Original Research

SERUM BIOMARKERS AND PREDICTIVE ALGORITHMS FOR EPITHELIAL OVARIAN CANCER DETECTION: A SYSTEMATIC REVIEW OF CA-125, HE4, AND ROMA

Nida Asif[1]*, Amol Wahane[2], Bidu Bhushan[3]

[1*]Senior Resident Doctor, Department of Clinical Oncology, Anugraha Narayan Magadh Medical College and Hospital, Gayaji, Bihar, India.

[2]Senior Resident, Department of Pathology, SSNK Medical College, Kopargaon, Maharashtra, India.

[3]Postgraduate Resident, Department of General Surgery, PGIMER and Capital Hospital, Bhubaneswar, Odisha, India.

Corresponding Author: Nida Asif

Senior Resident Doctor, Department of Clinical Oncology, Anugraha Narayan Magadh Medical College and Hospital, Gayaji, Bihar, India.

ABSTRACT

Background: Epithelial ovarian cancer is frequently diagnosed at an advanced stage because early symptoms are vague and reliable population-level screening strategies remain unavailable. Serum biomarkers such as cancer antigen 125 (CA-125) and human epididymis protein 4 (HE4), along with the Risk of Ovarian Malignancy Algorithm (ROMA), have been widely evaluated for differentiating malignant from benign adnexal masses and improving preoperative risk stratification.

Objective: This systematic review aimed to evaluate the diagnostic utility of CA-125, HE4, and ROMA in epithelial ovarian cancer detection, with emphasis on sensitivity, specificity, menopausal status, early-stage disease, and clinical applicability.

Methods: A systematic search was conducted using PubMed/MEDLINE, Scopus, Web of Science, Cochrane Library, Google Scholar, and reference screening. Studies were eligible if they evaluated CA-125, HE4, ROMA, or combined biomarker strategies in women with suspected ovarian malignancy, pelvic masses, or adnexal masses and reported diagnostic accuracy outcomes. Data were extracted regarding study design, study population, biomarker thresholds, menopausal stratification, reference standard, sensitivity, specificity, area under the curve, and major diagnostic conclusions. Methodological quality was assessed using diagnostic accuracy principles and QUADAS-2 domains.

Results: The search identified 892 records. After removal of 214 duplicates, 678 records were screened. A total of 587 records were excluded after title and abstract screening. Ninety-one full-text articles were assessed for eligibility, of which 67 were excluded. Finally, 24 studies were included in the systematic review. CA-125 demonstrated acceptable sensitivity, particularly in advanced-stage epithelial ovarian cancer, but had limited specificity in benign gynecological disease and premenopausal women. HE4 generally showed higher specificity than CA-125 and was less frequently elevated in benign conditions such as endometriosis. ROMA improved overall risk classification by integrating CA-125, HE4, and menopausal status. However, diagnostic performance varied across studies due to differences in disease stage, histological subtype, assay platform, cutoff value, renal function, and study population.

Conclusion: CA-125 remains useful in ovarian cancer assessment but is limited as a stand-alone diagnostic marker. HE4 improves specificity, while ROMA offers better combined risk stratification in women with adnexal masses. These biomarkers should be interpreted alongside clinical findings, menopausal status, imaging features, and histopathological confirmation. None of the evaluated strategies is sufficient as an independent screening tool for average-risk asymptomatic women.

Keywords: Epithelial Ovarian Cancer; CA-125; HE4; ROMA; Serum Biomarkers; Adnexal Mass; Diagnostic Accuracy; Risk Stratification; Systematic Review.

www.ajmrhs.com
eISSN: 2583-7761

Date of Received: 16-05-2026
Date Acceptance: 23-05-2026
Date of Publication: 25-06-2026

INTRODUCTION

Epithelial ovarian cancer is among the most clinically challenging gynecological malignancies because it is often diagnosed after extra-ovarian spread. Early-stage disease may present with vague symptoms such as abdominal bloating, pelvic

discomfort, urinary frequency, indigestion, or early satiety. These symptoms are common in benign conditions and therefore may not trigger early cancer evaluation. As a result, a substantial proportion of patients are diagnosed at an advanced stage, when treatment is more complex and survival outcomes are poorer.

Early detection and accurate preoperative classification of adnexal masses are important clinical priorities. Women with suspected epithelial ovarian cancer benefit from timely referral to gynecologic oncology services, appropriate surgical planning, complete staging, and optimized cytoreductive surgery where indicated. Conversely, unnecessary referral or extensive surgery for benign disease can increase cost, anxiety, and procedure-related morbidity. Therefore, diagnostic tools that can distinguish benign from malignant ovarian masses are clinically valuable.

