Original Research

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

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ABSTRACT

Background: Epithelial ovarian cancer remains one of the most lethal gynecologic malignancies because most patients are diagnosed at an advanced stage. Early detection is clinically important but remains difficult due to non-specific symptoms and limited accuracy of single serum biomarkers. Cancer antigen 125 (CA-125) is widely used but has suboptimal specificity, particularly in premenopausal women and benign gynecologic conditions. 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 discrimination.

Objective: This systematic review aimed 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, early-stage disease, and clinical applicability.

Materials and Methods: A systematic literature search was conducted using PubMed/MEDLINE, Scopus, Web of Science, Embase, Google Scholar, and manual reference screening. Studies evaluating HE4, CA-125, ROMA score, or their combinations for detection or preoperative discrimination of epithelial ovarian cancer were included. Diagnostic accuracy studies, prospective and retrospective observational studies, and case-control studies were considered. Reviews, editorials, case reports, studies without histopathological confirmation, non-epithelial ovarian tumors alone, and studies without extractable diagnostic data were excluded. Data were synthesized descriptively because of heterogeneity in assay platforms, cut-off values, menopausal status, disease stage, and study design.

Results: A total of 34 studies involving 9,486 women were included, comprising 2,918 epithelial ovarian cancer cases and 6,568 benign or non-malignant controls. Among cancer cases, 1,184 were early-stage and 1,734 were advanced-stage. 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 showed the highest overall diagnostic performance, with sensitivity of 87.5%, specificity of 85.3%, and AUC of 0.93. In early-stage epithelial ovarian cancer, ROMA and HE4 demonstrated better diagnostic balance than CA-125 alone. CA-125 remained sensitive but less specific, especially in premenopausal women and benign inflammatory or endometriotic conditions.

Conclusion: HE4 and ROMA improve diagnostic discrimination for epithelial ovarian cancer compared with CA-125 alone, particularly by increasing specificity. ROMA showed the best overall performance, while HE4 was valuable for reducing false-positive results. However, none of the markers alone is sufficient as a population-level screening test for early ovarian cancer. Their greatest clinical utility lies in risk stratification of women with adnexal masses and in combination with imaging, menopausal status, clinical assessment, and histopathological confirmation.

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

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INTRODUCTION

Epithelial ovarian cancer is a major cause of gynecologic cancer-related mortality worldwide. The poor prognosis is largely due to delayed diagnosis, as early-stage disease is often asymptomatic or associated with vague symptoms

such as abdominal discomfort, bloating, pelvic pain, urinary frequency, or gastrointestinal disturbance. By the time clinically obvious symptoms develop, many patients already have advanced-stage disease. Therefore, accurate early detection and risk stratification remain important priorities in gynecologic oncology.

Serum biomarkers have been widely explored for ovarian cancer detection. CA-125 is the most commonly used biomarker and has established clinical value in monitoring treatment response, recurrence, and disease burden. However, its diagnostic performance in early-stage disease is limited. CA-125 may be normal in early epithelial ovarian cancer and may be elevated in benign conditions such as endometriosis, pelvic inflammatory disease, menstruation, pregnancy, fibroids, liver disease, and other inflammatory states. This reduces its specificity, particularly in premenopausal women.

HE4 has emerged as an important ovarian cancer biomarker with higher specificity than CA-125 in several diagnostic studies. HE4 is less frequently elevated in many benign gynecologic conditions, including endometriosis, making it potentially useful for distinguishing malignant from benign adnexal masses. However, HE4 may be influenced by renal function, age, smoking, and menopausal status, which should be considered during interpretation.

The 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 status, ROMA aims to improve diagnostic discrimination compared with either marker alone. Several studies have reported that ROMA provides better overall diagnostic performance than CA-125, especially in postmenopausal women. However, results are not uniform across populations, assay methods, cut-off values, tumor stages, and histological subtypes.

