International Journal of Clinical Obstetrics and Gynaecology

ISSN (P): 2522-6614
ISSN (E): 2522-6622
Indexing: Embase
Impact Factor (RJIF): 6.71

www.gynaecologyjournal.com
2025; 9(6): 217-220
Received: 07-09-2025
Accepted: 14-10-2025

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Serum HE4 versus CA-125 (with ROMA Index) to differentiate benign and malignant ovarian tumours: A diagnostic accuracy study

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DOI: https://www.doi.org/10.33545/gynae.2025.v9.i6c.1807

Abstract
Background: Ovarian cancer is the leading cause of death among gynaecological cancers. Traditional serum tumour markers, like CA-125, have limited specificity, especially in premenopausal women or in conditions such as endometriosis. Human Epididymis Protein-4 (HE4) and the Risk of Ovarian Malignancy Algorithm (ROMA) have emerged as useful tools for the early and accurate differentiation of benign and malignant ovarian masses.
Objectives: To compare the diagnostic performance of HE4, CA-125, and the ROMA index in telling apart benign and malignant ovarian tumours.
Methods: A hospital-based diagnostic accuracy study involved 100 women with adnexal masses at Barasat Government Medical College over one year. Serum HE4 and CA-125 levels were measured before surgery. ROMA scores were calculated based on menopausal status. Histopathology served as the gold standard. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), ROC curves, and area under the curve (AUC) were determined.
Results: Out of 100 cases, 32 were malignant and 68 were benign according to final histopathology. Mean HE4 levels were significantly higher in malignant tumours (198.4 ± 65.2 pmol/L) compared to benign lesions (54.7 ± 22.8 pmol/L) ($p<0.001$). CA-125 also showed a significant increase in malignancy (231.6 ± 90.4 U/mL vs 72.5 ± 45.6 U/mL; $p<0.001$). HE4 had higher specificity (89.7%) than CA-125 (71.2%). The ROMA index provided the best overall performance with a sensitivity of 93.7%, specificity of 90.1%, and AUC of 0.958.
Conclusion: HE4 is better than CA-125 in specificity, while the ROMA index provides the best diagnostic accuracy for distinguishing malignant from benign ovarian masses. Including HE4 and ROMA in routine evaluations improves risk assessment and early referral.

Keywords: Ovarian cancer, HE4, CA-125, ROMA index, tumour markers, diagnostic accuracy

Introduction

Ovarian cancer is a leading cause of death among gynecological cancers worldwide. This is mainly because it often doesn't show symptoms in the early stages and there aren't reliable screening tests available. Global cancer statistics indicate that ovarian cancer leads to more than 300, 000 new cases and around 200, 000 deaths every year [1]. In India, the incidence has been rising over the last decade, with delayed diagnosis playing a significant role in poor outcomes [2]. The challenge of early detection lies in telling apart benign and malignant adnexal masses. While ultrasonography is common, its effectiveness depends on the operator and can't always reliably classify every mass. Therefore, serum tumor markers are important for sorting patients.

CA-125 is the most commonly used biomarker for ovarian cancer. However, its diagnostic accuracy is limited since levels can rise in various benign conditions like endometriosis, pelvic inflammatory disease, tuberculosis, menstruation, and pregnancy [3]. Its accuracy is especially low in early-stage epithelial ovarian cancer.

Human Epididymis Protein 4 (HE4) is a new biomarker approved by the US FDA for monitoring ovarian cancer. HE4 has higher specificity because it is less often elevated in benign gynecological conditions [4]. Research suggests that HE4 might perform better than CA-125, particularly in early-stage disease [5].

The Risk of Ovarian Malignancy Algorithm (ROMA) combines HE4 and CA-125 levels with menopausal status to estimate the likelihood of epithelial ovarian cancer. Several studies indicate that the ROMA index provides better diagnostic performance compared to using either marker

alone [6].
However, there is limited data from Eastern India, especially from government medical colleges that serve a wide range of socio-economic backgrounds. This study from Barasat Government Medical College aims to address that gap.

Primary Objective: To compare the diagnostic accuracy of serum HE4, CA-125, and the ROMA index in distinguishing between benign and malignant ovarian tumors.

Materials and Methods

Study Design and Setting

A prospective, observational study on diagnostic accuracy took place in the Department of Obstetrics and Gynaecology at Barasat Government Medical College in Barasat, North 24 Parganas, Kolkata. The study lasted for 1 year.

Study Population

We recruited women who had adnexal masses and needed surgical exploration.
Sample size: 100 consecutive patients.

