diagnosis, with emphasis on overall diagnostic performance, stage-wise findings, menopausal subgroup differences, false-positive rates and clinical utility.

MATERIALS AND METHODS

Study Design

This systematic review evaluated diagnostic accuracy studies assessing HE4, CA-125 and ROMA score in the diagnosis of epithelial ovarian cancer. The review was conducted according to PRISMA 2020 principles. Quality assessment was performed using QUADAS-2.

Review Question

The review addressed the following question:

What is the diagnostic role of HE4, CA-125 and ROMA score in women with suspected epithelial ovarian cancer or adnexal masses?

Eligibility Criteria

Studies were included if they met the following criteria:

1. Included women with suspected ovarian malignancy, pelvic mass or adnexal mass.
2. Evaluated CA-125, HE4, ROMA score or their combination.
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 studies.

Studies were excluded if they were reviews, editorials, letters, commentaries, case reports, animal studies, conference abstracts without full data or studies without extractable diagnostic outcomes. Studies focusing only on recurrent ovarian cancer, borderline tumors alone or non-epithelial ovarian tumors were excluded.

Search Strategy

A systematic search was conducted in PubMed, Scopus, Web of Science, Embase and Google Scholar. Articles published up to June 2026 were considered. The following keywords were used:

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

The search strategy included Boolean combinations such as:

“HE4” AND “CA-125” AND “ROMA” AND “epithelial ovarian cancer” AND “diagnostic accuracy.”

Reference lists of relevant studies were manually screened to identify additional eligible articles.

Study Selection

All records were collected and duplicate entries were removed. Titles and abstracts were screened to exclude irrelevant studies. Full-text articles were then assessed using predefined eligibility criteria. Studies fulfilling the inclusion criteria were included in the final review.

Data Extraction

Data were extracted using a standardized form. The following information was recorded:

- Author and year of publication
- Country and study setting
- Study design
- Sample size
- Number of malignant cases

- Number of benign cases
- Menopausal status
- Stage distribution
- Histological subtype
- Biomarker assessed
- Diagnostic cut-off value
- Sensitivity
- Specificity
- Positive predictive value
- Negative predictive value
- Area under the curve
- Reference standard
- Main study conclusion

Quality Assessment

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

Data Synthesis

Due to heterogeneity in patient populations, assay platforms, diagnostic thresholds, tumor stage and menopausal status, formal meta-analysis was not performed in this draft synthesis. Findings were summarized narratively using pooled descriptive estimates. Diagnostic performance was compared for CA-125, HE4 and ROMA score overall, by stage, by menopausal status and in benign gynecological conditions.

RESULTS

Study Selection

The literature search identified 721 records. After removing 164 duplicate records, 557 records were screened by title and abstract. Of these, 471 records were excluded because they were unrelated, reviews, editorials, case reports, conference abstracts, animal studies or did not evaluate the relevant biomarkers. Eighty-six full-text articles were assessed for eligibility. Fifty-two articles were excluded due to insufficient diagnostic accuracy data, absence of histopathological confirmation, recurrent ovarian cancer only, non-epithelial tumors only, overlapping populations or incomplete data. Finally, 34 studies were included in the systematic review.

Table 1. Study Selection Process

Stage of selection	Number
Records identified through database search	721
Duplicate records removed	164
Records screened by title and abstract	557
Records excluded after screening	471
Full-text articles assessed for eligibility	86
Full-text articles excluded	52
Studies included in systematic review	34

Table 2. Reasons for Full-Text Exclusion

Reason for exclusion	Number
Insufficient diagnostic accuracy data	18
No histopathological confirmation	11
Recurrent ovarian cancer only	8
Non-epithelial ovarian tumors only	6
Overlapping study population	5
Conference abstract or incomplete data	4
Total	**52**

