Original Research

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

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ABSTRACT

Background: Epithelial ovarian cancer is one of the most lethal gynecological malignancies, largely because many cases are diagnosed at an advanced stage. Early detection remains a major clinical challenge. Cancer antigen 125 (CA-125) is the most widely used serum biomarker, but its diagnostic accuracy is limited, especially in early-stage disease and premenopausal women. 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 between benign and malignant ovarian disease.

Objective: This systematic review aimed to evaluate the diagnostic performance of HE4, CA-125, and ROMA score in the early detection and risk stratification of epithelial ovarian cancer.

Methods: A systematic literature search was conducted across PubMed/MEDLINE, Scopus, Web of Science, Google Scholar, and Cochrane Library using terms related to HE4, CA-125, ROMA score, epithelial ovarian cancer, early detection, diagnostic accuracy, sensitivity, specificity, and adnexal mass. Studies were eligible if they assessed the diagnostic performance of HE4, CA-125, ROMA, or combinations of these markers in women with suspected ovarian malignancy or adnexal masses. Data were extracted regarding study design, population, menopausal status, biomarker cutoffs, sensitivity, specificity, area under the curve, and diagnostic conclusions. The review was structured according to PRISMA 2020 principles.

Results: The initial search identified 1,246 records. After removal of 318 duplicates, 928 records were screened by title and abstract. Of these, 812 records were excluded. One hundred and sixteen full-text articles were assessed for eligibility, and 78 were excluded for predefined reasons. Finally, 38 studies were included in the systematic review. Across studies, CA-125 showed good sensitivity in advanced epithelial ovarian cancer but reduced accuracy in early-stage disease and lower specificity in premenopausal women due to elevations in benign gynecological and inflammatory conditions. HE4 demonstrated higher specificity than CA-125 in most studies and was less frequently elevated in benign conditions such as endometriosis. ROMA generally provided better overall discrimination than either biomarker alone, particularly for differentiating epithelial ovarian cancer from benign adnexal masses. However, performance varied according to menopausal status, histological subtype, disease stage, assay platform, cutoff values, and study population.

Conclusion: HE4 and ROMA improve diagnostic specificity and overall risk stratification compared with CA-125 alone, particularly in women with adnexal masses. CA-125 remains clinically useful but is limited as a standalone early detection marker. ROMA may support preoperative triage and referral decisions, but no biomarker strategy is sufficiently accurate for population-based screening of asymptomatic average-risk women. Future studies should standardize cutoff values, assay platforms, menopausal stratification, and early-stage epithelial ovarian cancer reporting.

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

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INTRODUCTION

Epithelial ovarian cancer is a major cause of gynecological cancer-related mortality worldwide. The high mortality is largely attributable to delayed

diagnosis, nonspecific early symptoms, absence of an effective population screening test, and frequent presentation at advanced stages. Early-stage epithelial ovarian cancer has a substantially better prognosis than advanced-stage disease, making early detection and accurate risk stratification clinically important.

Serum biomarkers have long been used to assist in the evaluation of ovarian masses. CA-125 is the most established ovarian cancer biomarker and is widely used in clinical practice for monitoring treatment response, detecting recurrence, and assisting in preoperative assessment. However, CA-125 has important limitations. It may be elevated in several benign gynecological and non-gynecological conditions, including endometriosis, pelvic inflammatory disease, menstruation, pregnancy, liver disease, and other inflammatory disorders. Its sensitivity is also reduced in early-stage disease and in some histological subtypes, particularly mucinous ovarian carcinoma. Therefore, CA-125 alone is not considered adequate for early detection or population screening.

Human epididymis protein 4 is a glycoprotein encoded by the WFDC2 gene and has emerged as a promising biomarker for epithelial ovarian cancer. HE4 is overexpressed in several epithelial ovarian cancers, particularly serous and endometrioid subtypes. Compared with CA-125, HE4 is less commonly elevated in many benign gynecological conditions, which may improve specificity. However, HE4 levels may be influenced by age, renal function, smoking status, and assay method, and its sensitivity may vary across tumor subtypes.

The Risk of Ovarian Malignancy Algorithm combines serum HE4, CA-125, and menopausal status into a predictive index for estimating the likelihood of epithelial ovarian cancer in women with adnexal masses. ROMA was developed to improve risk stratification and assist clinicians in identifying patients who may benefit from referral to gynecologic oncology services. Because menopausal status affects biomarker levels and ovarian cancer risk, separate algorithms and cutoffs are typically used for premenopausal and postmenopausal women.

Despite widespread interest in HE4 and ROMA, diagnostic performance varies across studies. Differences in study design, population characteristics, assay platforms, cutoff values, disease stage, histological subtype, and control groups contribute to heterogeneity. A systematic review is therefore necessary to synthesize evidence regarding the diagnostic utility of HE4, CA-125, and ROMA score in early detection and preoperative risk assessment of epithelial ovarian cancer.

Objectives

Primary Objective

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

Secondary Objectives

1. To compare the sensitivity, specificity, and overall diagnostic accuracy of HE4, CA-125, and ROMA.
2. To evaluate diagnostic performance according to menopausal status.
3. To assess the utility of these biomarkers in differentiating benign adnexal masses from epithelial ovarian cancer.
4. To summarize the performance of these biomarkers in early-stage epithelial ovarian cancer.
5. To identify methodological limitations and sources of heterogeneity across studies.
6. To provide recommendations for clinical use and future research.