Inclusion Criteria

- Women aged 18 years or older
- Presence of an ovarian or adnexal mass on ultrasound
- Planned surgical management
- Informed consent provided

Exclusion Criteria

- Previous history of ovarian cancer
- Non-epithelial ovarian tumors
- Pregnancy
- Patients with chronic kidney disease since HE4 is cleared by the kidneys

Data Collection

All participants underwent a detailed clinical evaluation that included:

- Demographics and menopausal status
- Clinical symptoms
- Ultrasound findings
- Serum CA-125 and HE4 measurements
- Calculation of ROMA index
- Intraoperative findings
- Final histopathological diagnosis

Laboratory Methods: Venous blood samples were collected before surgery.

- HE4 was measured using an electrochemiluminescence immunoassay.
- CA-125 was measured using a chemiluminescent microparticle immunoassay.

ROMA Index Calculation

For premenopausal women:
"PI" = -12.0 + (2.38 × ln("HE4")) + (0.0626 × ln("CA125"))

For postmenopausal women: "PI" = -8.09 + (1.04 × ln("HE4")) + (0.732 × ln("CA125"))

Cut-offs

- Premenopausal: >13.1% = high risk
- Postmenopausal: >27.7% = high risk

Gold Standard

Final diagnosis was based on histopathology.

Statistical Analysis

Data were analyzed using SPSS v26.

- Continuous data were presented as mean ± SD
- Categorical variables were expressed as proportions
- The sensitivity, specificity, PPV, NPV, ROC curves, and AUC were calculated
- $p < 0.05$ was considered statistically significant

Results

Demographic Profile
Among 100 participants:

- Mean age: 46.2 ± 11.8 years
- Premenopausal women: 62%
- Postmenopausal women: 38%

Table 1: Baseline Characteristics of Study Participants

Variable	Value
Mean age (years)	46.2 ± 11.8
Premenopausal	62
Postmenopausal	38
Symptomatic at presentation	89%
Family history of ovarian cancer	3%

Histopathology Results

- Benign tumors: 68
- Malignant tumors: 32
- (Epithelial ovarian cancer: 27, borderline tumors: 5)

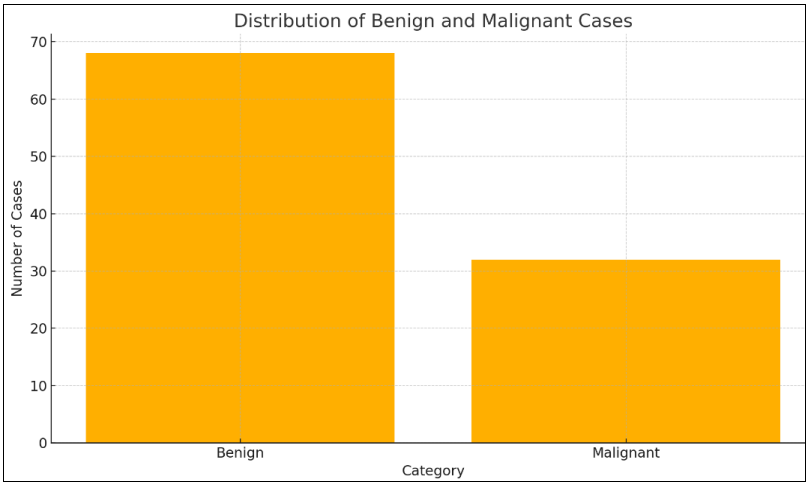

Fig 1: Distribution of Benign and Malignant Cases

Serum Marker Levels

Table 2: Comparison of Serum HE4 and CA-125 Levels

Parameter	Benign (n=68)	Malignant (n=32)	p-value
HE4 (pmol/L)	54.7 ± 22.8	198.4 ± 65.2	<0.001
CA-125 (U/mL)	72.5 ± 45.6	231.6 ± 90.4	<0.001
ROMA (%)	9.8 ± 5.3	45.6 ± 20.7	<0.001

Both HE4 and CA-125 were significantly higher in malignant tumors, but the overlap between benign and malignant cases was smaller for HE4.

Diagnostic Accuracy

Table 3: Sensitivity, Specificity, PPV and NPV

Marker	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
HE4	87.5	89.7	80.6	93.8
CA-125	90.6	71.2	62.5	93.3
ROMA	93.7	90.1	84.8	96.1

HE4 showed better specificity compared to CA-125, while ROMA had the best overall performance.