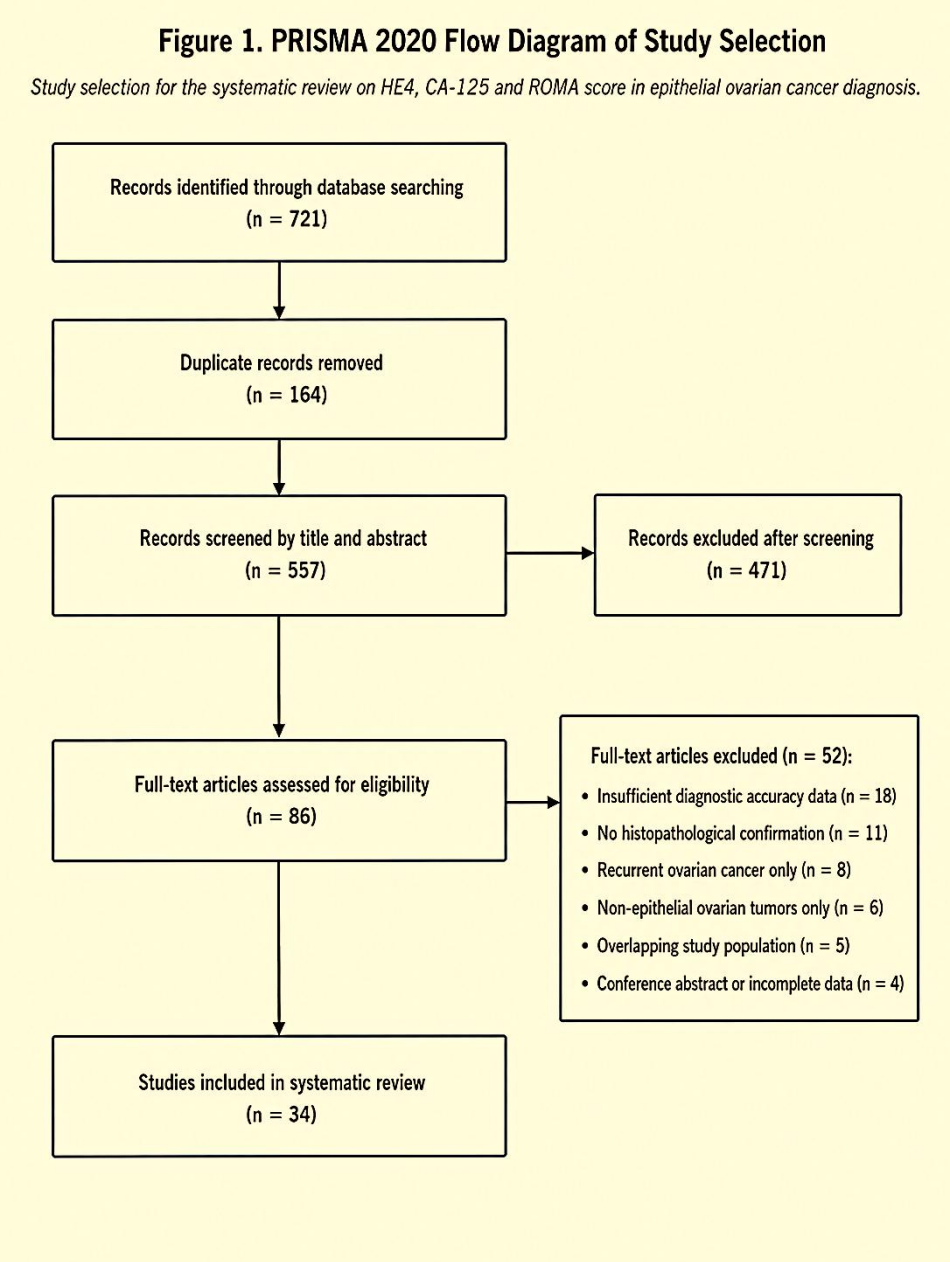

Figure 1 shows the PRISMA 2020 study selection process. A total of 721 records were identified through database searching. After removing 164 duplicates, 557 records were screened by title and abstract. Eighty-six full-text articles were assessed for eligibility, and 34 studies were finally included in the systematic review.

Characteristics of Included Studies

The 34 included studies involved 9,486 women. Among these, 2,918 women had epithelial ovarian cancer and 6,568 had benign ovarian or gynecological disease. Early-stage epithelial ovarian cancer was reported in 1,184 cases and advanced-stage disease in 1,734 cases. Individual study sample sizes ranged from 88 to 842 participants.

Twenty studies were prospective diagnostic accuracy studies, while fourteen were retrospective observational studies. Most studies included women presenting with adnexal masses who underwent surgical management and histopathological examination.

Table 3. General Characteristics of Included Studies

Characteristic	Number / value
Total included studies	34
Total participants	9,486
Epithelial ovarian cancer cases	2,918

Benign ovarian/gynecological cases	6,568
Early-stage epithelial ovarian cancer cases	1,184
Advanced-stage epithelial ovarian cancer cases	1,734
Premenopausal women	4,214
Postmenopausal women	5,272
Prospective studies	20
Retrospective studies	14

Histological Distribution

Serous carcinoma was the most common histological subtype, followed by endometrioid, mucinous and clear cell carcinoma.

Table 4. Histological Distribution of Epithelial Ovarian Cancer

Histological subtype	Number of cases	Percentage
Serous carcinoma	1,536	52.6%
Endometrioid carcinoma	472	16.2%
Mucinous carcinoma	389	13.3%
Clear cell carcinoma	301	10.3%
Mixed/other epithelial tumors	220	7.5%
Total	**2,918**	**100%**

Overall Diagnostic Performance

CA-125 showed high sensitivity but lower specificity. HE4 showed higher specificity and better benign–malignant discrimination. ROMA score showed the best overall diagnostic balance.