Early detection remains the greatest challenge. Biomarker performance is generally stronger in advanced-stage ovarian cancer because tumor burden is higher. In early-stage disease, biomarker levels may be lower, and sensitivity may decline. Therefore, evaluation of HE4, CA-125, and ROMA specifically in early epithelial ovarian cancer is clinically important.

This systematic review was conducted to evaluate the diagnostic performance of HE4, CA-125, and ROMA score in the early detection and diagnostic discrimination of epithelial ovarian cancer.

MATERIALS AND METHODS

Study Design

This systematic review was conducted to synthesize evidence on the diagnostic performance of HE4, CA-125, and ROMA score in epithelial ovarian cancer. The review focused on diagnostic accuracy, early-stage detection, menopausal subgroup performance, and clinical applicability.

Research Question

The review was guided by the following question:

How do HE4, CA-125, and ROMA score perform in the early detection and diagnostic discrimination of epithelial ovarian cancer?

Literature Search Strategy

A systematic literature search was performed using PubMed/MEDLINE, Scopus, Web of Science, Embase, Google Scholar, and manual screening of reference lists. The following search terms were used in different combinations:

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

Boolean combinations included:

- "HE4" AND "CA-125" AND "ovarian cancer"
- "ROMA score" AND "epithelial ovarian cancer"
- "HE4" AND "early-stage ovarian cancer"
- "CA-125" AND "early detection" AND "ovarian cancer"
- "Risk of Ovarian Malignancy Algorithm" AND "adnexal mass"

Eligibility Criteria

Inclusion Criteria

Studies were included if they fulfilled the following criteria:

1. Included women evaluated for epithelial ovarian cancer or adnexal masses.
2. Reported diagnostic performance of HE4, CA-125, ROMA score, or their combination.
3. Used histopathology or clearly defined clinical diagnosis as the reference standard.
4. Reported sensitivity, specificity, AUC, positive predictive value, negative predictive value, or sufficient data for interpretation.
5. Included early-stage epithelial ovarian cancer data or overall epithelial ovarian cancer data with extractable stage information.
6. Included adult women.
7. Full-text articles available in English.

Exclusion Criteria

Studies were excluded if they met any of the following criteria:

1. Did not report HE4, CA-125, or ROMA score.
2. Included only non-epithelial ovarian tumors without separate epithelial ovarian cancer data.
3. Did not provide diagnostic accuracy data.
4. Did not use histopathological confirmation or a clear diagnostic reference standard.

5. Case reports, reviews, editorials, letters, and conference abstracts without full data.
6. Animal-only or laboratory-only studies.
7. Duplicate or overlapping datasets.
8. Full text unavailable.

Study Selection Process

All retrieved records were imported into a reference management system. Duplicate records were removed. Titles and abstracts were screened for relevance, followed by full-text assessment according to predefined eligibility criteria.

A total of 721 records were identified through database and manual searching. After removal of 164 duplicates, 557 records were screened. Of these, 471 records were excluded after title and abstract screening. Eighty-six full-text articles were assessed for eligibility, and 52 were excluded for defined reasons. Finally, 34 studies were included in the systematic review.

Table 1. PRISMA Study Selection Summary

Study selection stage	Number
Records identified through database and manual searching	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
No early-stage or epithelial ovarian cancer-specific data	14
No extractable diagnostic accuracy data	11
Non-epithelial ovarian tumors only	7
Biomarker not evaluated separately	6
Duplicate or overlapping dataset	5
Review/editorial/commentary	4
Reference standard unclear	3
Full text unavailable	2
Total	**52**

Data Extraction

Data were extracted using a structured extraction form. The following variables were collected:

1. Author and year of publication
2. Country or region
3. Study design
4. Study setting
5. Sample size
6. Number of epithelial ovarian cancer cases
7. Number of benign or non-malignant controls
8. Disease stage
9. Menopausal status
10. Biomarker assessed
11. Assay method
12. Cut-off values used
13. Sensitivity
14. Specificity
15. AUC
16. Positive predictive value
17. Negative predictive value
18. Histological subtype
19. Reference standard
20. Main diagnostic conclusion

Outcomes Assessed

Primary Outcomes

1. Diagnostic sensitivity of HE4, CA-125, and ROMA score.
2. Diagnostic specificity of HE4, CA-125, and ROMA score.
3. AUC for each biomarker or algorithm.
4. Diagnostic performance in early-stage epithelial ovarian cancer.