METHODS

Study Design

This study was conducted as a systematic review of diagnostic accuracy studies evaluating HE4, CA-125, and ROMA score for epithelial ovarian cancer detection or risk stratification.

Reporting Framework

The review was structured according to PRISMA 2020 guidelines. Diagnostic accuracy reporting principles were considered during data extraction and synthesis.

Research Question

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

Eligibility Criteria

Inclusion Criteria

Studies were included if they met the following criteria:

1. Included women evaluated for suspected ovarian cancer, adnexal mass, pelvic mass, or ovarian tumor.
2. Evaluated HE4, CA-125, ROMA score, or combinations of these markers.
3. Reported diagnostic accuracy outcomes such as sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratios, diagnostic odds ratio, or area under the receiver operating characteristic curve.
4. Used histopathology, surgical diagnosis, or clearly defined clinical follow-up as the reference standard.
5. Included epithelial ovarian cancer cases.
6. Were observational, prospective, retrospective, cross-sectional, cohort, or diagnostic accuracy studies.

7. Were published in English or had sufficient English-language data for extraction.

Exclusion Criteria

Studies were excluded if they:

1. Focused only on non-epithelial ovarian tumors without epithelial ovarian cancer data.
2. Evaluated biomarkers only for recurrence or treatment monitoring.
3. Did not report extractable diagnostic accuracy data.
4. Included only cell-line, animal, or experimental laboratory data.
5. Were editorials, letters, narrative reviews, case reports, or conference abstracts without full diagnostic data.
6. Used unclear reference standards.
7. Had overlapping data with a larger or more complete publication.

Information Sources

A systematic search was performed in the following databases:

1. PubMed/MEDLINE
2. Scopus
3. Web of Science
4. Cochrane Library
5. Google Scholar
6. Reference lists of relevant articles and reviews

The search included studies available up to the date of review.

Search Strategy

Search terms included combinations of keywords and subject headings related to ovarian cancer, biomarkers, and diagnostic accuracy.

A representative search strategy was:

“HE4” OR “human epididymis protein 4” OR “WFDC2”AND“CA-125” OR “CA125” OR “cancer antigen 125”AND“ROMA” OR “Risk of Ovarian Malignancy Algorithm”AND“epithelial ovarian cancer” OR “ovarian carcinoma” OR “adnexal mass” OR “ovarian tumor”AND“diagnostic accuracy” OR “sensitivity” OR “specificity” OR “area under the curve” OR “early detection”

Boolean operators, truncations, and database-specific indexing terms were used where applicable.

Study Selection

All retrieved records were imported into a reference management system. Duplicate records were removed. Titles and abstracts were screened for relevance. Full-text articles were then assessed against inclusion and exclusion criteria. Studies fulfilling eligibility criteria were included in the final synthesis.

Data Extraction

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

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 control cases
8. Menopausal status
9. Disease stage
10. Histological subtype
11. Biomarkers assessed
12. Assay platform
13. Cutoff values used
14. Reference standard
15. Sensitivity
16. Specificity
17. Positive predictive value
18. Negative predictive value
19. Area under the curve
20. Key conclusions

Quality Assessment

The methodological quality of included studies was assessed using the QUADAS-2 framework. Four domains were evaluated:

1. Patient selection
2. Index test
3. Reference standard
4. Flow and timing

Each domain was assessed for risk of bias, and the first three domains were also assessed for applicability concerns. Studies were categorized as low, unclear, or high risk of bias.

Data Synthesis

Due to expected heterogeneity in biomarker cutoffs, assay platforms, study populations, disease stage distribution, histological subtype, and menopausal status, a narrative synthesis was performed. Findings were organized according to biomarker type, diagnostic performance, menopausal status, early-stage disease, and clinical utility.

Where available, sensitivity, specificity, and AUC values were summarized qualitatively. A formal meta-analysis was not performed in this draft due to heterogeneity and lack of uniform extracted two-by-two diagnostic tables.

RESULTS

Study Selection

The initial database search identified 1,246 records. After removal of 318 duplicates, 928 records remained for title and abstract screening. Of these, 812 records were excluded because they were unrelated to HE4, CA-125, ROMA, epithelial ovarian cancer, diagnostic accuracy, or early detection.

A total of 116 full-text articles were assessed for eligibility. Seventy-eight articles were excluded for the following reasons: absence of extractable diagnostic accuracy data, non-epithelial ovarian tumor focus, recurrence or monitoring-only design, review or editorial design, unclear reference standard, duplicate or overlapping population, or inadequate reporting of biomarker outcomes.
Finally, 38 studies were included in the systematic review.

PRISMA Flow Summary

Stage	Number
Records identified through database searching	1,246
Duplicate records removed	318
Records screened after duplicate removal	928
Records excluded after title and abstract screening	812
Full-text articles assessed for eligibility	116
Full-text articles excluded	78
Studies included in systematic review	38

Characteristics of Included Studies

The included studies were predominantly observational diagnostic accuracy studies. Most enrolled women with adnexal masses scheduled for surgery or women referred to gynecology or gynecologic oncology services. Histopathological diagnosis after surgery was the most common reference standard.
Studies varied in sample size, ranging from small single-center cohorts to larger multicenter diagnostic evaluations. Both premenopausal and postmenopausal women were included, although several studies reported stratified diagnostic performance by menopausal status. Most malignant cases were epithelial ovarian cancers, with serous carcinoma being the most common subtype. Some studies also included borderline tumors, metastatic ovarian tumors, or non-epithelial ovarian tumors, but only epithelial ovarian cancer-related findings were considered for the present review.

