Original Research

BIOMARKER-BASED DETECTION OF EPITHELIAL OVARIAN CANCER: A SYSTEMATIC REVIEW OF HE4, CA-125, AND ROMA SCORE

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ABSTRACT

Background: Epithelial ovarian cancer remains a leading cause of gynecological cancer mortality because many cases are diagnosed at an advanced stage. Early symptoms are often vague, and reliable population-level screening tools are lacking. Serum biomarkers, particularly cancer antigen 125 (CA-125) and human epididymis protein 4 (HE4), along with the Risk of Ovarian Malignancy Algorithm (ROMA), have been widely studied for detecting epithelial ovarian cancer and stratifying malignancy risk in women with adnexal masses.

Objective: This systematic review aimed to evaluate the diagnostic performance and clinical utility of HE4, CA-125, and ROMA score in biomarker-based detection and risk assessment of epithelial ovarian cancer.

Methods: A systematic search was conducted across PubMed/MEDLINE, Scopus, Web of Science, Cochrane Library, Google Scholar, and reference lists of relevant articles. Studies were included if they evaluated HE4, CA-125, ROMA, or combined biomarker strategies in women with suspected ovarian malignancy, pelvic masses, or adnexal masses and reported diagnostic accuracy outcomes. Data were extracted on study design, population, menopausal status, biomarker cutoffs, reference standard, sensitivity, specificity, area under the receiver operating characteristic curve, and major diagnostic conclusions. Methodological quality was assessed using 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, and 67 were excluded. Finally, 24 studies were included in the systematic review. CA-125 showed useful sensitivity, particularly in advanced epithelial ovarian cancer, but had limited specificity in benign gynecological disorders and premenopausal women. HE4 generally demonstrated higher specificity than CA-125 and was less frequently elevated in benign conditions such as endometriosis. ROMA score improved overall risk stratification by combining HE4, CA-125, and menopausal status. However, diagnostic performance varied across studies due to heterogeneity in cutoff values, assay platforms, menopausal distribution, histological subtype, disease stage, renal function, and study setting.

Conclusion: HE4 and ROMA score provide diagnostic advantages over CA-125 alone, particularly by improving specificity and supporting preoperative triage in women with adnexal masses. CA-125 remains clinically useful but is insufficient as a stand-alone early detection marker. None of the evaluated biomarker approaches is adequate as an independent screening tool for average-risk asymptomatic women. Biomarker interpretation should be integrated with clinical assessment, imaging findings, menopausal status, and histopathological confirmation.

Keywords: Epithelial Ovarian Cancer, He4, Ca-125, Roma Score, Serum Biomarkers, Adnexal Mass, Ovarian Cancer Detection, Diagnostic Accuracy, Systematic Review.

INTRODUCTION

Epithelial ovarian cancer is one of the most clinically significant gynecological malignancies because it is frequently diagnosed after spread beyond the ovary.

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Early-stage disease may be asymptomatic or associated with non-specific symptoms such as bloating, abdominal fullness, pelvic discomfort, urinary frequency, early satiety, or vague gastrointestinal complaints. These symptoms overlap with benign gynecological and gastrointestinal disorders, which contributes to diagnostic delay.

Improving early detection and preoperative identification of malignant adnexal masses is an important clinical priority. Women with suspected

epithelial ovarian cancer benefit from appropriate referral to gynecologic oncology services, specialized surgical planning, and comprehensive staging. Conversely, overestimation of malignancy risk may expose women with benign disease to unnecessary anxiety, additional testing, or more extensive surgical intervention. Therefore, accurate diagnostic tools are required to support clinical decision-making.

CA-125 is the most widely used serum biomarker in ovarian cancer evaluation. It has established value in treatment monitoring and recurrence surveillance and is frequently used in the assessment of women with adnexal masses. However, CA-125 has well-known diagnostic limitations. It can be elevated in benign gynecological conditions such as endometriosis, uterine fibroids, pelvic inflammatory disease, menstruation, and pregnancy. It may also rise in non-gynecological conditions, including liver disease and inflammatory disorders. In addition, CA-125 may be normal in some early-stage epithelial ovarian cancers and in certain histological subtypes, especially mucinous tumors.