CA-125 is the oldest and most widely used ovarian cancer biomarker. It is useful for treatment monitoring, recurrence detection, and risk assessment in women with adnexal masses. However, its diagnostic accuracy is limited. CA-125 may be elevated in benign gynecological conditions such as endometriosis, fibroids, menstruation, pregnancy, and pelvic inflammatory disease. It may also rise in non-gynecological disorders including liver disease, peritonitis, and inflammatory states. In addition, CA-125 may be normal in some early-stage cancers and in certain histological subtypes such as mucinous tumors.

HE4 has emerged as an important complementary biomarker. It is overexpressed in several epithelial ovarian cancers, particularly serous and endometrioid subtypes. Compared with CA-125, HE4 is less commonly elevated in benign gynecological conditions such as endometriosis, which may improve diagnostic specificity. Nevertheless, HE4 can be affected by renal function, age, smoking status, and assay variability, and its sensitivity is not uniform across histological subtypes.

ROMA combines serum HE4, CA-125, and menopausal status into a predictive algorithm. It is intended to estimate the risk of epithelial ovarian cancer in women with pelvic or adnexal masses and to support referral decisions. ROMA is not designed to replace imaging, clinical judgment, or histopathology; rather, it adds biomarker-based risk information to the diagnostic pathway.

The present systematic review synthesizes evidence on CA-125, HE4, and ROMA in epithelial ovarian cancer detection and preoperative risk stratification.

Objectives

Primary Objective

To systematically evaluate the diagnostic performance of CA-125, HE4, and ROMA in detecting epithelial ovarian cancer and differentiating malignant from benign adnexal masses.

Secondary Objectives

1. To compare the diagnostic strengths and limitations of CA-125, HE4, and ROMA.
2. To assess the influence of menopausal status on biomarker performance.
3. To summarize evidence related to early-stage epithelial ovarian cancer detection.
4. To identify factors responsible for heterogeneity across studies.
5. To evaluate the role of biomarkers in preoperative triage and referral.
6. To provide recommendations for clinical interpretation and future research.

MATERIALS AND METHODS

Study Design

This study was conducted as a systematic review of diagnostic accuracy studies evaluating serum biomarkers and predictive algorithms for epithelial ovarian cancer detection.

Reporting Framework

The review was prepared according to PRISMA 2020 principles. Risk of bias was considered using QUADAS-2 domains for diagnostic accuracy studies.

Eligibility Criteria

Inclusion Criteria

Studies were included if they met the following criteria:

1. Included women with suspected ovarian malignancy, pelvic mass, adnexal mass, or ovarian tumor.
2. Evaluated CA-125, HE4, ROMA, or combinations of these markers.
3. Reported diagnostic accuracy outcomes such as sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio, diagnostic odds ratio, or area under the receiver operating characteristic curve.
4. Included epithelial ovarian cancer cases or provided epithelial ovarian cancer-specific diagnostic information.
5. Used histopathology, surgical diagnosis, or clearly defined clinical diagnosis as the reference standard.
6. Were prospective, retrospective, cross-sectional, cohort, case-control, or diagnostic accuracy studies.
7. Were published in English or contained sufficient English-language data for extraction.

Exclusion Criteria

Studies were excluded if they:

1. Focused only on non-epithelial ovarian tumors.
2. Evaluated biomarkers only for prognosis, recurrence, or treatment monitoring.
3. Did not provide extractable diagnostic accuracy data.

4. Were case reports, editorials, letters, narrative reviews, or conference abstracts without full diagnostic data.
5. Used unclear reference standards.
6. Included duplicate or overlapping populations without additional relevant data.
7. Focused only on experimental, animal, or cell-line research.

Information Sources

The following databases and sources were searched:

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

Search Strategy

Search terms included combinations of disease-related, biomarker-related, and diagnostic accuracy terms.

Representative search terms were:

"epithelial ovarian cancer," "ovarian carcinoma," "adnexal mass," "pelvic mass," "CA-125," "CA125," "cancer antigen 125," "HE4," "human epididymis protein 4," "WFDC2," "ROMA," "Risk of Ovarian Malignancy Algorithm," "diagnostic accuracy," "sensitivity," "specificity," "AUC," "early detection," and "risk stratification."

A sample search string was:

("epithelial ovarian cancer" OR "ovarian carcinoma" OR "adnexal mass" OR "pelvic mass") AND
("CA-125" OR "CA125" OR "HE4" OR "human epididymis protein 4" OR "ROMA" OR "Risk of Ovarian Malignancy Algorithm") AND
("diagnostic accuracy" OR "sensitivity" OR "specificity" OR "area under the curve" OR "risk stratification")

Study Selection

All records were imported into a reference manager. Duplicate records were removed. Titles and abstracts were screened for relevance. Full-text articles were then reviewed according to inclusion and exclusion criteria. Studies meeting eligibility criteria were included in the final synthesis.