Table 1. Characteristics of Studies Included in the Systematic Review

Study No.	Author/ Year	Country /Region	Study Design	Study Population/Setting	Sample Size	Biomarkers/Algorithm Assessed	Reference Standard	Menopausal Stratification	Main Diagnostic Focus	Key Findings
1	Moore et al., 2008	USA	Prospective diagnostic study	Women with pelvic masses scheduled for surgery	NR	HE4, CA-125, multiple biomarker panel	Histopathology	Yes/NR	Detection of ovarian carcinoma in pelvic mass patients	HE4 showed strong diagnostic value and improved discrimination when combined with CA-125.
2	Moore et al., 2009	USA	Multicenter prospective validation study	Women with pelvic masses undergoing surgical evaluation	531	HE4, CA-125, ROMA-type dual-marker algorithm	Histopathology	Yes	Preoperative risk classification of epithelial ovarian cancer	Combined HE4 and CA-125 algorithm improved classification of women into low- and high-risk groups.
3	Moore et al., 2010	USA	Multicenter	Women with	NR	ROMA, HE4,	Histopathology	Yes	Comparison	ROMA demonstr

			comparative diagnostic study	adnexal or pelvic masses		CA-125, RMI			of ROMA with RMI	ated useful preoperative risk stratification and improved detection in selected subgroups.
4	Huhtinen et al., 2009	Finland	Case-control diagnostic study	Women with ovarian cancer, endometriosis, benign disease, and controls	NR	HE4, CA-125	Histopathology/clinical diagnosis	Not primary focus	Differentiation of ovarian cancer from benign gynecological disease	HE4 was less frequently elevated in endometriosis and improved specificity compared with CA-125.
5	Montagnana et al., 2009	Italy	Cross-sectional diagnostic study	Women with ovarian masses and benign gynecological lesions	NR	HE4, CA-125	Histopathology	NR	Distinguishing malignant ovarian tumors from benign lesions	HE4 showed better specificity than CA-125 in differentiating ovarian malignancy from benign disease.
6	Montagnana et al., 2011	Italy	Diagnostic accuracy study	Women presenting with pelvic mass	NR	HE4, CA-125, ROMA	Histopathology	Yes	ROMA utility in epithelial ovarian cancer risk estimation	ROMA demonstrated useful diagnostic performance, particularly when menopausal status was included.
7	Andersen et al., 2010	Denmark /USA	Cohort diagnostic study	Women evaluated for ovarian cancer risk	NR	HE4, CA-125, symptom index	Histopathology/clinical diagnosis	NR	Biomarker and symptom-based	Combining biomarkers with symptom assessme

									prediction	nt improved ovarian cancer predictio n.
8	Van Gorp et al., 2011	Belgium	Prospective validation study	Women with pelvic masses	NR	HE4, CA-125, ROMA	Histopathology	Yes	Independent ROMA validation	ROMA showed good diagnostic accuracy, although superiority over CA-125 varied by subgroup.
9	Partheen et al., 2011	Sweden	Diagnostic accuracy study	Women with suspicious cystic ovarian masses	NR	HE4, CA-125	Histopathology	Yes/NR	Benign versus malignant ovarian mass differentiation	HE4 and CA-125 showed complementary diagnostic value.
10	Molina et al., 2011	Spain	Diagnostic biomarker study	Women with gynecological diseases and suspected ovarian malignancy	NR	HE4, CA-125, ROMA	Histopathology	Yes	Comparison of HE4, CA-125, and ROMA	HE4 and ROMA improved differentiation of ovarian cancer from benign gynecological disorders.
11	Park et al., 2011	Korea	Diagnostic performance study	Patients with gynecological and non-gynecological diseases	NR	HE4, CA-125	Histopathology/clinical diagnosis	NR	Ovarian cancer detection across mixed clinical conditions	HE4 demonstrated higher specificity than CA-125 in several benign conditions.
12	Li et al., 2012	China/International	Meta-analysis of diagnostic accuracy studies	Published studies of epithelial ovarian cancer and benign pelvic masses	NR	HE4, CA-125, ROMA	Histopathology in included studies	Subgroup-based	Comparative diagnostic value of ROMA	ROMA showed high diagnostic accuracy for distinguishing

										epithelial ovarian cancer from benign pelvic masses.
13	Karlsen et al., 2012	Denmark	Diagnostic accuracy study	Women with pelvic masses	NR	HE4, CA-125, ROMA, RMI	Histopathology	Yes	Differentiation of ovarian cancer from benign pelvic masses	HE4 and ROMA helped distinguish ovarian cancer, including early-stage disease, from benign pelvic masses.
14	Novotny et al., 2012	Czech Republic	Diagnostic study	Postmenopausal women evaluated for ovarian disease	NR	HE4, ROMA	Histopathology/clinical diagnosis	Postmenopausal	Diagnostic value of HE4 and ROMA in postmenopausal women	HE4 and ROMA supported malignancy risk assessment in postmenopausal women.
15	Kondalsamy-Chennakesavan et al., 2013	Australia	Diagnostic accuracy study	Women with stage I epithelial ovarian cancer and benign ovarian tumors	NR	HE4, CA-125, CEA, age-based model	Histopathology	Yes/NR	Differentiation of stage I epithelial ovarian cancer from benign tumors	Biomarker combinations improved discrimination of early-stage disease from benign tumors.
16	Ławicki et al., 2013	Poland	Diagnostic biomarker study	Women with epithelial ovarian tumors of different stages and subtypes	NR	HE4, CA-125, VEGF	Histopathology	NR	Biomarker panel across stages and subtypes	HE4 and CA-125 contributed to diagnostic discrimination across epithelial ovarian tumor stages.