HE4 has emerged as a complementary biomarker for epithelial ovarian cancer. It is overexpressed in several epithelial ovarian cancer subtypes, especially serous and endometrioid carcinoma. HE4 appears to have higher specificity than CA-125 in many studies and is less frequently elevated in benign gynecological disease, particularly endometriosis. However, HE4 values may be influenced by renal function, age, smoking status, and assay method.

ROMA score combines HE4, CA-125, and menopausal status to estimate the probability of epithelial ovarian cancer in women with adnexal or pelvic masses. The inclusion of menopausal status is important because biomarker levels and baseline ovarian cancer risk differ between premenopausal and postmenopausal women. ROMA is intended to support preoperative risk stratification rather than function as a stand-alone diagnostic or screening test.

Although HE4, CA-125, and ROMA have been extensively studied, results vary across populations and clinical settings. Differences in study design, biomarker thresholds, assay systems, tumor stage distribution, histological subtype, and reference standards make interpretation challenging. This systematic review was undertaken to synthesize evidence regarding the diagnostic performance of HE4, CA-125, and ROMA score in biomarker-based detection of epithelial ovarian cancer.

Objectives

Primary Objective

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

Secondary Objectives

1. To compare the diagnostic strengths and limitations of HE4, CA-125, and ROMA score.
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 sources of heterogeneity across included studies.
5. To evaluate the role of biomarkers in preoperative triage and referral decisions.
6. To propose practical recommendations for clinical interpretation and future research.

MATERIALS AND METHODS

Study Design

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

Reporting Framework

The review was prepared according to PRISMA 2020 principles. Diagnostic study quality was evaluated using domains adapted from the QUADAS-2 framework.

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 HE4, CA-125, ROMA score, or combinations of these biomarkers.
3. Included epithelial ovarian cancer cases or provided epithelial ovarian cancer-specific diagnostic information.
4. Reported diagnostic accuracy outcomes, including sensitivity, specificity, positive predictive value, negative predictive value, diagnostic odds ratio, likelihood ratios, or area under the receiver operating characteristic curve.
5. Used histopathology, surgical diagnosis, or clearly defined clinical diagnosis as the reference standard.
6. Used prospective, retrospective, cross-sectional, cohort, case-control, or diagnostic accuracy designs.
7. Were published in English or provided 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 recurrence, prognosis, treatment response, or disease monitoring.
3. Did not provide extractable diagnostic accuracy data.
4. Were case reports, letters, editorials, conference abstracts without full data, or narrative reviews.
5. Used unclear reference standards.
6. Had duplicate or overlapping populations without additional relevant data.
7. Were limited to animal, cell-line, or experimental laboratory studies.

Information Sources

The following sources were searched:

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

Search Strategy

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

A representative search strategy was:

("epithelial ovarian cancer" OR "ovarian carcinoma" OR "adnexal mass" OR "pelvic mass" OR "ovarian tumor")

And

("HE4" OR "human epididymis protein 4" OR "WFDC2" OR "CA-125" OR "CA125" OR "cancer antigen 125" OR "ROMA" OR "Risk of Ovarian Malignancy Algorithm")

And

("diagnostic accuracy" OR "sensitivity" OR "specificity" OR "area under the curve" OR "AUC" OR "early detection" OR "risk stratification")

Database-specific filters and indexing terms were used where appropriate.

Study Selection

All identified 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 using predefined eligibility criteria. Studies satisfying inclusion criteria were selected for final synthesis.

Data Extraction

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

1. Author and year
2. Country or region
3. Study design
4. Study setting and population
5. Sample size
6. Number of malignant and benign cases
7. Menopausal status
8. Tumor 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 diagnostic 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 evaluated for risk of bias and applicability concerns. Particular attention was given to patient recruitment methods, prespecification of biomarker thresholds, use of histopathology as the reference standard, and whether all participants underwent the same diagnostic confirmation process.

Data Synthesis

A narrative synthesis was performed because studies varied in population characteristics, biomarker thresholds, assay platforms, menopausal stratification, histological subtype, stage distribution, and reference standards. Findings were organized by biomarker type, diagnostic performance, menopausal subgroup, early-stage disease, comparative utility, and clinical implications.

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 were unrelated to epithelial ovarian cancer diagnosis, did not evaluate HE4, CA-125, or ROMA score, lacked diagnostic accuracy outcomes, or focused on recurrence monitoring rather than primary detection.