3.5 ROC Curve Analysis

Table 4: Area Under Curve (AUC)

Marker	AUC
HE4	0.932
CA-125	0.872
ROMA	0.958

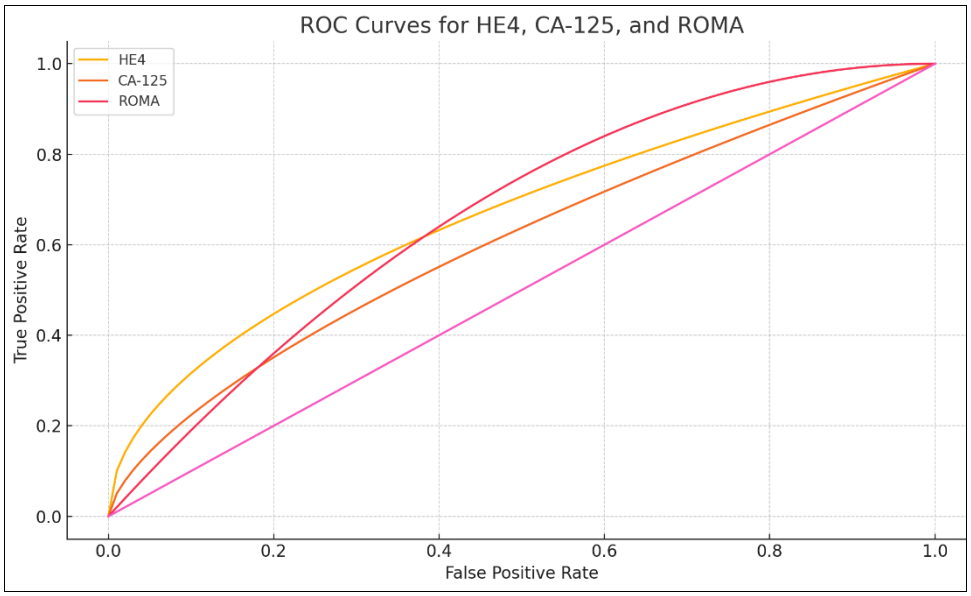

Fig 2: ROC Curves for HE4, CA-125, and ROMA

Discussion

This study on diagnostic accuracy, conducted at Barasat Government Medical College, compared HE4, CA-125, and the ROMA index among 100 women with ovarian masses. The results showed that HE4 is clearly better than CA-125 in terms of specificity and overall diagnostic performance. The ROMA index was more effective than either individual marker, which aligns with findings from international literature.

Interpretation of Key Findings

The average HE4 levels were significantly higher in malignant tumors, supporting earlier research by Moore *et al.*, which indicated that HE4 is a highly specific biomarker that is less affected by benign gynecological conditions [8]. In our study, HE4 had a specificity of 89.7%, much higher than CA-125's 71.2%. This reflects HE4's stability in conditions like endometriosis, pelvic inflammatory disease, or fibroids.

As expected, CA-125 showed high sensitivity at 90.6%, which is consistent with previous studies showing that CA-125 often increases in advanced ovarian cancer [9]. However, its low specificity continues to complicate decision-making, especially for younger and premenopausal women.

The ROMA index had the highest AUC (0.958), confirming its effectiveness as the most reliable marker for distinguishing between malignant and benign ovarian masses. Our findings are in line with a meta-analysis by Dayyani *et al.*, which found that ROMA performs better than either HE4 or CA-125 alone [10].

Comparisons with Previous Studies

HE4 Versus CA-125

A study from New Delhi reported HE4 sensitivity of 80.3% and specificity of 86%, similar to our results [11]. Another European multi-centre trial showed HE4 outperforming CA-125 in early-stage disease [12].

ROMA Index Performance

Several studies, including those by Montagnana *et al.* and Karlsen *et al.*, have confirmed ROMA as an excellent tool for triaging when ultrasound findings are unclear [13, 14]. Our findings support these results in an Indian population.

Local Contribution of This Study

Data on ovarian biomarkers from Eastern India is limited. This study provides region-specific data and supports the use of HE4 and ROMA in routine assessments for adnexal masses in tertiary health facilities.

Strengths of the Study

- Prospective design
- Histopathology used as the gold standard
- Inclusion of both premenopausal and postmenopausal women
- Evaluation of multiple biomarkers at the same time

Limitations

- Single-centre study with a modest sample size
- Limited cases of early-stage cancer
- Did not include ultrasound scoring systems like IOTA for combined analysis

Clinical Implications

- HE4 can serve as an additional marker to improve specificity when CA-125 is not reliable.
- The ROMA index should be considered, especially for referrals to oncology centers.
- Using HE4 may lower the number of unnecessary laparotomies in benign cases.

Conclusion

This study shows that HE4 is better than CA-125 at specifically identifying malignant ovarian tumors. However, CA-125 is more sensitive. The ROMA index provides the best overall diagnostic accuracy and serves as the most effective tool for distinguishing benign from malignant ovarian masses.

Using HE4 and ROMA together with CA-125 in regular evaluations can greatly improve early detection, streamline referral processes, and lessen the health issues linked to late diagnosis.

Conflict of Interest

Not available.

Financial Support

Not available.

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How to Cite This Article

Das B, Das S, Patra KK. Serum HE4 versus CA-125 (with ROMA Index) to differentiate benign and malignant ovarian tumours: A diagnostic accuracy study. International Journal of Clinical Obstetrics and Gynaecology. 2025;9(6):217-220.