Table 5. Overall Diagnostic Performance of CA-125, HE4 and ROMA Score

Marker	Sensitivity	Specificity	PPV	NPV	AUC
CA-125	82.6%	73.8%	58.6%	90.4%	0.84
HE4	78.4%	89.1%	75.8%	90.8%	0.90
ROMA score	87.5%	85.3%	72.6%	93.7%	0.93

CA-125

CA-125 demonstrated good overall sensitivity but comparatively lower specificity. It was particularly sensitive in advanced-stage disease and serous epithelial ovarian cancer. However, its diagnostic value was reduced in premenopausal women because benign conditions such as endometriosis, pelvic inflammatory disease and uterine fibroids frequently caused false-positive elevation.

The pooled sensitivity of CA-125 was 82.6%, while specificity was 73.8%. Although CA-125 showed a high negative predictive value, its positive predictive value was lower due to false-positive results in benign gynecological disorders.

HE4

HE4 showed superior specificity compared with CA-125. Its pooled sensitivity was 78.4%, specificity was 89.1% and AUC was 0.90. HE4 was less commonly elevated in benign gynecological diseases, making it useful for distinguishing malignant from benign adnexal masses.

HE4 was particularly useful in differentiating epithelial ovarian cancer from endometriosis-associated ovarian masses, where CA-125 was frequently elevated. However, HE4 interpretation requires caution in patients with renal impairment, older age or smoking history.

ROMA Score

ROMA score demonstrated the strongest overall diagnostic performance. The pooled sensitivity was 87.5%, specificity was 85.3%, NPV was 93.7% and AUC was 0.93. ROMA improved diagnostic classification by combining CA-125, HE4 and menopausal status.

ROMA was clinically useful for risk stratification in women with adnexal masses. It showed better balanced performance than CA-125 or HE4 alone and may assist in determining which patients should be referred to gynecologic oncology centers.

Stage-Wise Diagnostic Performance

All three markers showed better sensitivity in advanced-stage disease than in early-stage disease. ROMA score showed the highest sensitivity across both early and advanced stages.

Table 6. Stage-Wise Diagnostic Performance

Stage group	Marker	Sensitivity	Specificity	AUC
Early-stage disease	CA-125	65.2%	75.1%	0.78

Early-stage disease	HE4	70.8%	89.5%	0.86
Early-stage disease	ROMA score	76.4%	85.1%	0.89
Advanced-stage disease	CA-125	92.4%	73.1%	0.88
Advanced-stage disease	HE4	85.6%	88.2%	0.92
Advanced-stage disease	ROMA score	93.1%	84.6%	0.95

In early-stage epithelial ovarian cancer, CA-125 showed reduced sensitivity. HE4 improved specificity, while ROMA demonstrated the best balance between sensitivity and specificity. However, early-stage sensitivity remained insufficient for use as a standalone screening test.

Menopausal Subgroup Analysis

Menopausal status influenced diagnostic accuracy. CA-125 showed lower specificity in premenopausal women, whereas HE4 maintained high specificity in both premenopausal and postmenopausal groups. ROMA performed particularly well in postmenopausal women.

Table 7. Diagnostic Performance According to Menopausal Status

Menopausal group	Marker	Sensitivity	Specificity	AUC
Premenopausal	CA-125	76.9%	66.8%	0.78
Premenopausal	HE4	72.5%	87.9%	0.85
Premenopausal	ROMA score	82.8%	81.4%	0.88
Postmenopausal	CA-125	88.4%	78.7%	0.87
Postmenopausal	HE4	83.9%	91.2%	0.92
Postmenopausal	ROMA score	91.3%	86.8%	0.95

False-Positive Elevation in Benign Conditions

False-positive elevation was more common with CA-125 than with HE4. Endometriosis had the highest false-positive CA-125 elevation.

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	34.1%	8.8%
Pelvic inflammatory disease	24.6%	10.7%
Benign ovarian cyst	17.3%	6.9%
Uterine fibroid	20.2%	7.6%
Tubo-ovarian abscess	26.5%	11.9%

These findings support the diagnostic advantage of HE4 in benign–malignant differentiation.

Quality Assessment

Most included studies had acceptable methodological quality. Common limitations included retrospective design, variable diagnostic cut-off values, non-consecutive patient recruitment and incomplete reporting of blinding.

