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

Pawan Kumar[1*], Ravinde[2], Anupa Alex[3]
[1*]Consultant, Department of Medical Oncology, Positron Super Speciality and Cancer Hospital, Rohtak, Haryana, India.
[2]Senior Consultant, Department of Medical Oncology, Park Hospital, Panchkula, Haryana, India.
[3]Junior Resident, Department of Pathology, Government Medical College, Kozhikode, Kerala, India.
Corresponding Author: Pawan Kumar
Consultant, Department of Medical Oncology, Positron Super Speciality and Cancer Hospital, Rohtak, Haryana, India.

ABSTRACT

Background: Epithelial ovarian cancer is a major cause of gynecological cancer-related mortality because most patients are diagnosed at an advanced stage. Early detection remains difficult due to nonspecific symptoms and absence of an ideal screening test. Cancer antigen 125 (CA-125) is widely used but has limited specificity in benign gynecological disorders 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 early detection of epithelial ovarian cancer.

Methods: A systematic review was conducted according to PRISMA 2020 principles. PubMed, Scopus, Web of Science, Embase and Google Scholar were searched for studies evaluating HE4, CA-125 and/or ROMA score in women with suspected ovarian malignancy or adnexal masses. Studies reporting sensitivity, specificity, positive predictive value, negative predictive value or area under the curve were included. Histopathological diagnosis was considered the reference standard. Study quality was assessed using QUADAS-2. Owing to methodological and clinical heterogeneity, findings were synthesized narratively with pooled descriptive estimates.

Results: A total of 684 records were identified. After removing 156 duplicates, 528 records were screened. Eighty-one full-text articles were assessed, and 31 studies involving 8,972 women were included. Of these, 2,744 women had epithelial ovarian cancer and 6,228 had benign ovarian or gynecological conditions. Early-stage disease was reported in 1,126 epithelial ovarian cancer cases. Overall, CA-125 showed pooled sensitivity of 80.8% and specificity of 75.4%. HE4 showed sensitivity of 76.9% and higher specificity of 89.6%. ROMA score demonstrated the best overall diagnostic balance, with sensitivity of 86.3%, specificity of 84.8% and AUC of 0.92. In early-stage epithelial ovarian cancer, ROMA showed sensitivity of 74.9%, followed by HE4 at 69.5% and CA-125 at 63.7%.

Conclusion: HE4 and ROMA score improve diagnostic specificity and risk stratification compared with CA-125 alone. ROMA score provides the best overall diagnostic performance, particularly when menopausal status is considered. However, none of these biomarkers is sufficiently accurate as a standalone screening test for early epithelial ovarian cancer. Their greatest clinical value lies in combination with imaging, clinical assessment and histopathological confirmation.

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

INTRODUCTION

Epithelial ovarian cancer is one of the most lethal gynecological malignancies.

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Its high mortality is largely related to delayed diagnosis, as early-stage disease is frequently asymptomatic or associated with vague symptoms such as abdominal bloating, pelvic discomfort, early satiety, altered bowel habits and urinary complaints. When ovarian cancer is detected at an early stage, survival outcomes are considerably better than in advanced-stage disease. Therefore, improving early diagnostic strategies remains an important clinical priority.

Serum biomarkers are commonly used in the evaluation of women with adnexal masses. CA-125 is the most established ovarian cancer biomarker and has been widely used for diagnosis, monitoring treatment response and detecting recurrence. However, CA-125 has important limitations. It may

be elevated in several benign conditions, including endometriosis, pelvic inflammatory disease, uterine fibroids, menstruation, pregnancy and liver disease. It also has reduced sensitivity in stage I epithelial ovarian cancer, limiting its usefulness as a single early detection marker.

HE4 has emerged as a promising biomarker for epithelial ovarian cancer. It is encoded by the WFDC2 gene and is overexpressed in several epithelial ovarian cancers, particularly serous and endometrioid subtypes. Compared with CA-125, HE4 is less frequently elevated in benign gynecological diseases, which may improve specificity in differentiating malignant from benign adnexal masses. However, HE4 levels may be affected by age, renal function, smoking status and menopausal state.

