ACCSCIENCE PUBLISHING

Eurasian Journal of Medicine and Oncology

ORIGINAL RESEARCH ARTICLE

# Diagnostic performance of human epididymis protein 4 in predicting occult endometrial carcinoma among women with endometrial intraepithelial neoplasia

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## Abstract

**Introduction**: Endometrial intraepithelial neoplasia (EIN) carries a substantial risk of concurrent occult endometrial carcinoma. Accurate preoperative risk assessment is important for appropriate surgical planning

**Objective**: To assess the diagnostic accuracy of serum human epididymis protein 4 (HE4) in identifying occult endometrial carcinoma in women with EIN, compare its performance with cancer antigen 125 (CA-125) and the Risk of Ovarian Malignancy Algorithm (ROMA) index, and assess the value of integrating clinical, ultrasonographic, histopathological, and biomarker variables into a preoperative prediction model.

**Methods**: This retrospective study included 113 women with histologically confirmed EIN who underwent hysterectomy between 2019 and 2025. Clinical, ultrasonographic, histopathological, and biomarker data, including serum CA-125, HE4, and ROMA, were evaluated. Diagnostic performance was assessed using receiver operating characteristic analysis, and independent predictors were identified by multivariable logistic regression.

**Results**: Occult endometrial carcinoma was identified in 46/113 women (40.7%). Malignant postoperative findings were associated with age > 50 years, obesity, postmenopausal status, endometrial thickness >10 mm, and high-risk preoperative histopathology. HE4 showed the highest diagnostic performance (area under the curve [AUC] = 0.912; 95% confidence interval [CI]: 0.832–0.961; $p < 0.001$), compared with ROMA (AUC = 0.846) and CA-125 (AUC=0.563). High-risk preoperative histopathology (odds ratio = 31.85; 95% CI: 8.71–116.42; $p < 0.001$) and HE4 (OR = 4.53 per 50 pmol/L increase; 95% CI: 1.86–11.02; $p = 0.001$) were independent predictors. The final model demonstrated excellent discrimination (AUC = 0.951), with 84.8% sensitivity, 97.0% specificity, and 92.0% accuracy.

**Conclusion**: HE4 outperformed CA-125 and ROMA and remained an independent predictor of occult carcinoma. Integrating HE4 with clinicopathological variables may improve preoperative risk stratification and surgical decision-making in women with EIN.

***Keywords:*** Endometrial intraepithelial neoplasia; Occult endometrial carcinoma; Human epididymis protein 4; Cancer antigen 125; Risk of Ovarian Malignancy Algorithm index; Logistic regression; Risk prediction

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**Citation:** Mammadova A, Jafarova G. Diagnostic performance of human epididymis protein 4 in predicting occult endometrial carcinoma among women with endometrial intraepithelial neoplasia. *Eurasian J Med Oncol*. doi: 10.36922/EJMO026340435

**Received:** August 18, 2026

**Revised:** September 12, 2026

**Accepted:** September 23, 2026

**Published online:** October 22, 2026

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## 1. Introduction

Endometrial intraepithelial neoplasia (EIN) is a clinically significant premalignant condition and a recognized precursor of endometrioid endometrial carcinoma. Although not all EIN cases progress to carcinoma, the risk is substantially higher than that associated with benign endometrial conditions, warranting definitive management in women who have completed childbearing.[1-3] Although hysterectomy is the established definitive treatment for EIN, final histopathological assessment may unexpectedly identify an endometrial carcinoma that was not detected preoperatively.[4-6] Recent evidence indicates that occult carcinoma is identified in approximately 40%–50% of women undergoing surgery for EIN, highlighting the limitations of preoperative endometrial sampling and the need for more accurate methods of risk stratification before definitive surgical treatment.[4-7]