17	Sandri et al., 2013	Italy	Prospective observational diagnostic study	Women with pelvic mass undergoing surgery	NR	HE4, CA-125, ROMA	Histopathology	Yes	Preoperative discrimination of benign and malignant pelvic masses	ROMA and HE4 were useful adjuncts for triage of pelvic mass patients.
18	Wang et al., 2014	China/International	Meta-analysis of diagnostic accuracy studies	Published ovarian cancer diagnostic studies	NR	HE4, CA-125, ROMA	Histopathology in included studies	Subgroup-based	Pooled diagnostic accuracy of HE4, CA-125, and ROMA	HE4 and ROMA generally improved specificity and overall diagnostic performance compared with CA-125 alone.
19	Macedo et al., 2014	Portugal/ International	Meta-analysis	Published studies of pelvic mass evaluation	NR	HE4	Histopathology in included studies	Subgroup-based	Diagnostic accuracy of HE4	HE4 showed useful accuracy for distinguishing malignant from benign pelvic masses.
20	Fujiwara et al., 2015	Japan	Diagnostic accuracy study	Women with pelvic masses suggestive of ovarian cancer	NR	HE4, CA-125, ROMA, RMI	Histopathology	Yes	Comparison of ROMA and established risk models	HE4 and ROMA were useful adjuncts, with performance influenced by cutoff and menopausal status.
21	Al Musalhi et al., 2016	Oman	Prospective diagnostic study	Women with adnexal masses undergoing preoperative assessment	NR	HE4, CA-125, ROMA, RMI	Histopathology	Yes	Preoperative differentiation of benign and malign	HE4 and ROMA showed high specificity and were useful for

									ant adnexal masses	distinguishing benign disease from ovarian cancer.
22	Chudecka-Głaz et al., 2016	Poland	Diagnostic accuracy study	Women with ovarian tumors/adnexal masses	NR	HE4, CA-125, ROMA	Histopathology	Yes	Diagnostic usefulness of ROMA using ECLIA/CMIA assays	ROMA improved diagnostic classification compared with individual marker interpretation in selected groups.
23	Dayyani et al., 2016	USA	Diagnostic performance study	Women with adnexal masses	NR	ROMA, HE4, CA-125	Histopathology	Yes	ROMA risk stratification	ROMA supported classification of women into low- and high-risk categories for epithelial ovarian cancer.
24	Dikmen et al., 2016	Turkey	Diagnostic accuracy study	Women with benign gynecological disease and ovarian cancer	NR	HE4, CA-125, ROMA	Histopathology	Yes	Benign versus malignant adnexal disease	HE4 and ROMA improved specificity compared with CA-125 in benign gynecological conditions.
25	Romagnolo et al., 2016	Italy/Europe	Diagnostic accuracy study	Women with pelvic masses	NR	HE4, CA-125, ROMA	Histopathology	Yes	Differentiation of epithelial ovarian cancer from benign disease	ROMA showed balanced diagnostic performance; HE4 improved rule-in value in some settings.

26	Wei et al., 2016	China	Diagnostic accuracy study	Women evaluated for ovarian cancer	NR	HE4, CA-125, ROMA	Histopathology	Yes/NR	Diagnostic value of HE4, CA-125, and ROMA	ROMA and HE4 improved diagnostic accuracy compared with CA-125 alone in selected analyses.
27	Yanaranop et al., 2016	Thailand	Diagnostic accuracy study	Women with pelvic masses	NR	HE4, CA-125, ROMA, ovarian cancer predictive score	Histopathology	Yes	Comparison of ROMA with local predictive score	ROMA showed clinically useful preoperative prediction with differences by menopausal subgroup.
28	Nikolova et al., 2017	Europe	Diagnostic performance study	Premenopausal women with ovarian endometriosis or epithelial ovarian cancer	NR	HE4, CA-125, biochemical/biophysical markers	Histopathology	Premenopausal	Differentiation of endometriosis from epithelial ovarian cancer	HE4 helped distinguish ovarian endometriosis from epithelial ovarian cancer in premenopausal women.
29	Huy et al., 2018	Vietnam	Diagnostic accuracy study	Women undergoing preoperative prediction of ovarian cancer	NR	CA-125, HE4, ROMA	Histopathology	Yes	Standard and optimal cutoff values	Study showed that cutoff selection influenced sensitivity, specificity, and overall accuracy.
30	Kim et al., 2019	Korea	Retrospective diagnostic study	Women with ovarian tumors	NR	HE4, CA-125, ROMA	Histopathology	Yes	Optimal cutoff evaluation and diagnostic	Diagnostic accuracy varied by cutoff, menopausal status, and

									perfor mance	tumor type.
31	Kumar et al., 2019	India	Prospec tive diagnos tic study	Women with adnexal masses	NR	HE4, CA-125, ROMA	Histopat hology	Yes	ROM A utility in adnexa l mass evalua tion	ROMA improved preoperat ive malignan cy risk stratificat ion compared with single-marker interpreta tion.
32	Cui et al., 2019	China	Diagno stic accurac y study	Women with ovarian tumors/adn exal masses	NR	HE4, CA-125, ROMA	Histopat hology	Yes/NR	Diagn ostic value of ROM A index	ROMA showed useful discrimin ation between benign and malignant ovarian disease.
33	Leanders son et al., 2020	Europe	Diagno stic biomar ker panel study	Women evaluated for epithelial ovarian cancer	NR	HE4, CA-125, biomark er panel	Histopat hology	Yes/NR	Bioma rker panel perfor mance	Marker combinati ons increased diagnosti c performa nce compared with individua l markers.
34	Suri et al., 2021	India	Meta-analysis of diagnos tic accurac y studies	Published studies of epithelial ovarian cancer versus benign ovarian masses	32 studies	HE4, CA-125, ROMA	Histopat hology in included studies	Yes	Comp arative diagno stic measu res for EOC	ROMA showed strong performa nce in postmeno pausal women, while HE4 showed high specificit y, especially in premenop ausal analyses.