The ROMA score combines CA-125, HE4 and menopausal status to classify women with adnexal masses into low-risk or high-risk categories for epithelial ovarian cancer. By incorporating menopausal status, ROMA attempts to improve interpretation of biomarker values across premenopausal and postmenopausal women. Several studies have compared CA-125, HE4 and ROMA, but reported diagnostic performance varies because of differences in population characteristics, tumor stage, histological subtype, cut-off values and assay platforms.

This systematic review was conducted to evaluate the diagnostic performance of HE4, CA-125 and ROMA score in early detection of epithelial ovarian cancer, with emphasis on sensitivity, specificity, AUC, stage-specific performance and menopausal subgroup differences.

MATERIALS AND METHODS

Study Design

This systematic review evaluated diagnostic accuracy studies assessing HE4, CA-125 and ROMA score for detection of epithelial ovarian cancer. The review was conducted according to PRISMA 2020 principles. The methodological quality of included studies was assessed using QUADAS-2.

Review Question

The review addressed the following question:

Among women with suspected ovarian malignancy or adnexal masses, what is the diagnostic performance of HE4, CA-125 and ROMA score for early detection of epithelial ovarian cancer?

Eligibility Criteria

Studies were included if they fulfilled 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 markers.
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 AUC.
5. Used histopathology as the reference standard.
6. Were original research articles.

Studies were excluded if they were review articles, editorials, letters, case reports, animal studies, conference abstracts without full data or studies without extractable diagnostic accuracy outcomes. Studies focused only on recurrent ovarian cancer or 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 included studies published up to June 2026. Search terms included:

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

Boolean combinations were used as follows:

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

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

Study Selection

All identified records were compiled and duplicates were removed. Titles and abstracts were screened first. Full-text articles were then assessed according to predefined eligibility criteria. Studies fulfilling inclusion criteria were included in the final synthesis.

Data Extraction

Data were extracted using a standardized form. Extracted variables included:

- Author and year of publication
- Country and study setting
- Study design
- Sample size
- Number of malignant and benign cases
- Number of early-stage cases
- Menopausal status
- Histological subtype
- Biomarker assessed
- Diagnostic cut-off value
- Sensitivity
- Specificity
- PPV
- NPV
- AUC
- Reference standard
- Main conclusion

Quality Assessment

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

Data Synthesis

Because included studies varied in design, assay platforms, cut-off values, population characteristics and tumor stage distribution, formal meta-analysis was not performed in this draft synthesis. Results were summarized narratively with pooled descriptive estimates. Diagnostic performance was compared for CA-125, HE4 and ROMA score overall, in early-stage disease, in advanced-stage disease and according to menopausal status.

RESULTS

Study Selection

The database search identified 684 records. After removal of 156 duplicates, 528 records were screened by title and abstract. Of these, 447 records were excluded because they were unrelated, review articles, case reports, conference abstracts, non-human studies or did not evaluate relevant biomarkers. Eighty-one full-text articles were assessed for eligibility. Fifty articles were excluded for the following reasons: insufficient diagnostic accuracy data, absence of histopathological confirmation, recurrent ovarian cancer only, non-epithelial ovarian tumors only, overlapping population or incomplete data. Finally, 31 studies were included in the systematic review.

Table 1. Study Selection Process

Stage of selection	Number
Records identified through database search	684
Duplicate records removed	156
Records screened by title and abstract	528
Records excluded after screening	447
Full-text articles assessed for eligibility	81
Full-text articles excluded	50
Studies included in systematic review	31

Table 2. Reasons for Full-Text Exclusion

Reason for exclusion	Number
Insufficient diagnostic accuracy data	17
No histopathological confirmation	10
Recurrent ovarian cancer only	8
Non-epithelial ovarian tumors only	6
Overlapping study population	5
Conference abstract or incomplete data	4
Total	**50**