Reliable preoperative identification of concurrent endometrial carcinoma is clinically important because it may influence the extent of surgery, the need for intraoperative frozen-section assessment, lymph node evaluation, and preoperative patient counseling. Over 20 years, the cumulative risk of endometrial carcinoma was below 5% among women with non-atypical endometrial hyperplasia, but reached 28% in those with atypical hyperplasia.[8,9] However, distinguishing isolated EIN from occult carcinoma before hysterectomy remains challenging. Conventional clinical and imaging parameters, including age, menopausal status, obesity, diabetes mellitus, and endometrial thickness, have been associated with an increased risk of concurrent carcinoma, but their individual diagnostic performance is insufficient for accurate clinical decision-making.[3,10,11]

In recent years, increasing attention has been directed toward serum biomarkers as adjunctive tools for the preoperative evaluation of women with suspected endometrial malignancy. Human epididymis protein 4 (HE4), a secretory glycoprotein encoded by the *WFDC2* gene, is overexpressed in several gynecologic malignancies and has emerged as one of the most promising biomarkers in endometrial cancer.[12-14] Elevated HE4 concentrations have been associated with advanced stage, extensive myometrial infiltration, lymphovascular involvement, nodal metastasis, and poorer oncological outcomes. Compared with cancer antigen 125 (CA-125), HE4 generally demonstrates superior specificity and is less frequently influenced by benign gynecological conditions, making it an attractive candidate for preoperative risk assessment.[15-17]

Although the diagnostic value of HE4 has been extensively investigated in patients with established endometrial carcinoma, evidence regarding its usefulness in women with EIN remains limited. Most published studies have evaluated HE4 in heterogeneous populations of endometrial cancer patients, whereas relatively few have specifically examined its ability to identify occult carcinoma among women initially diagnosed with EIN. Moreover, comparative data evaluating HE4 alongside CA-125 and the Risk of Ovarian Malignancy Algorithm (ROMA) in this clinical setting remain scarce.[18,19]

Given the substantial proportion of women with EIN who are subsequently diagnosed with concurrent carcinoma, identifying a reliable biomarker capable of improving preoperative risk assessment could facilitate more individualized surgical planning and optimize perioperative management.[20,21] Therefore, further evaluation of HE4 as a diagnostic biomarker in this patient population is warranted.

The aim is to assess the diagnostic accuracy of serum HE4 in identifying occult endometrial carcinoma in women with EIN, compare its performance with CA-125 and the ROMA index, and assess the value of integrating clinical, ultrasonographic, histopathological, and biomarker variables into a preoperative prediction model.

## 2. Materials and methods

### 2.1. Study population and research design

We retrospectively analyzed 113 consecutive women with histologically confirmed EIN who received surgical management at the Oncology Clinic of Azerbaijan Medical University between January 2019 and December 2025. For biomarker comparisons, a control group of 28 healthy women without endometrial pathology was also included.

Eligible patients were aged ≥ 18 years and had a preoperative diagnosis of EIN confirmed by endometrial sampling, complete clinical and laboratory records, available transvaginal ultrasonography findings, and definitive postoperative histopathological evaluation. Patients with a previous diagnosis of endometrial carcinoma, other gynecologic malignancies, neoadjuvant hormonal or oncologic treatment, or incomplete clinical data were excluded.

The research was conducted in accordance with the ethical principles of the Declaration of Helsinki and received approval from the local ethics committee.

### 2.2. Clinical and ultrasonographic assessment

Demographic and clinical characteristics were extracted from medical records, including age, menopausal status, body mass index (BMI), gynecological history, infertility, hypertension, diabetes mellitus, thyroid disease, and

abnormal uterine bleeding. BMI was categorized according to World Health Organization criteria. Endometrial thickness was measured preoperatively using transvaginal ultrasonography and was evaluated as a continuous measure as well as across clinically relevant categories (<5 mm, 5–10 mm, and >10 mm).

### 2.3. Histopathological evaluation

Endometrial tissue obtained before surgery by biopsy or uterine curettage was reviewed to establish the initial histopathological diagnosis. After hysterectomy, all resected uterine specimens were examined according to routine pathological protocols, and the final diagnosis was based on the postoperative histopathological assessment.

For analytical purposes, the preoperative histopathological diagnosis was stratified into two categories reflecting the estimated probability of underlying carcinoma. The low-risk group comprised benign endometrial lesions, whereas the high-risk group included premalignant lesions, primarily EIN.