Data Extraction

The following data were extracted:

1. Author and year
2. Country or region
3. Study design
4. Study population
5. Sample size
6. Number of malignant and benign cases
7. Menopausal status
8. Disease stage
9. Histological subtype
10. Biomarkers or algorithms assessed
11. Assay method and cutoff values
12. Reference standard
13. Sensitivity
14. Specificity
15. Positive predictive value
16. Negative predictive value
17. Area under the curve
18. Main conclusion

Quality Assessment

Methodological quality was assessed using QUADAS-2 principles across four domains:

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

Studies were assessed for risk of bias and applicability concerns. Particular attention was given to whether the study population represented real-world adnexal mass evaluation, whether biomarker thresholds were prespecified, whether histopathology was used as the reference standard, and whether all participants received the same reference standard.

Data Synthesis

Due to heterogeneity in population characteristics, biomarker thresholds, assay methods, stage distribution, histological subtype, and menopausal stratification, a narrative synthesis was performed. Findings were grouped according to marker type, clinical setting, menopausal status, early-stage disease, and comparative diagnostic utility.

RESULTS

Study Selection

The database search identified 892 records. After removing 214 duplicates, 678 records remained for title and abstract screening. Of these, 587 records were excluded because they did not address epithelial ovarian cancer diagnosis, did not evaluate CA-125, HE4, or ROMA, lacked diagnostic accuracy outcomes, or focused only on recurrence monitoring.

A total of 91 full-text articles were assessed for eligibility. Of these, 67 articles were excluded due to non-epithelial tumor focus, inadequate diagnostic data, absence of histopathological confirmation, review-only design, overlapping study populations, or insufficient subgroup reporting. Finally, 24 studies were included in the systematic review.

Prisma Flow Summary

Stage	Number
Records Identified Through Database Searching	892
Duplicate Records Removed	214

Records Screened After Duplicate Removal	678
Records Excluded After Title And Abstract Screening	587
Full-Text Articles Assessed For Eligibility	91
Full-Text Articles Excluded	67
Studies Included In Final Systematic Review	24

Characteristics of Included Studies

The final review included 24 studies evaluating CA-125, HE4, ROMA, or combined biomarker approaches in women with suspected epithelial ovarian cancer or adnexal masses. Most studies were observational diagnostic accuracy studies conducted in gynecology, oncology, or tertiary referral settings. Histopathological diagnosis after surgery was the most frequently used reference standard.

The studies differed in sample size, menopausal composition, tumor stage distribution, histological subtype, biomarker assay platform, and cutoff values. Several studies reported separate diagnostic performance for premenopausal and postmenopausal women, while others presented pooled results. Most studies focused on differentiating epithelial ovarian cancer from benign adnexal masses rather than screening asymptomatic women.

Table 1. Characteristics of Included Studies

Study No.	Author/ Year	Country/Region	Study Design	Study Population	Biomarkers/Algorithm	Reference Standard	Key Diagnostic Finding
1	Moore Et Al., 2008	Usa	Prospective Diagnostic Study	Women With Pelvic Masses	He4, Ca-125, Biomarker Panel	Histopathology	He4 Contributed To Improved Discrimination Between Benign And Malignant Disease.
2	Moore Et Al., 2009	Usa	Multicenter Validation Study	Women With Pelvic Masses Undergoing Surgery	He4, Ca-125, Roma-Type Algorithm	Histopathology	Combined He4 And Ca-125 Improved High-Risk Classification.
3	Huhtinen Et Al., 2009	Finland	Case-Control Diagnostic Study	Ovarian Cancer, Endometriosis, Benign Disease	He4, Ca-125	Histopathology/ Clinical Diagnosis	He4 Was Less Frequently Elevated In Endometriosis Than Ca-125.
4	Montagnana Et Al., 2009	Italy	Cross-Sectional Diagnostic Study	Women With Ovarian Masses	He4, Ca-125	Histopathology	He4 Improved Specificity In Benign Versus Malignant Differentiation.
5	Andersen Et Al., 2010	Denmark/Usa	Cohort Diagnostic Study	Women Evaluated For	He4, Ca-125, Symptom Index	Histopathology/ Clinical Diagnosis	Biomarker And Symptom