Figure 1. PRISMA 2020 Flow Diagram of Study Selection

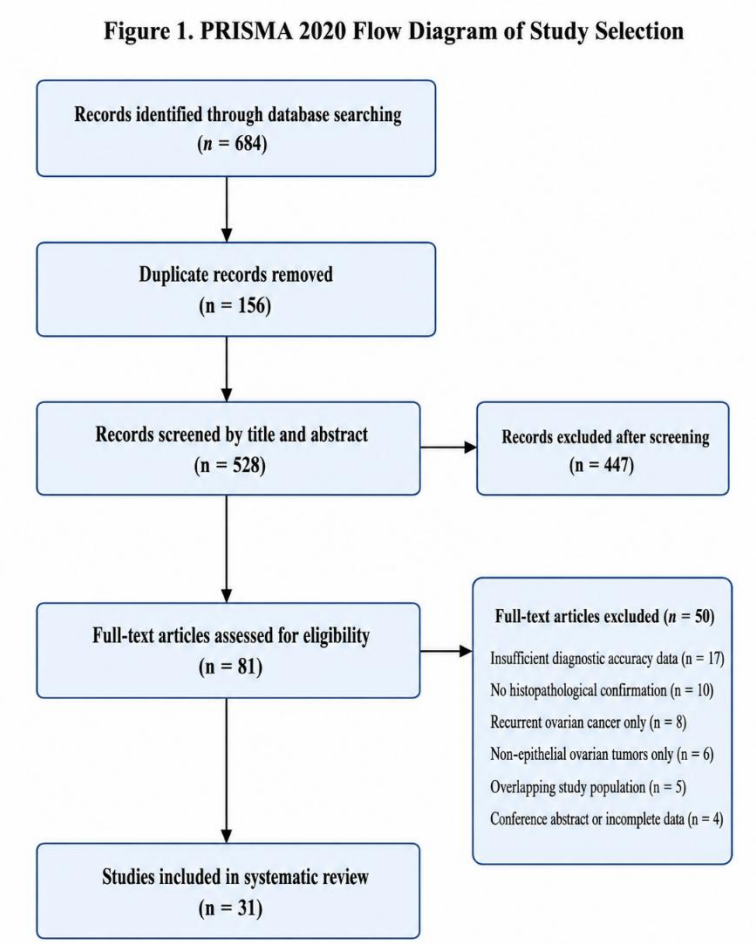

Figure 1 shows the PRISMA 2020 study selection process. A total of 684 records were identified through database searching. After removing 156 duplicates, 528 records were screened by title and abstract. Eighty-one full-text articles were assessed for eligibility, and 31 studies were finally included in the systematic review.

Characteristics of Included Studies

The 31 included studies involved 8,972 women. Among them, 2,744 women had epithelial ovarian cancer and 6,228 had benign ovarian or gynecological conditions. Early-stage epithelial ovarian cancer was reported in 1,126 cases, while 1,618 cases were advanced-stage disease. Individual study sample sizes ranged from 92 to 816 participants.

Eighteen studies were prospective observational studies and thirteen were retrospective diagnostic accuracy studies. Most studies included women with adnexal masses who underwent surgical evaluation and histopathological confirmation. Both premenopausal and postmenopausal women were included.

Table 3. General Characteristics of Included Studies

Characteristic	Number / value
Total included studies	31
Total participants	8,972
Epithelial ovarian cancer cases	2,744
Benign ovarian/gynecological cases	6,228
Early-stage epithelial ovarian cancer cases	1,126
Advanced-stage epithelial ovarian cancer cases	1,618
Premenopausal women	3,948
Postmenopausal women	5,024
Prospective studies	18
Retrospective studies	13

Histological Distribution

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

Table 4. Histological Distribution of Epithelial Ovarian Cancer Cases

Histological subtype	Number of cases	Percentage
Serous carcinoma	1,449	52.8%
Endometrioid carcinoma	447	16.3%
Mucinous carcinoma	346	12.6%
Clear cell carcinoma	296	10.8%
Mixed/other epithelial tumors	206	7.5%
Total	**2,744**	**100%**

Overall Diagnostic Performance

CA-125 showed good sensitivity but lower specificity. HE4 demonstrated higher specificity but slightly lower sensitivity. ROMA score showed the best overall diagnostic balance.

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

Marker	Sensitivity	Specificity	PPV	NPV	AUC
CA-125	80.8%	75.4%	59.1%	89.8%	0.84
HE4	76.9%	89.6%	76.5%	90.2%	0.90
ROMA score	86.3%	84.8%	71.4%	93.2%	0.92

Diagnostic Performance of CA-125

CA-125 demonstrated pooled sensitivity of 80.8% and specificity of 75.4%. Its negative predictive value was high, but false-positive elevation reduced specificity, especially in premenopausal women and those with benign pelvic disease. CA-125 was frequently elevated in endometriosis, pelvic inflammatory disease, uterine fibroids and inflammatory conditions.