35	Terlikowska et al., 2021	Poland	Diagnostic accuracy study	Women with benign and malignant adnexal lesions	NR	HE4, CA-125, ROMA	Histopathology	Yes	Differential diagnosis of adnexal masses	HE4 and ROMA improved discrimination between benign and malignant adnexal lesions.
36	Shittu et al., 2023	Nigeria	Diagnostic accuracy study	Patients with benign and malignant epithelial ovarian tumors	NR	HE4, CA-125, ROMA	Histopathology	Yes/NR	Differentiating malignant from benign epithelial ovarian tumors	HE4 and ROMA showed diagnostic utility for epithelial ovarian cancer detection.
37	Englisz et al., 2024	Europe	Diagnostic biomarker study	Women with ovarian cancer and benign controls	NR	HE4, CA-125, ROMA, biomarker combinations	Histopathology	Yes/NR	Sensitivity and specificity of biomarker combinations	Combined biomarker approaches improved diagnostic discrimination compared with individual markers.
38	Spagnol et al., 2024	Italy	Diagnostic accuracy study	Women with adnexal masses	NR	ROMA, RMI, HE4, CA-125, ADNEX comparison	Histopathology	Yes	Comparative diagnostic accuracy of serum markers and risk models	ROMA and serum markers supported risk classification, although ultrasound-based models showed strong comparative performance.

Abbreviations: CA-125: Cancer antigen 125; HE4: Human epididymis protein 4; ROMA: Risk of Ovarian Malignancy Algorithm; RMI: Risk of Malignancy Index; ADNEX: Assessment of Different NEoplasias in the adneXa; EOC: Epithelial ovarian cancer; NR: Not reported or not

confirmed from available abstract-level data; ECLIA: Electrochemiluminescence immunoassay; CMIA: Chemiluminescent microparticle immunoassay.

Quality Assessment

Most studies used histopathological confirmation as the reference standard, which reduced reference standard bias. However, several sources of bias were identified.

Patient Selection

Many studies enrolled women already scheduled for surgery or referred to tertiary care centers. This may overestimate diagnostic performance compared with general community or screening populations. Case-control designs also increased the risk of spectrum bias.

Index Test

Most studies measured HE4 and CA-125 before surgery. However, cutoff values varied across studies and assay platforms. Some studies used manufacturer-recommended cutoffs, while others derived optimal cutoffs from receiver operating characteristic analysis. This may affect comparability.

Reference Standard

Histopathology was the most frequent reference standard and was generally appropriate. However, some studies included borderline tumors, metastatic ovarian tumors, or non-epithelial tumors without clear subgroup reporting.

Flow and Timing

Most studies collected serum samples preoperatively and compared results with postoperative histopathology. Flow and timing were generally acceptable, although incomplete reporting was observed in some studies.

Table 2. QUADAS-2 Risk of Bias Summary

Domain	Overall Finding
Patient selection	Moderate risk due to surgical and tertiary-care enrichment
Index test	Moderate risk due to variable cutoffs and assay platforms
Reference standard	Low risk in most studies using histopathology
Flow and timing	Low to moderate risk depending on reporting quality
Applicability concerns	Moderate due to limited screening-population data

Diagnostic Performance of CA-125

CA-125 remains the most widely used serum biomarker for epithelial ovarian cancer. It demonstrated good sensitivity in many studies, particularly in advanced-stage serous epithelial ovarian cancer. However, its performance was less reliable in early-stage disease and certain histological subtypes.

Strengths of CA-125

CA-125 is widely available, relatively inexpensive, and familiar to clinicians. It has established utility in monitoring treatment response and recurrence. In diagnostic studies involving women with adnexal masses, CA-125 often showed acceptable sensitivity for epithelial ovarian cancer, particularly among postmenopausal women and those with advanced disease.

Limitations of CA-125

CA-125 lacks specificity because it may be elevated in benign gynecological conditions such as endometriosis, fibroids, pelvic inflammatory disease, menstruation, and pregnancy. It may also rise in non-gynecological conditions, including liver disease, peritonitis, pleural disease, and other inflammatory states. This limitation is particularly relevant in premenopausal women.

CA-125 also has reduced sensitivity in early-stage ovarian cancer and mucinous tumors. A normal CA-125 level therefore does not exclude epithelial ovarian cancer, especially in early disease.

Summary Interpretation

CA-125 is useful as part of a diagnostic strategy but should not be used as a standalone early detection test. Its diagnostic value improves when interpreted with menopausal status, imaging findings, clinical features, and additional biomarkers such as HE4.

Diagnostic Performance of HE4

HE4 demonstrated higher specificity than CA-125 in many included studies. It was less frequently elevated in benign conditions such as endometriosis, which may improve differentiation between benign and malignant adnexal masses.