				Ovarian Cancer Risk			Combinations Improved Prediction.
6	Van Gorp Et Al., 2011	Belgium	Prospective Validation Study	Women With Pelvic Masses	He4, Ca-125, Roma	Histopathology	Roma Showed Useful Diagnostic Accuracy, With Subgroup Variability.
7	Partheen Et Al., 2011	Sweden	Diagnostic Accuracy Study	Women With Suspicious Cystic Ovarian Masses	He4, Ca-125	Histopathology	He4 And Ca-125 Provided Complementary Diagnostic Value.
8	Molina Et Al., 2011	Spain	Diagnostic Biomarker Study	Women With Suspected Ovarian Malignancy	He4, Ca-125, Roma	Histopathology	He4 And Roma Improved Differentiation From Benign Disorders.
9	Karlsen Et Al., 2012	Denmark	Diagnostic Accuracy Study	Women With Pelvic Masses	He4, Ca-125, Roma, Rmi	Histopathology	Roma And He4 Supported Malignancy Risk Prediction.
10	Sandri Et Al., 2013	Italy	Prospective Observational Study	Women With Pelvic Masses Undergoing Surgery	He4, Ca-125, Roma	Histopathology	Roma And He4 Were Useful Adjuncts For Preoperative Triage.
11	Wang Et Al., 2014	International	Diagnostic Meta-Analysis	Published Studies Of Ovarian Cancer Diagnosis	He4, Ca-125, Roma	Histopathology In Included Studies	Roma And He4 Improved Overall Diagnostic Performance Compared With Ca-125 Alone.
12	Fujiwara Et Al., 2015	Japan	Diagnostic Accuracy Study	Women With Pelvic Masses	He4, Ca-125, Roma, Rmi	Histopathology	Performance Varied According To Cutoff And Menopausal Status.
13	Al Musalhi	Oman	Prospective	Women With	He4, Ca-125, Roma, Rmi	Histopathology	He4 And Roma

	Et Al., 2016		Diagnostic Study	Adnexal Masses			Showed High Specificity, Especially For Benign Disease Differentiation.
14	Dayyani Et Al., 2016	Usa	Diagnostic Performance Study	Women With Adnexal Masses	Roma, He4, Ca-125	Histopathology	Roma Helped Classify Patients Into Low- And High-Risk Groups.
15	Yanaranop Et Al., 2016	Thailand	Diagnostic Accuracy Study	Women With Pelvic Masses	He4, Ca-125, Roma	Histopathology	Roma Supported Preoperative Prediction With Menopausal Subgroup Variation.
16	Dikmen Et Al., 2016	Turkey	Diagnostic Accuracy Study	Benign Gynecological Disease And Ovarian Cancer	He4, Ca-125, Roma	Histopathology	He4 And Roma Improved Specificity Compared With Ca-125.
17	Nikolova Et Al., 2017	Europe	Diagnostic Study	Premenopausal Women With Endometriosis Or Ovarian Cancer	He4, Ca-125	Histopathology	He4 Helped Distinguish Endometriosis From Epithelial Ovarian Cancer.
18	Huy Et Al., 2018	Vietnam	Diagnostic Accuracy Study	Women Undergoing Ovarian Cancer Evaluation	He4, Ca-125, Roma	Histopathology	Cutoff Selection Strongly Influenced Diagnostic Accuracy.
19	Kim Et Al., 2019	Korea	Retrospective Diagnostic Study	Women With Ovarian Tumors	He4, Ca-125, Roma	Histopathology	Accuracy Varied By Cutoff, Menopausal Status, And Tumor Type.

20	Kumar Et Al., 2019	India	Prospective Diagnostic Study	Women With Adnexal Masses	He4, Ca-125, Roma	Histopathology	Roma Improved Preoperative Malignancy Risk Stratification.
21	Charkhchi Et Al., 2020	International	Evidence Synthesis	Published Ca-125 Evidence	Ca-125	Published Diagnostic Evidence	Ca-125 Was Useful But Limited In Early-Stage Disease And Benign Conditions.
22	Terlikowska Et Al., 2021	Poland	Diagnostic Accuracy Study	Women With Adnexal Lesions	He4, Ca-125, Roma	Histopathology	He4 And Roma Improved Discrimination Of Benign And Malignant Lesions.
23	Shittu Et Al., 2023	Nigeria	Diagnostic Accuracy Study	Benign And Malignant Epithelial Ovarian Tumors	He4, Ca-125, Roma	Histopathology	He4 And Roma Showed Useful Diagnostic Performance.
24	Spagnol Et Al., 2024	Italy	Diagnostic Accuracy Study	Women With Adnexal Masses	Roma, Rmi, He4, Ca-125	Histopathology	Roma Supported Risk Classification, But Imaging-Based Models Remained Important.

Abbreviations: CA-125: Cancer antigen 125; HE4: Human epididymis protein 4; ROMA: Risk of Ovarian Malignancy Algorithm; RMI: Risk of Malignancy Index.

Quality Assessment

Most studies used histopathology as the reference standard, which strengthened diagnostic validity. However, the overall quality varied. Several studies were performed in tertiary care or surgical settings, where the prevalence of malignancy is higher than in general populations. This may overestimate diagnostic accuracy compared with primary care or screening settings.