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 24 included studies evaluated HE4, CA-125, ROMA score, or combined biomarker strategies in women with suspected epithelial ovarian cancer or adnexal masses. Most 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 included studies differed in sample size, study setting, menopausal composition, tumor stage distribution, histological subtype, assay platform, and cutoff values. Several studies reported separate diagnostic performance for premenopausal and postmenopausal women, while others provided pooled estimates. Most studies evaluated biomarker performance for differentiating epithelial ovarian cancer from benign adnexal masses rather than for screening asymptomatic women.

Table 1. Characteristics of Studies Included in the Systematic Review

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 ovarian cancer risk	HE4, CA-125, symptom index	Histopathology/clinical diagnosis	Biomarker and symptom 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	Den mark	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 et al., 2016	Oman	Prospective diagnostic study	Women with adnexal masses	HE4, CA-125, ROMA, RMI	Histopathology	HE4 and ROMA 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, study quality varied. Several studies were conducted in tertiary referral or surgical settings, where the prevalence of malignancy is higher than in general practice. This may overestimate diagnostic performance compared with primary care or screening populations.

Table 2. Risk of Bias Summary

QUADAS-2 Domain	Overall Assessment	Main Concern
Patient selection	Moderate risk	Many studies enrolled surgical or tertiary referral populations
Index test	Moderate risk	Variable assay platforms and cutoff values
Reference standard	Low risk	Most studies used histopathology
Flow and timing	Low to moderate risk	Some studies incompletely reported sample timing or exclusions
Applicability	Moderate concern	Findings mainly apply to women with adnexal masses, not screening populations

Diagnostic Performance of CA-125

CA-125 was the most frequently evaluated biomarker. It showed useful sensitivity for epithelial ovarian cancer, particularly in advanced-stage disease and high-grade serous carcinoma. Its widespread clinical availability and long history of use make it an important component of ovarian cancer evaluation.

However, CA-125 has limited specificity. In premenopausal women, benign gynecological conditions such as endometriosis, fibroids, menstruation, pregnancy, and pelvic inflammatory disease may increase CA-125 levels. Non-gynecological inflammatory conditions and liver disease may also cause elevation. These false positives reduce diagnostic reliability when CA-125 is used alone.

CA-125 also has limited sensitivity in early-stage disease. Some early epithelial ovarian cancers do not produce markedly elevated CA-125. Mucinous tumors may also be less reliably detected. Therefore, a normal CA-125 level cannot exclude ovarian cancer when clinical or imaging findings are suspicious.

Overall, CA-125 remains useful as an adjunctive biomarker but should not be interpreted in isolation.

Diagnostic Performance of HE4

HE4 generally demonstrated higher specificity than CA-125 across included studies. Its major diagnostic advantage was lower false-positive elevation in benign gynecological conditions, particularly endometriosis. This makes HE4 valuable in differentiating benign adnexal lesions from epithelial ovarian cancer.

HE4 was especially useful as a complementary biomarker because it provides information that differs from CA-125. Several studies showed improved diagnostic discrimination when HE4 and CA-125 were combined. HE4 appeared particularly useful in serous and endometrioid epithelial ovarian cancer.

However, HE4 is not without limitations. Serum HE4 levels may rise in renal impairment and may vary with age, smoking status, and assay method. HE4 may also have lower sensitivity in certain histological subtypes. Therefore, HE4 should be considered a specificity-enhancing adjunct rather than a stand-alone test.

Diagnostic Performance of ROMA Score

ROMA score combines HE4, CA-125, and menopausal status to estimate the probability of epithelial ovarian cancer. This algorithmic approach is clinically useful because it incorporates two biomarkers with different performance profiles and adjusts interpretation according to menopausal status.

Across included studies, ROMA generally improved overall diagnostic discrimination compared with CA-125 alone. ROMA was particularly useful for classifying women with adnexal masses into low-risk and high-risk categories before surgery. This can support referral to gynecologic oncology services and guide surgical planning.

In postmenopausal women, ROMA often demonstrated stronger diagnostic performance because baseline malignancy risk is higher and benign causes of CA-125 elevation are less frequent. In premenopausal women, ROMA performance was more variable, but HE4 inclusion helped improve specificity compared with CA-125 alone.

ROMA should be used as part of an integrated diagnostic approach and not as a replacement for imaging, clinical assessment, or histopathological confirmation.