The study endpoint was defined as histopathological confirmation of occult endometrial carcinoma in the hysterectomy specimen. Accordingly, the final postoperative diagnosis was categorized as either non-malignant pathology or occult endometrial carcinoma.

### 2.4. Biomarker assessment

Peripheral venous blood samples were obtained before surgery. Serum CA-125 concentrations were measured using the Cobas e411 automated analyzer (Roche Diagnostics, Switzerland). HE4 concentrations were determined using the Fujirebio HE4 EIA assay (cat no.:404-10, Fujirebio Inc., Japan) on a Stat Fax 304 semi-automated analyzer. The ROMA index was calculated according to the manufacturer's recommendations using CA-125, HE4, and menopausal status.

### 2.5. Development of the prediction model

Potential predictors of occult endometrial carcinoma included age, menopausal status, BMI, endometrial thickness, preoperative histological risk category, CA-125, HE4, and ROMA index. Initially, univariable analyses were conducted to determine which variables were related to adverse postoperative pathology. Variables showing statistical significance or clinical relevance were then included in multivariable logistic regression models. The analyses yielded odds ratios (ORs) with corresponding 95% confidence intervals (CIs).

The final multivariable prediction model was developed using clinical, ultrasonographic, histological, and biomarker variables. Predicted probabilities were calculated using logistic regression coefficients.

### 2.6. Statistical analysis

The IBM Statistical Package for Social Sciences software, version 26.0 (IBM Corp., United States), was used for all statistical analyses. Continuous variables were summarized according to their distribution as mean ± standard deviation or median with interquartile range (IQR), whereas categorical variables were expressed as frequencies and percentages. Group differences for continuous variables were evaluated using Student's *t*-test or the Mann–Whitney *U* test, while categorical variables were compared using the $\chi^2$ test or Fisher's exact test.

The diagnostic utility of HE4, CA-125, and the ROMA index was assessed by receiver operating characteristic (ROC) curve analysis. Diagnostic accuracy was summarized using the area under the curve (AUC), with optimal cut-off points determined according to the Youden index, together with sensitivity, specificity, positive predictive value, and negative predictive value. Logistic regression was applied at both the univariable and multivariable levels to determine factors independently associated with occult endometrial carcinoma. The findings are reported as ORs together with their corresponding 95% CIs. A two-sided $p$-value < 0.05 was considered indicative of statistical significance.

## 3. Results

### 3.1. Clinical features of the study participants

A total of 113 women with histologically confirmed EIN who had received definitive surgical treatment were enrolled in the study. The median age of the study population was over 50 years, with 87 women (77.0%) aged >50 years and 26 (23.0%) aged ≤50 years. Most patients were postmenopausal (73.5%), whereas 26.5% were premenopausal.

Excess body weight was common in the study population. Overall, 64 patients (56.6%) were overweight or obese, including 47 (41.6%) with obesity (BMI 30–40 kg/m$^2$) and 17 (15.0%) with morbid obesity (BMI >40 kg/m$^2$). Hypertension and diabetes mellitus were present in 38.4% and 34.8% of patients, respectively.

Preoperative transvaginal ultrasonography demonstrated an endometrial thickness >10 mm in 76 patients (67.3%), whereas 29 (25.7%) had an endometrial thickness of 5–10 mm and only 8 (7.1%) had an endometrial thickness <5 mm. Table 1 presents the baseline demographic and clinical profile of the study participants.

Postoperative histopathological examination identified occult endometrial carcinoma in 46 women (40.7%), while 67 patients (59.3%) had non-malignant postoperative

findings (Figure 2).