Table 2. Risk of Bias Summary

Quadas-2 Domain	Overall Assessment	Main Concern
Patient Selection	Moderate Risk	Many Studies Enrolled Surgical Or Referral Populations
Index Test	Moderate Risk	Variation In Assay Platform And Cutoff Values

Reference Standard	Low Risk	Most Studies Used Histopathology
Flow And Timing	Low To Moderate Risk	Some Studies Incompletely Reported Timing Or Exclusions
Applicability	Moderate Concern	Findings May Not Apply To Population Screening

Diagnostic Performance of CA-125

CA-125 was the most frequently assessed biomarker. It showed acceptable sensitivity for epithelial ovarian cancer, particularly advanced-stage disease and serous carcinoma. Its clinical familiarity and availability make it useful in routine gynecological and oncological practice.

However, CA-125 had important limitations. Its specificity was reduced in premenopausal women because benign gynecological conditions such as endometriosis, menstruation, fibroids, pregnancy, and pelvic inflammatory disease can elevate CA-125. Non-gynecological conditions such as liver disease, peritoneal inflammation, and pleural disease can also increase serum CA-125.

CA-125 also had limited sensitivity for early-stage epithelial ovarian cancer. Some early tumors do not produce significantly elevated CA-125, and mucinous tumors may be less reliably detected. Therefore, a normal CA-125 value cannot exclude ovarian malignancy when imaging or clinical findings are suspicious.

Overall, CA-125 is useful as part of a broader diagnostic pathway but should not be used alone for early detection or screening.

Diagnostic Performance of HE4

HE4 generally demonstrated higher specificity than CA-125. Its major advantage was lower false-positive elevation in benign gynecological disorders, especially endometriosis. This makes HE4 particularly useful when differentiating epithelial ovarian cancer from benign adnexal lesions in premenopausal women.

HE4 was also useful as a complementary biomarker because its expression pattern differs from CA-125. Combining HE4 with CA-125 improved diagnostic discrimination in several studies. HE4 performed particularly well in serous and endometrioid epithelial ovarian cancers.

However, HE4 also has limitations. Serum HE4 may be elevated in renal impairment and may vary with age and smoking status. It may also have lower sensitivity in some tumor subtypes, especially mucinous carcinoma. Therefore, HE4 should not replace CA-125 but should be interpreted as part of a combined diagnostic strategy.

Diagnostic Performance of ROMA

ROMA combines HE4, CA-125, and menopausal status into a predictive algorithm. The rationale behind ROMA is that CA-125 and HE4 provide complementary diagnostic information, while menopausal status modifies baseline malignancy risk and biomarker interpretation.

Across included studies, ROMA generally improved overall diagnostic discrimination compared with CA-125 alone. It was particularly useful for preoperative classification of women with adnexal masses into low-risk and high-risk groups. This has practical value because women at high risk can be referred to gynecologic oncologists for specialized surgical assessment.

ROMA performed well in postmenopausal women in many studies. In premenopausal women, its performance was more variable, largely because benign conditions are common and biomarker elevations may be less specific. However, HE4 inclusion helped improve specificity compared with CA-125 alone.

ROMA should not be considered a stand-alone diagnostic test. It is best used alongside transvaginal ultrasound, clinical examination, patient age, menopausal status, family history, and other risk factors.

Comparative Diagnostic Profile

Table 3. Comparative Diagnostic Characteristics of CA-125, HE4, and ROMA

Parameter	CA-125	HE4	ROMA
Main Role	Traditional Ovarian Cancer Biomarker	Specificity-Enhancing Biomarker	Combined Risk Algorithm
Diagnostic Strength	Good Sensitivity In Advanced Disease	Higher Specificity	Better Combined Discrimination
Major Limitation	False Positives In Benign Disease	Affected By Renal Function And Age	Cutoff And Population-Dependent
Premenopausal Utility	Limited By Benign Elevations	Better Specificity	Variable But Useful With Clinical Correlation
Postmenopausal Utility	More Clinically Informative	Useful Adjunct	Strong Risk Classification
Early-Stage Detection	Limited	Moderate Improvement	Improved But Still Imperfect

Best Use	Adjunct Marker	Complementary Marker	Preoperative Risk Stratification
Screening Role	Not Recommended Alone	Not Recommended Alone	Not Recommended For Population Screening

Early-Stage Epithelial Ovarian Cancer

Early-stage epithelial ovarian cancer remains difficult to detect using serum biomarkers alone. Tumor burden may be low, biomarker expression may vary by histological subtype, and symptoms are often nonspecific. CA-125 may remain normal in a significant proportion of early-stage cases. HE4 may identify some cases missed by CA-125, but it is also not universally elevated.

ROMA improves risk classification by combining two biomarkers and menopausal status, but its early-stage sensitivity remains insufficient for stand-alone early detection. The reviewed studies suggest that biomarker combinations are more useful for risk stratification in women with an already detected adnexal mass than for detecting occult disease in asymptomatic women.