Comparative Diagnostic Profile

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

Parameter	CA-125	HE4	ROMA Score
Main role	Traditional ovarian cancer biomarker	Specificity-enhancing biomarker	Combined risk algorithm
Diagnostic strength	Good sensitivity in advanced disease	Higher specificity	Better combined risk stratification
Major limitation	False positives in benign disease	Affected by renal function and age	Performance depends on cutoff and population
Premenopausal utility	Limited by benign elevations	Better specificity	Variable but useful with clinical correlation
Postmenopausal utility	More informative than in premenopause	Useful adjunct	Stronger risk classification
Early-stage detection	Limited	May improve detection in some cases	Improved but still imperfect
Best use	Adjunctive assessment	Complementary biomarker	Preoperative triage
Screening role	Not recommended alone	Not recommended alone	Not recommended for routine screening

Early-Stage Epithelial Ovarian Cancer Detection

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

ROMA improves risk classification by combining biomarker information with menopausal status, but early-stage sensitivity remains insufficient for independent early detection. The reviewed evidence indicates that biomarker-based tools are more useful for evaluating women with an already detected adnexal mass than for detecting occult disease in asymptomatic women.

Influence of Menopausal Status

Menopausal status was an important determinant of biomarker interpretation. In premenopausal women, benign causes of CA-125 elevation are common, which reduces specificity. HE4 may be more useful in this group because it is less frequently elevated in endometriosis and other benign gynecological conditions.

In postmenopausal women, suspicious adnexal masses carry a higher baseline probability of malignancy. CA-125, HE4, and ROMA generally showed stronger risk stratification in this group.

ROMA is particularly relevant because menopausal status is incorporated directly into the algorithm.

Clinical Implications

The findings support the use of HE4, CA-125, and ROMA score as adjunctive tools in women with adnexal masses. Their main value lies in preoperative risk assessment rather than routine population screening. Biomarker results may help determine whether a patient can be managed in a general gynecology setting or should be referred to a gynecologic oncology center.

A practical clinical pathway includes:

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

Sources of Heterogeneity

The reviewed studies showed variation in diagnostic performance because of multiple factors:

1. Differences in patient selection.
2. Referral-center versus general gynecology populations.
3. Variable disease prevalence.
4. Different proportions of early-stage and advanced-stage disease.
5. Differences in histological subtype distribution.
6. Inclusion or exclusion of borderline tumors.
7. Different biomarker assay platforms.
8. Different cutoff values.
9. Separate versus pooled menopausal analysis.
10. Variable adjustment for renal function, age, or smoking.

These sources of heterogeneity limit direct comparison across studies and explain why reported sensitivity, specificity, and AUC values vary.

DISCUSSION

This systematic review found that HE4, CA-125, and ROMA score each have distinct roles in epithelial ovarian cancer detection. CA-125 remains clinically useful because it is widely available and shows good sensitivity in advanced disease. However, its specificity is reduced in benign gynecological conditions and its sensitivity is insufficient for reliable early-stage detection.

HE4 improves diagnostic specificity and is particularly useful in distinguishing epithelial ovarian cancer from benign conditions such as endometriosis. This makes it valuable in premenopausal women, where false-positive CA-125 elevation is common. However, HE4 interpretation requires caution in women with renal impairment, older age, or other factors that may influence serum levels.

ROMA score provides a more integrated biomarker-based risk estimate by combining HE4, CA-125, and menopausal status. It generally improves combined diagnostic discrimination and can support preoperative classification of adnexal masses. This has practical value because appropriate referral to gynecologic oncology services can improve surgical planning and management.

A key finding is that these tools should not be used as stand-alone screening tests in asymptomatic average-risk women. Most included studies evaluated women with known adnexal masses or suspected ovarian malignancy, not general screening populations. Therefore, their results are most applicable to diagnostic evaluation and preoperative triage rather than population-level screening.

Early-stage detection remains a major challenge. Although HE4 and ROMA may improve diagnostic performance compared with CA-125 alone, none of the evaluated biomarkers provides sufficient sensitivity and specificity for independent early detection. Future diagnostic strategies should integrate biomarkers with imaging, symptoms, genetic risk, and advanced predictive modeling.