**Table 1. Baseline clinical, ultrasonographic, and preoperative histological characteristics of patients with endometrial intraepithelial neoplasia (*n* = 113)**

| Variable | Category | *n* | % |
|---|---|---|---|
| Age | ≤50 years | 26 | 23.0 |
| | >50 years | 87 | 77.0 |
| Menopausal status | Premenopausal | 30 | 26.5 |
| | Postmenopausal | 83 | 73.5 |
| Body mass index (BMI) | 20–25.9 kg/m² | 22 | 19.5 |
| | 26–29.9 kg/m² | 27 | 23.9 |
| | 30–40 kg/m² | 47 | 41.6 |
| | >40 kg/m² | 17 | 15.0 |
| Hypertension | Present | 43 | 38.4 |
| | Absent | 70 | 61.6 |
| Diabetes mellitus | Present | 39 | 34.8 |
| | Absent | 74 | 65.2 |
| Thyroid disease | Present | 16 | 14.3 |
| | Absent | 97 | 85.7 |
| Infertility history | Present | 11 | 9.7 |
| | Absent | 102 | 90.3 |
| Breast cancer history | Present | 7 | 6.2 |
| | Absent | 106 | 93.8 |
| Ovarian cancer history | Present | 1 | 0.9 |
| | Absent | 112 | 99.1 |
| Endometrial thickness | <5 mm | 8 | 7.1 |
| | 5–10 mm | 29 | 25.7 |
| | >10 mm | 76 | 67.3 |
| Preoperative histology | Benign | 3 | 2.7 |
| | Endometrial intraepithelial neoplasia | 78 | 69.0 |
| | Endometrial intraepithelial neoplasia with suspicion of concurrent carcinoma | 31 | 27.4 |
| | Carcinoma suspected | 1 | 0.9 |
| Biopsy method | Pipelle biopsy | 16 | 14.2 |
| | Endometrial curettage | 96 | 85.0 |
| | Not performed | 1 | 0.9 |

Among the 46 patients with malignant postoperative histopathological outcomes, all tumors were endometrioid adenocarcinomas. Myometrial invasion was absent in 4 patients (8.7%), ≤50% in 21 (45.7%), and >50% in 21 (45.7%). Histological grade was G1 in 11 patients (23.9%), G2 in 18 (39.1%), and G3 in 16 (34.8%). Lymphovascular space invasion was present in 34 patients (73.9%). Most tumors were stage IA (22, 47.8%) or IB (20, 43.5%), while the remaining cases included stages IC, IIA, IIIA, and IIIC2 (1 patient each, 2.2%). No cervical involvement was observed, and lymph-node metastasis was identified in 1 patient (2.2%).

Patients with malignant postoperative histopathological findings were significantly older than those with non-malignant outcomes: 42 of 46 women (91.3%) were aged >50 years, compared with 45 of 67 (67.2%) in the non-malignant group ($p = 0.008$). Obesity (BMI ≥30 kg/m²) was present in 28 patients (60.9%) with malignant pathology versus 19 (28.4%) in the non-malignant group ($p = 0.002$). Likewise, an endometrial thickness >10 mm was observed in 39 patients (84.8%) with malignant findings compared with 37 (55.2%) in the non-malignant group ($p = 0.003$). High-risk preoperative histopathological findings were substantially more frequent in the malignant group (27/46, 58.7%) than in the non-malignant group (5/67, 7.5%; $p < 0.001$). Hypertension, diabetes mellitus, thyroid disease, infertility, and previous breast or ovarian cancer showed no significant differences between the groups (all $p > 0.05$).

### 3.2. Relationship between preoperative histopathological risk classification and postoperative outcomes

Based on the preoperative histopathological assessment, 81 women were classified as having low-risk lesions and 32 as having high-risk lesions. Among patients in the low-risk group, 61 (75.3%) had non-malignant postoperative histopathological findings, whereas occult endometrial carcinoma was identified in 20 (24.7%). In contrast, malignant postoperative pathology was confirmed in 27 of 32 women (84.4%) classified as high risk, while only 5 (15.6%) had non-malignant postoperative findings. Overall, malignant postoperative histopathological outcomes were identified in 46 of the 113 patients (40.7%).

The diagnostic performance of the preoperative histopathological risk classification demonstrated a sensitivity of 57.4% (95% CI: 43.3%–70.5%) and a specificity of 92.4% (95% CI: 83.5%–96.7%). The positive predictive value was 84.4% (95% CI: 68.2%–93.1%), the negative predictive value was 75.3% (95% CI: 64.9%–83.4%), and the overall diagnostic accuracy was 77.9% (95% CI: 69.4%–84.5%).