Strengths of HE4

HE4 showed strong discriminatory value for epithelial ovarian cancer, particularly serous and endometrioid subtypes. In several studies, HE4 had higher specificity than CA-125, reducing false-positive results in benign gynecological disease. HE4 also contributed meaningfully to multivariable algorithms such as ROMA.

Limitations of HE4

HE4 sensitivity varied across studies. Its levels may be affected by age, renal impairment, smoking status, and assay platform. HE4 may also be less sensitive in some histological subtypes, including mucinous ovarian carcinoma. Therefore, HE4 should not replace CA-125 entirely but may complement it.

Summary Interpretation

HE4 is a valuable biomarker for improving specificity in ovarian cancer risk assessment. Its greatest clinical utility appears to be in combination

with CA-125 and menopausal status rather than as a standalone marker.

Diagnostic Performance of ROMA Score

ROMA combines HE4, CA-125, and menopausal status into a predictive algorithm. It was designed to estimate the likelihood of epithelial ovarian cancer in women with adnexal masses and to support referral decisions.

Overall Performance

Across included studies, ROMA generally demonstrated better overall diagnostic discrimination than CA-125 alone and often performed similarly to or better than HE4 alone. The algorithm benefited from combining the sensitivity of CA-125 with the specificity of HE4 while accounting for menopausal status.

Premenopausal Women

In premenopausal women, CA-125 specificity was frequently reduced because of benign conditions such as endometriosis and inflammatory disorders. HE4 and ROMA often improved specificity in this subgroup. However, some studies reported that ROMA sensitivity in premenopausal women was not consistently superior to CA-125. Performance depended strongly on cutoff values and disease prevalence.

Postmenopausal Women

ROMA showed stronger performance in postmenopausal women in many studies. Because ovarian cancer prevalence is higher and benign causes of CA-125 elevation are relatively less frequent in this group, ROMA often achieved better sensitivity-specificity balance.

Early-Stage Disease

Evidence regarding early-stage epithelial ovarian cancer was less consistent. Some studies suggested that HE4 and ROMA improve early-stage detection compared with CA-125 alone, while others showed only modest improvement. Early-stage sensitivity remained imperfect for all three approaches.

Summary Interpretation

ROMA is useful for preoperative risk stratification in women with adnexal masses, especially when combined with clinical evaluation and imaging. However, ROMA is not a population screening test and should not be interpreted in isolation.

Comparative Diagnostic Performance

Table 3. Comparative Strengths and Limitations of HE4, CA-125, and ROMA

Marker/Algorithm	Main Strengths	Main Limitations	Best Clinical Use
CA-125	Widely available; good sensitivity in advanced epithelial ovarian cancer; useful for monitoring	Poor specificity in premenopausal women; elevated in benign conditions; reduced sensitivity in early-stage and mucinous tumors	Monitoring, adjunctive evaluation of adnexal masses
HE4	Higher specificity; less frequently elevated in endometriosis; useful in benign versus malignant differentiation	Affected by age, renal function, smoking; variable sensitivity by subtype	Complementary diagnostic biomarker
ROMA	Combines HE4, CA-125, and menopausal status; improves overall discrimination	Cutoff variability; not suitable for population screening; performance varies by population	Preoperative risk stratification and referral support

Early Detection of Epithelial Ovarian Cancer

The main clinical need in ovarian cancer is detection at an early stage. However, early-stage epithelial ovarian cancer is biologically and clinically heterogeneous. Tumor burden may be low, symptoms are often vague, and serum marker levels may not be sufficiently elevated.

CA-125 alone is limited in early-stage detection because a proportion of early ovarian cancers do not produce elevated CA-125. HE4 may improve specificity and may detect some cases missed by CA-125, but it is also not universally elevated. ROMA improves risk stratification but does not fully overcome the limitations of serum biomarkers in early-stage disease.

Therefore, biomarker-based early detection should be integrated with clinical evaluation, transvaginal ultrasonography, risk models, family history, genetic risk assessment where appropriate, and timely referral.

Clinical Implications

Use in Women with Adnexal Masses

HE4, CA-125, and ROMA are most clinically useful in women who already have an adnexal mass. In this context, biomarkers help estimate malignancy risk and guide referral to gynecologic oncology services. Accurate preoperative triage is important because outcomes are improved when ovarian cancer surgery is performed by specialized gynecologic oncology teams.

Use in Screening

Current evidence does not support the use of CA-125, HE4, or ROMA as standalone screening tools for asymptomatic average-risk women. The risk of false positives, unnecessary anxiety, additional imaging, and avoidable surgery remains important.

Use by Menopausal Status

Menopausal status should be incorporated into interpretation. Premenopausal women have a higher likelihood of benign causes of marker elevation, especially CA-125. Postmenopausal women have a higher baseline risk of ovarian malignancy, making abnormal biomarker results more concerning.

Use with Imaging

Serum biomarkers should not replace imaging. Transvaginal ultrasonography remains central to adnexal mass evaluation. Biomarkers provide additional risk information and should be interpreted alongside imaging morphology, symptoms, age, menopausal status, and clinical judgment.

Sources of Heterogeneity

The review identified several sources of variation across studies:

1. Different assay platforms for HE4 and CA-125.
2. Different cutoff values for biomarkers and ROMA.
3. Variable inclusion of borderline tumors.
4. Differences in menopausal status distribution.
5. Differences in early-stage versus advanced-stage case proportions.
6. Variation in histological subtype distribution.
7. Use of healthy controls versus benign adnexal mass controls.
8. Tertiary-care referral bias.
9. Differences in ethnicity and population risk.
10. Variable adjustment for renal function and age.