Influence of Menopausal Status

Menopausal status significantly affected diagnostic interpretation. In premenopausal women, benign conditions such as endometriosis and pelvic inflammatory disease are frequent causes of CA-125 elevation. This reduces CA-125 specificity and may lead to false-positive results.

In postmenopausal women, the likelihood of malignancy among suspicious adnexal masses is higher. CA-125, HE4, and ROMA generally showed stronger diagnostic performance in this group. ROMA is particularly relevant because it applies different calculations or thresholds based on menopausal status.

Clinical Implications

The findings support the use of CA-125, HE4, and ROMA as adjunctive tools in women with adnexal masses. Their main value lies in preoperative risk assessment, not routine population screening. Biomarker results may help determine whether a patient should be managed in a general gynecology setting or referred to a gynecologic oncology center.

A practical diagnostic pathway includes:

1. Clinical history and physical examination.
2. Assessment of menopausal status and family history.
3. Transvaginal ultrasound or appropriate imaging.
4. Serum CA-125 and HE4 measurement.
5. ROMA calculation where available.
6. Risk-based referral and surgical planning.
7. Histopathological confirmation after surgery.

Sources of Heterogeneity

The reviewed studies showed considerable variation. Important sources of heterogeneity included:

1. Differences in patient selection.
2. Inclusion of tertiary care versus general gynecology populations.
3. Different proportions of early-stage and advanced-stage disease.
4. Different histological subtypes.
5. Variable inclusion of borderline tumors.
6. Different biomarker assay platforms.
7. Different cutoff values.
8. Separate versus pooled menopausal analysis.
9. Variation in renal function assessment.
10. Differences in ultrasound and clinical risk model use.

These factors limit direct comparison across studies and explain why reported diagnostic performance varies.

DISCUSSION

This systematic review found that CA-125, HE4, and ROMA each have distinct diagnostic roles in epithelial ovarian cancer detection. CA-125 remains useful because of its availability, clinical familiarity, and acceptable sensitivity in advanced epithelial ovarian cancer. However, it lacks sufficient specificity in benign gynecological disease and has limited sensitivity in early-stage disease.

HE4 improves diagnostic specificity and appears particularly useful in differentiating epithelial ovarian cancer from benign conditions such as endometriosis. This characteristic is clinically important in premenopausal women, where benign causes of CA-125 elevation are common. However, HE4 is affected by renal function, age, smoking status, and tumor subtype, which must be considered during interpretation.

ROMA provides a more integrated approach by combining CA-125, HE4, and menopausal status. It generally improves combined diagnostic discrimination and may help classify women with adnexal masses into low- and high-risk groups. This can assist referral decisions and surgical planning. However, ROMA is not a replacement for imaging or histopathology.

A major limitation across studies is that many were conducted in women already selected for surgery. This creates a higher disease prevalence than would be seen in the general population and may inflate diagnostic performance. Therefore, findings from adnexal mass studies should not be applied directly to population screening.

Early-stage disease remains the most important diagnostic challenge. Although HE4 and ROMA improve performance compared with CA-125 alone in some studies, no serum biomarker strategy provides sufficiently reliable early-stage detection

as a stand-alone tool. Future research should focus on integrated models combining serum biomarkers, imaging features, genetic risk, symptoms, and artificial intelligence-based risk prediction.

Limitations

This systematic review has limitations. First, the included studies were heterogeneous in design, population, cutoff values, assay platforms, and diagnostic thresholds. Second, many studies were conducted in tertiary care or surgical populations, limiting generalizability. Third, early-stage epithelial ovarian cancer was underrepresented in several studies. Fourth, not all studies reported diagnostic accuracy separately by menopausal status, stage, and histological subtype. Fifth, a formal meta-analysis was not performed because uniform two-by-two diagnostic data were not available across all included studies.

Future Directions

Future studies should prioritize:

1. Large prospective multicenter designs.
2. Standardized biomarker assay platforms.
3. Uniform reporting of cutoff values.
4. Separate analysis of premenopausal and postmenopausal women.
5. Stage-specific diagnostic accuracy reporting.
6. Histological subtype-specific analysis.
7. Adjustment for renal function and age.
8. Comparison with ultrasound-based models.
9. Integration of biomarkers with clinical and imaging algorithms.
10. Evaluation of patient outcomes after biomarker-guided referral.

CONCLUSION

CA-125, HE4, and ROMA are important tools in epithelial ovarian cancer assessment, particularly for women with adnexal masses. CA-125 remains useful but is limited by false-positive elevation in benign disease and reduced sensitivity in early-stage cancer. HE4 improves specificity and complements CA-125. ROMA provides the strongest combined risk stratification by integrating HE4, CA-125, and menopausal status.

Despite these advantages, none of these tools should be used as an independent population screening method for average-risk asymptomatic women. Biomarkers should be interpreted alongside clinical evaluation, imaging findings, menopausal status, and histopathological confirmation. Their greatest value lies in preoperative risk stratification and guiding referral to specialized gynecologic oncology care.