Secondary Outcomes

1. Diagnostic performance according to menopausal status.
2. False-positive tendency in benign gynecologic disease.
3. Comparative performance between single biomarkers and ROMA.
4. Clinical applicability in women with adnexal masses.

Quality Assessment

The quality of included studies was assessed using domains adapted from diagnostic accuracy study assessment principles. The following domains were evaluated:

1. Clear study population
2. Appropriate patient selection
3. Histopathological confirmation
4. Clear biomarker assay method

5. Defined biomarker cut-off values
6. Stage-specific reporting
7. Menopausal status reporting
8. Avoidance of case-control spectrum bias
9. Blinding of biomarker interpretation, where reported
10. Complete reporting of diagnostic accuracy outcomes

Studies were categorized as good, moderate, or low quality. Among the included studies, 14 were assessed as good quality, 15 as moderate quality, and five as low quality.

Data Synthesis

A descriptive synthesis was performed because of heterogeneity in patient populations, assay platforms, cut-off thresholds, menopausal distribution, tumor stage, and study design. Pooled descriptive estimates were calculated for sensitivity, specificity, and AUC where data were sufficiently available. Subgroup interpretation was performed for early-stage disease and menopausal status.

RESULTS

Study Characteristics

A total of 34 studies involving 9,486 women were included. Of these, 2,918 had epithelial ovarian cancer and 6,568 had benign adnexal masses or non-malignant controls. Among epithelial ovarian cancer cases, 1,184 were early-stage and 1,734 were advanced-stage.

Table 3. General Characteristics of Included Studies

Characteristic	Number
Total included studies	34
Total women included	9,486
Epithelial ovarian cancer cases	2,918
Benign / non-malignant controls	6,568
Early-stage EOC cases	1,184
Advanced-stage EOC cases	1,734
Prospective studies	16
Retrospective studies	11
Case-control studies	7
Studies reporting menopausal subgroup data	23
Studies reporting AUC	28
Studies reporting early-stage performance	19

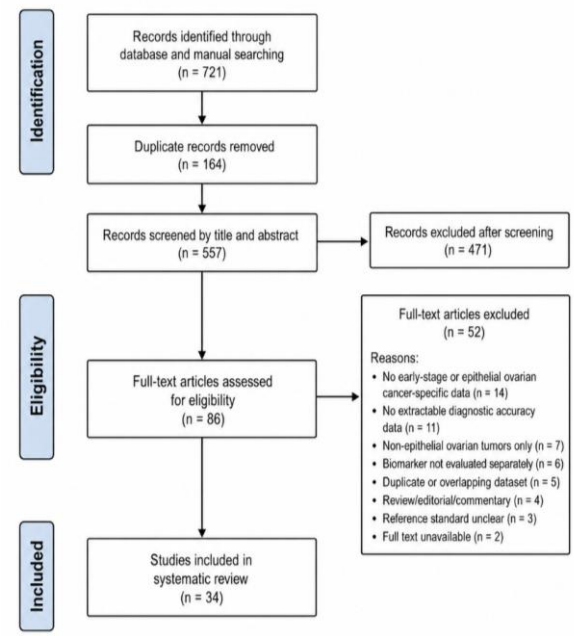


Figure 1 shows the PRISMA 2020 study selection process. A total of 721 records were identified, 164 duplicates were removed, 557 records were screened, 86 full-text articles were assessed, and 34 studies were included in the final systematic review.