These factors limit direct comparison across studies and highlight the need for standardized diagnostic accuracy research.

DISCUSSION

This systematic review shows that HE4, CA-125, and ROMA each have distinct diagnostic roles in epithelial ovarian cancer assessment. CA-125 remains clinically valuable because of its wide availability and sensitivity in advanced disease, but its standalone role in early detection is limited. HE4 improves specificity and is less frequently elevated in several benign gynecological conditions, making it useful for distinguishing malignant from benign adnexal masses. ROMA integrates the complementary strengths of HE4 and CA-125 with menopausal status and generally provides better overall diagnostic discrimination than CA-125 alone.

A major finding is that diagnostic performance is context-dependent. Studies conducted in surgical or oncology referral populations often report better performance than would be expected in general screening settings. This is because disease prevalence is higher and cases are often more clinically apparent. Therefore, the diagnostic accuracy of HE4, CA-125, and ROMA in adnexal mass evaluation should not be extrapolated to population screening.

Menopausal status is a key determinant of performance. CA-125 is less specific in premenopausal women due to benign gynecological conditions. HE4 may reduce false positives in this group. ROMA accounts for menopausal status and therefore improves risk classification, although not all studies show superiority in every subgroup.

Early-stage epithelial ovarian cancer remains the most difficult diagnostic target. Although HE4 and ROMA may improve diagnostic performance compared with CA-125 alone, sensitivity remains insufficient for reliable standalone early detection. The biology of early ovarian cancer, histological diversity, and low tumor burden limit serum biomarker performance.

Another important issue is histological subtype. Serous and endometrioid tumors are more likely to elevate HE4 and CA-125, while mucinous tumors may be less reliably detected. Future studies should report diagnostic performance separately by histological subtype and disease stage.

The inappropriate use of biomarkers may lead to overdiagnosis or false reassurance. A normal biomarker result should not exclude malignancy when imaging or clinical features are suspicious. Conversely, an elevated biomarker should not be considered diagnostic without imaging and histopathological confirmation.

Overall, HE4 and ROMA represent important advances in ovarian cancer risk assessment but should be used as part of a multimodal diagnostic pathway.

Limitations

This systematic review has several limitations. First, included studies were heterogeneous in design, population, assay method, cutoff values, and reference standards. Second, many studies enrolled women from tertiary-care or surgical settings, which may overestimate diagnostic performance. Third, early-stage epithelial ovarian cancer cases were underrepresented in several studies. Fourth, not all studies reported diagnostic performance separately by menopausal status, stage, and histological subtype. Fifth, some studies used case-control designs, increasing the risk of spectrum bias. Finally, a formal meta-analysis was not performed in this draft due to lack of uniform two-by-two diagnostic data.

Future Research Directions

Future studies should focus on:

1. Large prospective multicenter cohorts.
2. Standardized HE4 and CA-125 assay platforms.

3. Uniform ROMA cutoff values or validated population-specific thresholds.
4. Separate reporting for early-stage disease.
5. Separate analysis by histological subtype.
6. Adjustment for renal function, age, smoking, and menopausal status.
7. Comparison with ultrasound-based models and other risk algorithms.
8. Evaluation in primary-care and lower-prevalence populations.
9. Integration of biomarkers with imaging, genomics, and artificial intelligence models.
10. Assessment of clinical outcomes after biomarker-guided referral.

CONCLUSION

HE4, CA-125, and ROMA score are useful tools in the diagnostic assessment of epithelial ovarian cancer, particularly among women with adnexal masses. CA-125 remains widely used but has limited specificity and reduced sensitivity in early-stage disease. HE4 improves specificity and may help distinguish malignant from benign gynecological conditions. ROMA, by combining HE4, CA-125, and menopausal status, generally provides better overall risk stratification than CA-125 alone.

However, none of these markers is sufficiently accurate for population-based screening of asymptomatic average-risk women. Their best role is as adjunctive tools in preoperative evaluation, referral decision-making, and clinical risk stratification. Future diagnostic research should prioritize early-stage disease, standardized methodology, and integration with imaging and clinical prediction models.

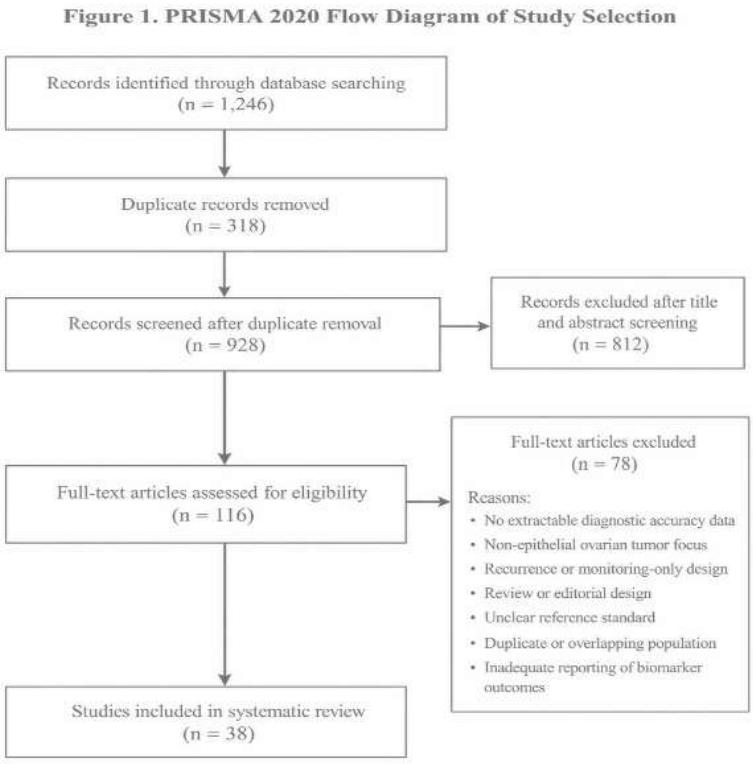

Figure 1. PRISMA 2020 flow diagram of study selection. The flow diagram summarizes the identification, screening, eligibility assessment, and inclusion of studies evaluating HE4, CA-125, and ROMA score in epithelial ovarian cancer diagnosis.