**Table 2. Detailed cross-tabulation of preoperative and postoperative histological diagnoses**

| Preoperative histological diagnosis | EIN not confirmed, *n* (%) | EIN confirmed, *n* (%) | EIN + EC, *n* (%) | Endometrioid adenocarcinoma, *n* (%) | Carcinoma *in situ*, *n* (%) | Total *n* (%) |
|---|---|---|---|---|---|---|
| Benign | 0 (0.0) | 2 (66.7) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 3 (100.0) |
| EIN | 44 (56.4) | 16 (20.5) | 6 (7.7) | 12 (15.4) | 0 (0.0) | 78 (100.0) |
| EIN with suspicion of concurrent carcinoma | 2 (6.5) | 2 (6.5) | 2 (6.5) | 25 (80.6) | 0 (0.0) | 31 (100.0) |
| Carcinoma suspected | 0 (0.0) | 1 (100.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (100.0) |
| Total | 46 (40.7) | 21 (18.6) | 8 (7.1) | 37 (32.7) | 1 (0.9) | 113 (100.0) |

Note: Percentages were calculated within each preoperative histological diagnosis group (row percentages). EIN + EC indicates EIN with concurrent endometrial carcinoma (EC).
Abbreviation: EIN: Endometrial intraepithelial neoplasia.

Patients classified as high risk preoperatively had 16.47-fold higher odds of malignant postoperative histopathological outcomes than those classified as low risk (OR = 16.47, 95% CI: 5.60–48.48; $p < 0.001$). Agreement between the preoperative risk classification and the final postoperative diagnosis was moderate (Cohen's $\kappa = 0.523$, 95% CI: 0.366–0.680; $p < 0.001$), with an overall agreement of 77.9%.

These findings indicate that preoperative histopathological assessment alone has high specificity but only moderate sensitivity for detecting occult endometrial carcinoma, supporting the integration of serum HE4 together with clinical and ultrasonographic variables to improve preoperative risk prediction.

### 3.3. Serum biomarker characteristics according to menopausal status

In the premenopausal subgroup, median serum CA-125 concentrations were 19.47 U/mL (IQR: 13.85–31.63) in women with EIN compared with 9.80 U/mL (IQR, 7.02–10.82) in healthy controls, representing a 1.99-fold increase ($p < 0.001$). Median HE4 concentrations increased from 43.55 pmol/L (IQR: 30.88–49.90) in controls to 62.05 pmol/L (IQR: 47.68–78.38) in patients with EIN, corresponding to a 42.5% increase ($p = 0.003$). Similarly, the median ROMA index increased from 5.39% (IQR: 2.38–7.08) to 11.76% (IQR: 6.42–19.54), representing a 2.18-fold increase ($p = 0.003$).

Among postmenopausal women, median HE4 concentrations were 108.90 pmol/L (IQR: 69.55–228.00) in patients with EIN and 64.30 pmol/L (IQR: 48.23–77.60) in healthy controls, corresponding to a 69.4% increase ($p < 0.001$). Likewise, the median ROMA index was 24.45% (IQR: 14.15–48.14) in patients and 13.95% (IQR: 11.06–16.53) in controls, representing a 75.3% increase ($p = 0.002$). In contrast, median CA-125 concentrations were only 10.3% higher in patients with EIN than in controls (17.49 [IQR: 11.62–24.93] vs. 15.85 [IQR: 12.00–18.12] U/mL), and this difference was not statistically significant ($p = 0.201$).

Within the EIN cohort, postmenopausal women had median HE4 concentrations 75.5% higher than premenopausal women ($p< 0.001$), while the median ROMA index was 2.08-fold higher ($p = 0.002$). Median CA-125 concentrations were 10.2% lower in postmenopausal women; however, the observed difference was not statistically significant ($p = 0.449$).