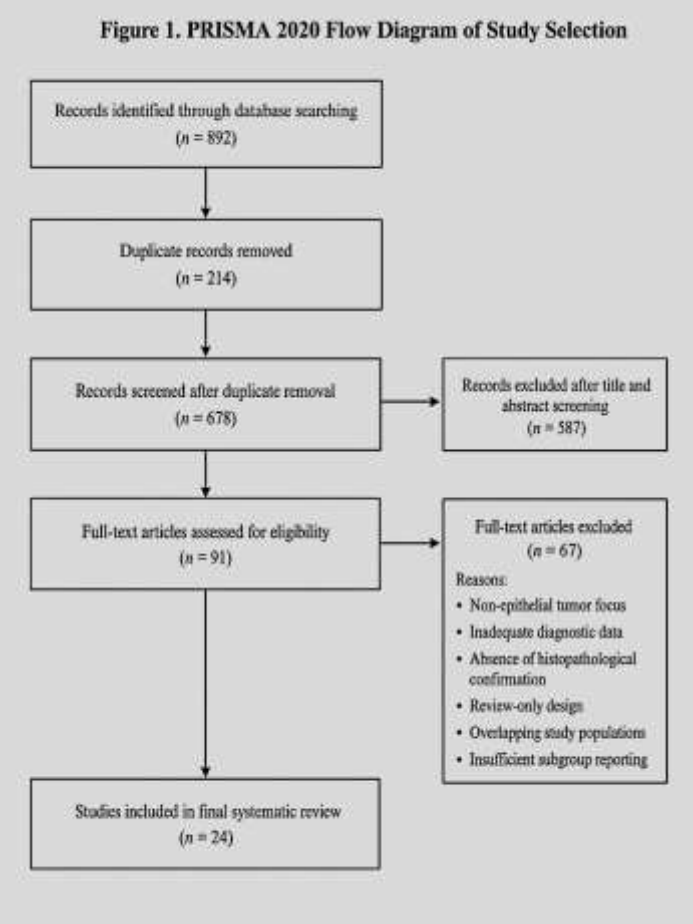

Figure 1. PRISMA 2020 Flow Diagram of Study Selection.

The flow diagram summarizes the identification, screening, eligibility assessment, and inclusion of studies evaluating CA-125, HE4, and ROMA in epithelial ovarian cancer diagnosis.