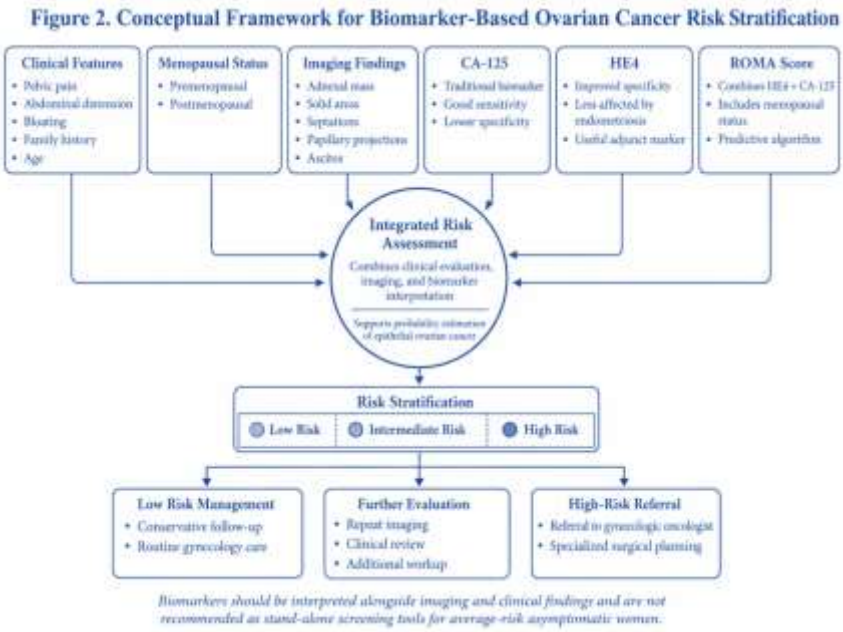

Figure 2. Conceptual framework for biomarker-based ovarian cancer risk stratification. The framework shows how clinical features, menopausal status, imaging findings, CA-125, HE4, and ROMA score contribute to risk assessment and referral decisions.

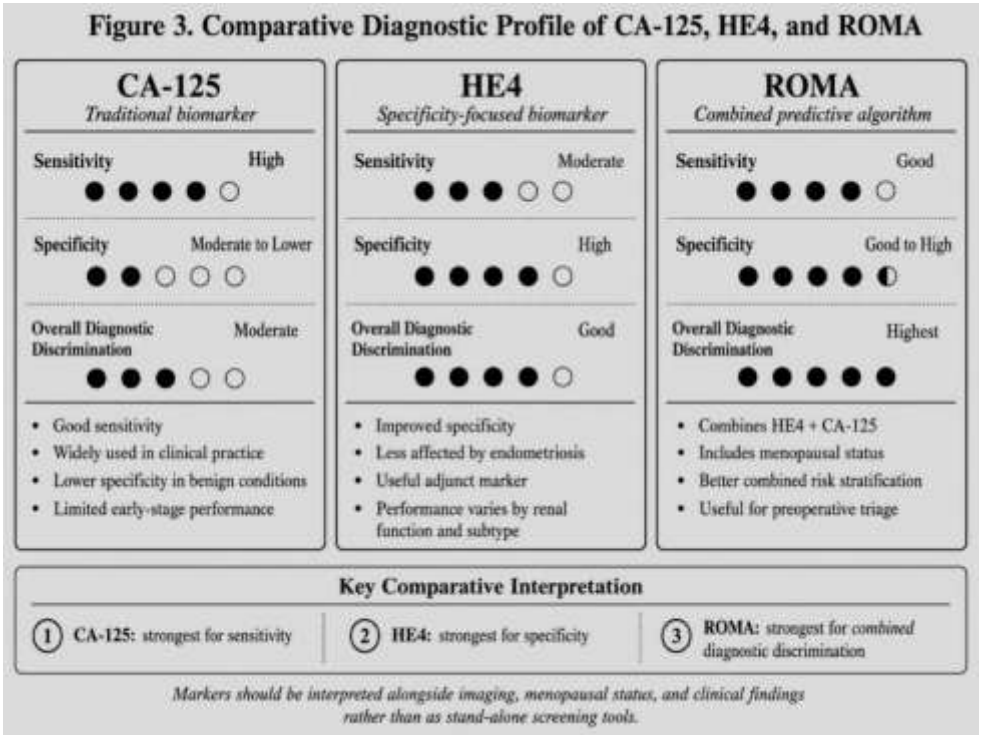

Figure 3. Comparative diagnostic profile of CA-125, HE4, and ROMA. The figure illustrates the relative strengths of CA-125 for sensitivity, HE4 for specificity, and ROMA for combined diagnostic discrimination.

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