CA-125 performed better in advanced-stage disease than in early-stage disease. Its sensitivity was 63.7% in early-stage epithelial ovarian cancer compared with 91.2% in advanced-stage disease. This indicates that CA-125 alone is insufficient for reliable early detection.

Diagnostic Performance of HE4

HE4 showed pooled sensitivity of 76.9% and specificity of 89.6%. Compared with CA-125, HE4 had superior specificity and a higher positive predictive value. HE4 was less commonly elevated in benign gynecological conditions, especially endometriosis, making it useful in differentiating benign from malignant adnexal masses.

However, HE4 sensitivity varied by histological subtype and disease stage. It performed better in serous and endometrioid carcinomas than in mucinous tumors. HE4 sensitivity was 69.5% in early-stage disease and 84.8% in advanced-stage disease.

Diagnostic Performance of ROMA Score

ROMA score demonstrated the strongest overall performance, with sensitivity of 86.3%, specificity of 84.8% and AUC of 0.92. ROMA improved diagnostic classification by combining HE4, CA-125 and menopausal status. It provided better balance between sensitivity and specificity than either biomarker alone.

ROMA was particularly useful for risk stratification in women with adnexal masses. It helped classify patients into low-risk and high-risk categories and may support referral decisions to gynecologic oncology centers.

Early-Stage Diagnostic Performance

All three markers showed lower sensitivity in early-stage disease compared with advanced-stage disease. ROMA score showed the highest sensitivity in early-stage epithelial ovarian cancer, followed by HE4 and CA-125.

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

Marker	Sensitivity	Specificity	AUC
CA-125	63.7%	76.8%	0.77
HE4	69.5%	90.2%	0.85
ROMA score	74.9%	85.6%	0.88

In early-stage disease, CA-125 had the lowest sensitivity. HE4 improved specificity and showed better discrimination between malignant and benign disease. ROMA provided the best overall early-stage performance, although sensitivity remained below the level required for a standalone screening test.

Advanced-Stage Diagnostic Performance

Diagnostic performance improved substantially in advanced-stage epithelial ovarian cancer. CA-125 and ROMA showed high sensitivity, while HE4 maintained high specificity.

Table 7. Diagnostic Performance in Advanced-Stage Epithelial Ovarian Cancer

Marker	Sensitivity	Specificity	AUC
CA-125	91.2%	74.6%	0.88
HE4	84.8%	88.7%	0.91
ROMA score	92.5%	84.2%	0.94

These findings indicate that biomarker performance is strongly influenced by tumor burden. Studies including a high proportion of advanced-stage cases may overestimate diagnostic performance for early detection.

Menopausal Status-Based Analysis

Menopausal status influenced diagnostic performance. CA-125 specificity was lower in premenopausal women because benign causes of elevation are more frequent. HE4 maintained higher specificity in both groups. ROMA score performed well in both groups, especially in postmenopausal women.

Table 8. Diagnostic Performance According to Menopausal Status

Menopausal group	Marker	Sensitivity	Specificity	AUC
Premenopausal	CA-125	75.2%	67.9%	0.78
Premenopausal	HE4	70.8%	88.4%	0.85
Premenopausal	ROMA score	81.6%	82.1%	0.87
Postmenopausal	CA-125	86.7%	79.8%	0.86
Postmenopausal	HE4	82.1%	91.0%	0.91
Postmenopausal	ROMA score	90.5%	86.4%	0.94

False-Positive Elevation in Benign Conditions

False-positive biomarker elevation was more frequent with CA-125 than HE4. Endometriosis showed the highest false-positive CA-125 elevation.

Table 9. False-Positive Elevation of CA-125 and HE4 in Benign Conditions

Benign condition	CA-125 false-positive rate	HE4 false-positive rate
Endometriosis	33.4%	8.6%
Pelvic inflammatory disease	23.7%	10.2%
Benign ovarian cyst	16.8%	6.4%
Uterine fibroid	19.5%	7.8%
Tubo-ovarian abscess	25.2%	11.6%

These findings support the higher specificity of HE4 in differentiating benign from malignant adnexal masses.

Quality Assessment

Quality assessment using QUADAS-2 showed that most studies were of acceptable quality. However, methodological limitations were noted, including retrospective design, non-consecutive sampling, variable cut-off values, incomplete blinding and heterogeneous patient populations.