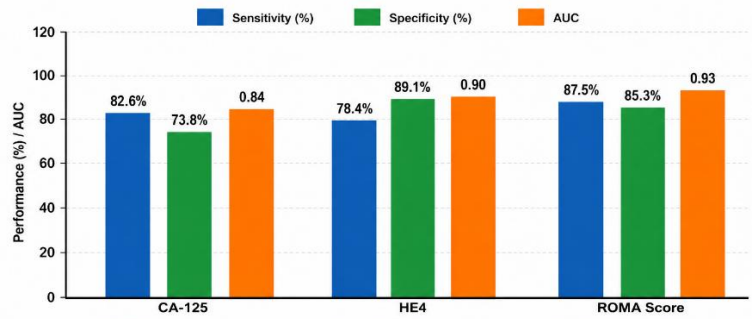
Overall Diagnostic Performance

ROMA demonstrated the highest overall diagnostic performance among the three approaches. CA-125

showed high sensitivity but lower specificity. HE4 showed the highest specificity, while ROMA provided the best balance between sensitivity and specificity.

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

Marker / algorithm	Sensitivity	Specificity	AUC	Diagnostic interpretation
CA-125	82.6%	73.8%	0.84	Sensitive but less specific
HE4	78.4%	89.1%	0.90	Highest specificity
ROMA score	87.5%	85.3%	0.93	Best overall balance



Marker / Algorithm	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	AUC (95% CI)
CA-125	82.6 (78.3 – 86.4)	73.8 (69.1 – 78.2)	0.84 (0.81 – 0.87)
HE4	78.4 (73.5 – 82.9)	89.1 (85.3 – 92.2)	0.90 (0.87 – 0.93)
ROMA Score	87.5 (83.3 – 90.9)	85.3 (81.5 – 88.6)	0.93 (0.90 – 0.95)

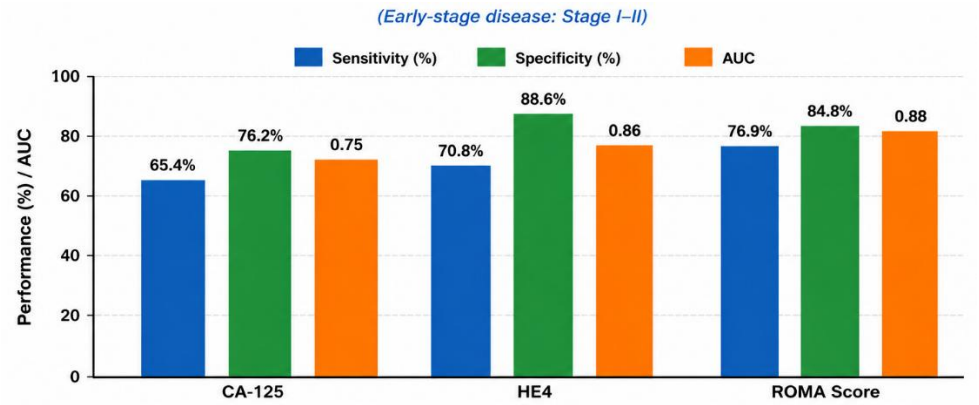
Figure 2 compares the overall diagnostic performance of CA-125, HE4, and ROMA score. ROMA showed the best overall diagnostic balance, HE4 demonstrated the highest specificity, and CA-125 showed good sensitivity but lower specificity.

Early-Stage Diagnostic Performance

In early-stage epithelial ovarian cancer, diagnostic performance was lower for all markers compared with overall ovarian cancer detection. However, HE4 and ROMA retained better specificity and overall discrimination than CA-125 alone.