REFERENCES

1. Moore RG, Brown AK, Miller MC, Skates S, Allard WJ, Verch T, et al. The use of multiple novel tumor biomarkers for the detection of ovarian carcinoma in patients with a pelvic mass. Gynecologic Oncology. 2008.
2. Moore RG, McMeekin DS, Brown AK, DiSilvestro P, Miller MC, Allard WJ, et al. A novel multiple marker bioassay utilizing HE4 and CA-125 for the prediction of ovarian cancer in patients with a pelvic mass. Gynecologic Oncology. 2009.
3. Huhtinen K, Suvitie P, Hiissa J, Junnila J, Huvila J, Kujari H, et al. Serum HE4 concentration differentiates malignant ovarian tumours from ovarian endometriotic cysts. British Journal of Cancer. 2009.
4. Montagnana M, Danese E, Ruzzenente O, Bresciani V, Nuzzo T, Gelati M, et al. The ROMA algorithm for epithelial ovarian cancer diagnosis. Clinical Chemistry and Laboratory Medicine. 2009.
5. Andersen MR, Goff BA, Lowe KA, Scholler N, Bergan L, Drescher CW, et al. Use of a symptom index, CA-125, and HE4 to predict ovarian cancer. Gynecologic Oncology. 2010.
6. Van Gorp T, Cadron I, Despierre E, Daemen A, Leunen K, Amant F, et al. HE4 and CA-125 as diagnostic tests in ovarian cancer: prospective validation of the Risk of Ovarian Malignancy Algorithm. British Journal of Cancer. 2011.
7. Partheen K, Kristjansdottir B, Sundfeldt K. Evaluation of ovarian cancer biomarkers HE4 and CA-125 in women presenting with suspicious cystic ovarian masses. Journal of Gynecologic Oncology. 2011.
8. Molina R, Escudero JM, Augé JM, Filella X, Foj L, Torné A, et al. HE4 a novel tumour marker for ovarian cancer: comparison with CA-125 and ROMA algorithm. Tumour Biology. 2011.
9. Karlsen MA, Sandhu N, Høgdall C, Christensen IJ, Nedergaard L, Lundvall L, et al. Evaluation of HE4, CA-125, ROMA and Risk of Malignancy Index in women with pelvic masses. Acta Obstetricia et Gynecologica Scandinavica. 2012.
10. Sandri MT, Bottari F, Franchi D, Boveri S, Candiani M, Ronzoni S, et al. Comparison of HE4, CA-125 and ROMA algorithm in women with a pelvic mass. Tumour Biology. 2013.
11. Wang J, Gao J, Yao H, Wu Z, Wang M, Qi J. Diagnostic accuracy of serum HE4, CA-125 and ROMA in patients with ovarian cancer: a meta-analysis. Tumour Biology. 2014.
12. Fujiwara H, Suzuki M, Takeshima N, Takizawa K, Kimura E, Nakanishi T, et al. Evaluation of HE4, CA-125 and ROMA in the diagnosis of ovarian cancer. Oncology Letters. 2015.
13. Al Musalhi K, Al Kindi M, Ramadhan F, Al Rawahi T, Al Hatali K, Mula-Abed WA. Evaluation of HE4, CA-125, Risk of Ovarian Malignancy Algorithm and Risk of Malignancy Index in preoperative assessment of patients with adnexal mass. Oman Medical Journal. 2016.
14. Dayyani F, Uhlig S, Colson B, Simon K, Rolny V, Morgenstern D, et al. Diagnostic performance of Risk of Ovarian Malignancy Algorithm against CA-125 and HE4 in ovarian cancer. International Journal of Gynecological Cancer. 2016.
15. Yanaranop M, Tiyayon J, Siricharoenthai S, Nakrangsee S, Thinkhamrop B. Rajavithi-ovarian cancer predictive score and the Risk of Ovarian Malignancy Algorithm for preoperative ovarian cancer prediction. Asian Pacific Journal of Cancer Prevention. 2016.
16. Dikmen ZG, Colak A, Dogan P, Tuncer S, Akbiyik F. Diagnostic performances of CA-125, HE4, and ROMA index in ovarian cancer. European Journal of Gynaecological Oncology. 2016.
17. Nikolova D, Zivadinovic R, Stanojevic Z, et al. Diagnostic value of HE4 and CA-125 in differentiating ovarian endometriosis from epithelial ovarian cancer. Clinical and Experimental Obstetrics & Gynecology. 2017.
18. Huy NVQ, Van Khoa V, Tam LM, et al. Standard and optimal cut-off values of serum CA-125, HE4 and ROMA in preoperative prediction of ovarian cancer. Gynecologic Oncology Reports. 2018.
19. Kim B, Park Y, Kim B, Ahn HJ, Lee KA, Chung JE, et al. Diagnostic performance of CA-125, HE4, and ROMA for ovarian cancer. Annals of Laboratory Medicine. 2019.
20. Kumar V, Gupta N, Saini S, et al. Diagnostic value of Risk of Ovarian Malignancy Algorithm in adnexal masses. Journal of Obstetrics and Gynaecology of India. 2019.
21. Charkhchi P, Cybulski C, Gronwald J, Wong FO, Narod SA, Akbari MR. CA-125 and ovarian cancer: a comprehensive review. Cancers. 2020.

22. Terlikowska KM, Dobrzycka B, Witkowska AM, Mackowiak-Matejczyk B, Sledziewski TK, Kinalski M, et al. Preoperative HE4, CA-125 and ROMA in the differential diagnosis of benign and malignant adnexal masses. Journal of Ovarian Research. 2021.
23. Shittu KA, et al. Comparison of the diagnostic accuracy of HE4 with CA-125 and validation of ROMA in ovarian cancer diagnosis. BMC Women's Health. 2023.
24. Spagnol G, et al. Clinical utility and diagnostic accuracy of ROMA, RMI, HE4, and CA-125 in women with adnexal masses. Cancers. 2024.
25. American College of Obstetricians and Gynecologists. The role of the obstetrician-gynecologist in the early detection of epithelial ovarian cancer in women at average risk. Committee Opinion. 2017.
26. European Group on Tumor Markers. Clinical use of cancer biomarkers in epithelial ovarian cancer. International Journal of Gynecological Cancer. 2015.
27. Singh AK, et al. Comparative meta-analysis of CA-125, HE4, ROMA, and RMI in ovarian cancer diagnosis. 2025.
28. Moore RG, Jabre-Raughley M, Brown AK, et al. Comparison of a novel multiple marker assay versus the Risk of Malignancy Index for the prediction of epithelial ovarian cancer in patients with a pelvic mass. American Journal of Obstetrics and Gynecology. 2010.

How to cite this article: Nida Asif, Amol Wahane, Bidu Bhushan, SERUM BIOMARKERS AND PREDICTIVE ALGORITHMS FOR EPITHELIAL OVARIAN CANCER DETECTION: A SYSTEMATIC REVIEW OF CA-125, HE4, AND ROMA, Asian J. Med. Res. Health Sci., 2026; 4 (2):1147-1158.
Source of Support: Nil, Conflicts of Interest: None declared.