Limitations

This review has several limitations. First, included studies were heterogeneous in design, population, cutoff values, assay platforms, and reference standards. Second, many studies were conducted in tertiary referral or surgical populations, which may overestimate diagnostic performance. Third, early-stage epithelial ovarian cancer was underrepresented in several studies. Fourth, not all studies reported results 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 research should focus on:

1. Large prospective multicenter studies.
2. Standardized HE4 and CA-125 assay platforms.
3. Uniform ROMA cutoff reporting.
4. Separate analysis by menopausal status.
5. Stage-specific diagnostic accuracy reporting.
6. Histological subtype-specific analysis.
7. Adjustment for renal function, age, and smoking status.
8. Comparison with ultrasound-based models.
9. Integration of biomarkers with genetic and clinical risk models.
10. Evaluation of outcomes after biomarker-guided referral.

CONCLUSION

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

Despite these advantages, none of these approaches should be used as an independent 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.

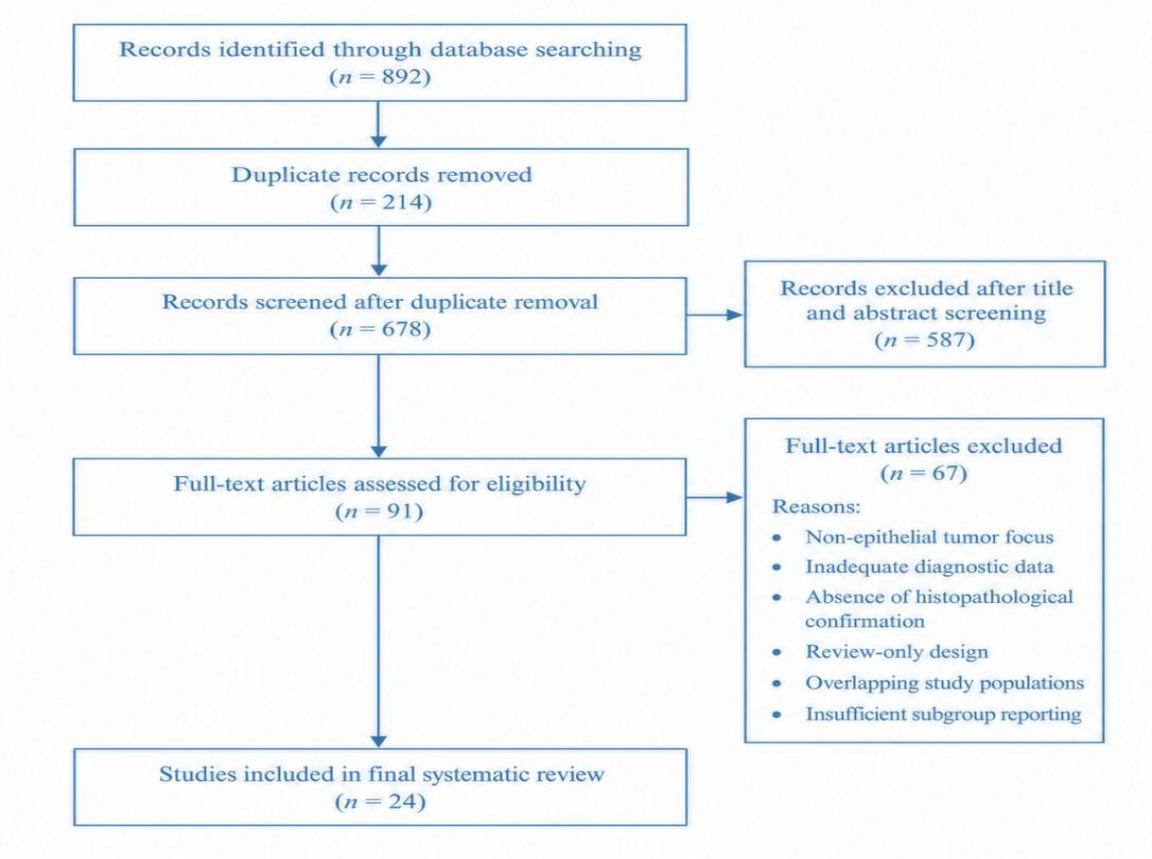

Figure 1. PRISMA 2020 Flow Diagram of Study Selection. The Flow Diagram Summarizes the Identification, Screening, Eligibility Assessment, and Inclusion of Studies Evaluating HE4, CA-125, and ROMA Score in Epithelial Ovarian Cancer Diagnosis

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