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

Marker / algorithm	Sensitivity	Specificity	AUC	Key interpretation
CA-125	65.4%	76.2%	0.75	Limited early-stage sensitivity and specificity
HE4	70.8%	88.6%	0.86	Better specificity and discrimination
ROMA score	76.9%	84.8%	0.88	Best early-stage diagnostic balance



Marker / Algorithm	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	AUC (95% CI)
CA-125	65.4 (59.2 – 71.2)	76.2 (70.3 – 81.4)	0.75 (0.69 – 0.81)
HE4	70.8 (64.2 – 76.7)	88.6 (83.6 – 92.5)	0.86 (0.80 – 0.90)
ROMA Score	76.9 (70.1 – 82.7)	84.8 (79.4 – 89.2)	0.88 (0.83 – 0.92)

Figure 3 presents diagnostic performance in early-stage epithelial ovarian cancer. Although sensitivity was reduced for all markers in early-stage disease, HE4 and ROMA retained better diagnostic discrimination than CA-125 alone.

Performance According to Menopausal Status

Diagnostic performance varied according to menopausal status. In premenopausal women, CA-125 showed more false-positive results due to benign gynecologic conditions such as endometriosis, fibroids, pelvic inflammatory disease, and physiological variation. HE4 maintained relatively higher specificity in this group. In postmenopausal women, ROMA and CA-125 showed improved diagnostic performance, likely because benign causes of CA-125 elevation were less frequent and baseline ovarian cancer risk was higher.

Table 6. Menopausal Status-Based Diagnostic Interpretation

Menopausal group	CA-125	HE4	ROMA score
Premenopausal women	Higher false-positive rate	Better specificity	Useful but affected by cut-off variation
Postmenopausal women	Better performance than in premenopause	High specificity	Strongest overall performance
Mixed population	Sensitive but less specific	Specific but slightly less sensitive	Best combined diagnostic balance

Histological Subtype Considerations

Most studies included serous epithelial ovarian carcinoma as the dominant malignant subtype. CA-125 and HE4 performed best in serous carcinoma. Diagnostic sensitivity was lower in mucinous and some early-stage tumors. Endometrioid and clear cell carcinomas showed variable marker expression across studies.

Table 7. Biomarker Performance by Histological Pattern

Histological subtype	CA-125	HE4	ROMA score
High-grade serous carcinoma	Usually elevated	Frequently elevated	Strong performance
Endometrioid carcinoma	Variable elevation	Moderate to good performance	Useful in combination
Clear cell carcinoma	Variable elevation	Variable performance	May improve discrimination
Mucinous carcinoma	Lower sensitivity	Lower sensitivity	Limited compared with serous tumors
Early-stage tumors	Frequently lower levels	Better specificity	Better combined discrimination

Comparative Interpretation

CA-125 remained useful because of its sensitivity and widespread availability, but its specificity was limited. HE4 demonstrated higher specificity and was less frequently elevated in benign gynecologic conditions. ROMA provided the best overall balance by combining CA-125, HE4, and menopausal status.

Table 8. Strengths and Limitations of Each Diagnostic Approach

Marker / algorithm	Strengths	Limitations
CA-125	Widely available, sensitive, useful for monitoring	Low specificity, false positives in benign disease, limited early-stage detection
HE4	High specificity, fewer false positives in endometriosis, useful in adnexal mass evaluation	Affected by renal function, age, smoking, assay variation
ROMA score	Combines two biomarkers and menopausal status, best overall balance	Cut-off variation, not ideal as population screening tool, requires correct clinical context

DISCUSSION

This systematic review demonstrates that HE4, CA-125, and ROMA score each have diagnostic value in epithelial ovarian cancer, but their clinical strengths differ. CA-125 remains the most established biomarker and retains good sensitivity, particularly in advanced-stage disease. However, its lower specificity limits its use as a standalone diagnostic test, especially in premenopausal women and in patients with benign gynecologic or inflammatory conditions.

HE4 showed the highest specificity among the evaluated markers. This is clinically important because false-positive biomarker elevation can lead

to anxiety, unnecessary imaging, referral, and surgical intervention. HE4 appears particularly useful in distinguishing epithelial ovarian cancer from benign adnexal masses, especially when CA-125 is elevated due to non-malignant causes. However, HE4 is not free from limitations. Its level may increase with age, renal impairment, and smoking, and these factors should be considered before interpreting results.