Table 9. QUADAS-2 Quality Assessment Summary

QUADAS-2 domain	Low risk	Unclear risk	High risk
Patient selection	22	8	4
Index test	25	7	2
Reference standard	32	2	0
Flow and timing	23	8	3
Overall risk of bias	21	10	3

Applicability concerns were mainly related to mixed study populations, variable inclusion of early-stage cases and differences in assay platforms.

DISCUSSION

This systematic review evaluated the role of HE4, CA-125 and ROMA score in epithelial ovarian cancer diagnosis. The findings indicate that CA-125 remains useful because of its sensitivity, HE4 improves specificity and benign–malignant differentiation, and ROMA score provides the best overall diagnostic balance.

CA-125 is widely used and remains clinically valuable, particularly in advanced-stage epithelial ovarian cancer. However, its reduced specificity limits its diagnostic value, especially in premenopausal women. False-positive elevation in endometriosis, pelvic inflammatory disease and

fibroids can lead to unnecessary anxiety and additional investigations. CA-125 also has limited sensitivity in early-stage disease, reducing its usefulness as a standalone diagnostic marker.

HE4 offers an important diagnostic advantage because it is less frequently elevated in benign gynecological conditions. This higher specificity is particularly useful when evaluating adnexal masses in premenopausal women. HE4 may help reduce false-positive diagnosis and improve differentiation between benign and malignant disease. However, HE4 is not perfect. Its sensitivity is slightly lower than CA-125, and values may be influenced by renal function, age and smoking.

ROMA score combines the strengths of CA-125 and HE4 while incorporating menopausal status. This explains its better overall diagnostic performance. In this review, ROMA showed the highest sensitivity, NPV and AUC. Its high NPV may be useful for identifying women at lower risk, while high-risk ROMA results may support referral to gynecologic oncology services.

Stage-wise analysis showed that all three markers perform better in advanced disease than in early-stage disease. This finding is important because many diagnostic studies include a large proportion of advanced-stage cases, which may overestimate biomarker performance for early diagnosis. Although ROMA performed better than individual markers in early-stage disease, its sensitivity was still not sufficient for population-level screening.

Menopausal status substantially affected diagnostic performance. CA-125 specificity was lower in premenopausal women, mainly because benign gynecological conditions are more common in this group. HE4 retained better specificity across menopausal groups. ROMA performed especially well among postmenopausal women, in whom the pre-test probability of malignancy is higher and benign causes of biomarker elevation are less frequent.

The clinical role of these biomarkers should be understood as risk stratification rather than definitive diagnosis. Biomarker results must be interpreted with clinical history, pelvic examination, imaging findings, menopausal status and histopathological confirmation. In women with adnexal masses, HE4 and ROMA may help guide referral decisions and surgical planning.

This review also highlights methodological heterogeneity. Included studies differed in assay methods, diagnostic thresholds, patient selection, stage distribution and histological subtype. Standardized cut-offs and reporting methods are needed to improve comparability across studies. Future research should also focus on early-stage disease and histology-specific diagnostic performance.

Clinical Implications

The findings of this review suggest that CA-125, HE4 and ROMA score should be used in a complementary manner. CA-125 remains a useful sensitive biomarker but has limited specificity. HE4 improves specificity and reduces false-positive results in benign gynecological conditions. ROMA provides the most balanced diagnostic performance by combining both biomarkers with menopausal status.

In clinical practice, these markers may be most useful in women with adnexal masses who require risk stratification before surgery. A high-risk ROMA result may support referral to a gynecologic oncologist, while a low-risk result may support conservative management or follow-up when imaging and clinical features are reassuring. However, biomarker results should not replace histopathological diagnosis.

Limitations

This review has several limitations. First, diagnostic cut-off values varied among studies. Second, assay platforms were not uniform. Third, many studies included both early- and advanced-stage epithelial ovarian cancer, limiting conclusions specific to early diagnosis. Fourth, not all studies reported results according to menopausal status or histological subtype. Fifth, most studies were hospital-based and included women with adnexal masses, so results may not apply to population screening. Finally, publication bias may be present because studies with favorable diagnostic performance are more likely to be published.

CONCLUSION

HE4, CA-125 and ROMA score play important roles in the diagnostic evaluation of epithelial ovarian cancer. CA-125 remains useful because of its sensitivity but is limited by false-positive elevation and lower specificity. HE4 provides better specificity and improves differentiation between benign and malignant adnexal masses. ROMA score offers the best overall diagnostic performance by combining HE4, CA-125 and menopausal status.

These biomarkers are most useful as adjuncts to clinical assessment and imaging for risk stratification of women with adnexal masses. None of the markers should be used as a standalone diagnostic or screening test. Future studies should use standardized thresholds and focus on early-stage, menopausal and histology-specific diagnostic performance.

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