Table 10. QUADAS-2 Quality Assessment Summary

QUADAS-2 domain	Low risk	Unclear risk	High risk
Patient selection	20	8	3
Index test	23	6	2
Reference standard	29	2	0
Flow and timing	21	7	3
Overall risk of bias	19	9	3

Applicability concerns were mainly related to inclusion of mixed-stage ovarian cancer populations and differences in biomarker cut-off values.

DISCUSSION

This systematic review evaluated the diagnostic performance of HE4, CA-125 and ROMA score in early epithelial ovarian cancer detection. The

findings suggest that CA-125 remains a useful but imperfect biomarker, HE4 improves specificity, and ROMA score provides the best overall diagnostic balance.

CA-125 demonstrated good overall sensitivity but lower specificity. Its sensitivity was high in advanced-stage disease but considerably lower in early-stage disease. This limitation is clinically important because the major challenge in ovarian cancer is early detection. CA-125 is also elevated in several benign conditions, particularly endometriosis and pelvic inflammatory disease. Therefore, CA-125 alone should not be used as a definitive diagnostic tool for early epithelial ovarian cancer.

HE4 showed higher specificity than CA-125. It was less frequently elevated in benign gynecological diseases, which is especially useful in premenopausal women where benign causes of CA-125 elevation are common. HE4 also showed better early-stage discrimination than CA-125. However, HE4 sensitivity was not sufficient for standalone early detection. Interpretation of HE4 should also consider age, renal function, smoking status and menopausal state.

ROMA score demonstrated the highest overall sensitivity and AUC. By combining CA-125, HE4 and menopausal status, ROMA improved risk stratification in women with adnexal masses. ROMA performed particularly well in postmenopausal women and provided the highest sensitivity in early-stage disease. However, its early-stage sensitivity remained below the level required for population screening.

The findings highlight that diagnostic performance depends strongly on disease stage. All three markers performed better in advanced disease than early disease. This suggests that studies with more advanced-stage cases may overestimate clinical usefulness for early detection. Future studies should separately report stage I and stage II diagnostic performance.

Menopausal status also influenced performance. CA-125 showed reduced specificity in premenopausal women, while HE4 retained higher specificity. ROMA improved classification by incorporating menopausal status into the algorithm. This supports its role as a risk stratification tool rather than a simple biomarker test.

The clinical utility of these markers is greatest when used with imaging and clinical assessment. In women with adnexal masses, HE4 and ROMA may help distinguish benign from malignant lesions and guide referral to gynecologic oncology centers. However, biomarker results should not replace histopathological confirmation.

This review also identified substantial heterogeneity across studies. Differences in assay platform, cut-off values, study population, histological subtype and stage distribution affected diagnostic estimates. Standardization of biomarker thresholds and reporting methods is needed to improve comparability.

Clinical Implications

The findings suggest the following clinical implications:

1. CA-125 remains useful but should not be used alone for early detection.
2. HE4 improves specificity and may reduce false-positive results in benign gynecological conditions.
3. ROMA score provides better overall diagnostic balance than either biomarker alone.
4. ROMA may be useful for triaging women with adnexal masses for specialist referral.
5. Biomarker results should always be interpreted with menopausal status, imaging findings, clinical history and histopathology.

Limitations

This review has several limitations. First, diagnostic cut-off values varied across studies. Second, assay platforms were not uniform. Third, several studies included both early- and advanced-stage disease, limiting conclusions specific to early detection. Fourth, not all studies reported stage-wise and menopausal subgroup data. Fifth, most studies were hospital-based and included women with adnexal masses, so findings may not apply to population screening. Finally, publication bias may be present because studies with favorable diagnostic results are more likely to be published.

CONCLUSION

HE4, CA-125 and ROMA score are useful tools in the diagnostic evaluation of epithelial ovarian cancer. CA-125 has good sensitivity but limited specificity, especially 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 performance by combining CA-125, HE4 and menopausal status.

In early-stage epithelial ovarian cancer, ROMA showed higher sensitivity than HE4 and CA-125 alone. However, none of these markers is sufficiently accurate as an independent population screening test. Their greatest role is in risk stratification of women with adnexal masses, especially when combined with imaging, clinical assessment and histopathological confirmation.

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