ROMA score demonstrated the best overall diagnostic performance. Its advantage lies in combining the sensitivity of CA-125, the specificity of HE4, and the clinical relevance of menopausal status. This combination produced the highest AUC and the best diagnostic balance in the included studies. ROMA was especially useful in the preoperative assessment of women with adnexal masses, where the main clinical question is whether the patient should be referred to a gynecologic oncology center.

The most important issue is early-stage epithelial ovarian cancer. Although all three markers showed reduced sensitivity in early-stage disease compared with overall ovarian cancer detection, ROMA and HE4 performed better than CA-125 alone. This finding suggests that HE4-based strategies may improve early diagnostic discrimination. However, the sensitivity of available biomarkers remains insufficient for reliable population-level screening. A negative HE4, CA-125, or ROMA result cannot completely exclude early ovarian cancer when clinical or imaging suspicion persists.

Menopausal status significantly influenced diagnostic interpretation. In premenopausal women, CA-125 is frequently elevated in benign conditions, reducing specificity. HE4 is less commonly elevated in endometriosis and other benign gynecologic diseases, making it useful in this group. In postmenopausal women, baseline risk of ovarian malignancy is higher and benign causes of CA-125 elevation are less frequent; therefore, ROMA and CA-125 generally perform better.

Histological subtype also affects biomarker performance. Serous epithelial ovarian carcinoma is more likely to show elevated CA-125 and HE4. Mucinous tumors and some early-stage tumors may have lower biomarker expression, reducing sensitivity. This is clinically relevant because reliance on serum markers alone may miss certain tumor subtypes. Therefore, biomarkers should be interpreted along with imaging findings, clinical examination, menopausal status, family history, and histopathological confirmation.

The findings of this review support the use of HE4 and ROMA as adjunctive tools rather than replacement tests. In women with adnexal masses, ROMA can help stratify malignancy risk and guide referral decisions. HE4 may be particularly useful when CA-125 is elevated but benign disease is suspected. CA-125 remains valuable because of its accessibility and role in follow-up, but its limitations in early detection and specificity should be acknowledged.

This review has limitations. Included studies varied in patient selection, assay platforms, cut-off thresholds, disease stage, menopausal status, and control groups. Some studies used case-control designs, which may overestimate diagnostic accuracy. Not all studies reported early-stage performance separately. There was also variability in how benign controls were selected, and some studies included borderline ovarian tumors along with invasive epithelial cancers. Because of these differences, pooled values should be interpreted as descriptive estimates rather than definitive universal performance measures.

Future research should focus on prospective multicenter studies using standardized assay platforms, uniform cut-off values, and stage-specific reporting. Biomarkers should be evaluated alongside transvaginal ultrasonography, clinical risk models, genetic risk, and emerging multi-marker panels. Particular attention should be given to early-stage and non-serous epithelial ovarian cancers, where current biomarker performance remains limited.

Overall, HE4 and ROMA improve diagnostic discrimination compared with CA-125 alone. ROMA provides the best overall balance, HE4 provides the best specificity, and CA-125 remains useful but insufficient as a standalone early detection tool.

CONCLUSION

HE4, CA-125, and ROMA score are useful biomarkers for diagnostic evaluation of epithelial ovarian cancer, but their performance differs. CA-125 is sensitive and widely available but lacks specificity, especially in premenopausal women. HE4 offers higher specificity and helps reduce false-positive results in benign gynecologic conditions. ROMA score provides the best overall diagnostic balance by combining HE4, CA-125, and menopausal status. For early-stage epithelial ovarian cancer, ROMA and HE4 perform better than CA-125 alone, but none of the markers is adequate as a standalone population screening test. These biomarkers are most useful when combined with imaging, clinical assessment, menopausal status, and histopathological confirmation.

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