Baseline distributions of serum biomarker levels were first compared between patients with non-malignant and malignant postoperative histopathological outcomes. Because the biomarker distributions were non-normal, summary data are expressed as median values with IQRs, while differences between groups were assessed using the Mann–Whitney *U* test with Holm correction for multiple comparisons (Table 3).

The biomarker analyses were performed among the 113 women with EIN, including 46 with malignant and 67 with non-malignant postoperative histopathological outcomes. HE4 and the ROMA index were significantly higher in patients with malignant postoperative histopathological outcomes than in those with non-malignant findings

**Table 3. Comparison of serum biomarker levels according to postoperative histopathological outcome**

| Biomarker | Non-malignant outcome group, median (IQR) | Malignant outcome group, median (IQR) | Mann–Whitney *U* | *p*-value | Holm-adjusted *p*-value | Rank-biserial *r* |
|---|---|---|---|---|---|---|
| CA-125 | 17.18 (12.67) | 19.91 (23.20) | 1374.5 | 0.369 | 0.369 | 0.100 |
| HE4 | 66.35 (33.38) | 220.60 (229.85) | 322.0 | <0.001 | <0.001 | 0.792 |
| ROMA index | 14.19 (13.12) | 45.08 (34.19) | 518.0 | <0.001 | <0.001 | 0.661 |

Note: Values are presented as median (IQR), where IQR represents the interquartile range (Q3–Q1). A positive rank-biserial correlation coefficient (*r*) indicates higher biomarker levels in the malignant postoperative histopathological outcome group. As the three biomarkers were evaluated across identical outcome groups, the Holm correction was used to account for multiple testing.
Abbreviations: CA-125: Cancer antigen 125; HE4: Human epididymis protein 4; ROMA: Risk of Ovarian Malignancy Algorithm.

(both adjusted $p < 0.001$). HE4 showed the largest effect size (rank-biserial $r = 0.792$), followed by the ROMA index ($r = 0.661$), indicating large effects. In contrast, CA-125 did not differ significantly between the two groups ($p = 0.369$; adjusted $p = 0.369$) and demonstrated only a small effect size ($r = 0.100$).

The statistical significance of HE4 and the ROMA index remained unchanged after Holm correction for multiple comparisons.

Based on these findings, ROC curve analysis was subsequently conducted to compare the diagnostic capacity of CA-125, HE4, and the ROMA index in distinguishing malignant postoperative histopathological outcomes.

### 3.4. Diagnostic performance of serum biomarkers

Receiver operating characteristic curve analysis revealed that CA-125 had limited diagnostic value (AUC = 0.563, $p = 0.388$), while HE4 demonstrated the highest diagnostic performance (AUC = 0.912; 95% CI: 0.832–0.961; $p < 0.001$). The ROMA index also demonstrated strong discriminatory performance (AUC = 0.846; $p < 0.001$). These findings indicate that HE4 is the most informative biomarker for distinguishing patients with EIN from healthy controls (Figure 1; Table 4).

The evaluation of optimal cut-off points revealed notable differences in the diagnostic performance of CA-125, HE4, and the ROMA index. For CA-125, the optimal threshold was ≥25.98 U/mL, with a sensitivity of 36.2% and specificity of 80.0%, indicating its limited diagnostic value. For HE4, the optimal cut-off point was ≥113.80 pmol/L; at this level, the test demonstrated high diagnostic performance, with a sensitivity of 76.6%, specificity of 90.9%, positive predictive value of 85.7%, negative predictive value of 84.5%, and an overall accuracy of 85.0%, confirming its strong clinical utility. For the ROMA index, the optimal threshold was ≥33.36%, yielding a sensitivity of 70.2%, specificity of 89.2%, and a diagnostic accuracy of 81.3% (Table 5).

**Table 4. Diagnostic characteristics of CA-125, HE4, and the ROMA index in predicting malignant postoperative histopathological findings**

| Biomarkers | AUC | AUC (95% CI) | *p* |
|---|---|---|---|
| CA-125 | 0.563 | 0.436–0.664 | 0.388 |
| HE-4 | 0.912 | 0.832–0.961 | <0.001 |
| ROMA index | 0.846 | 0.749–0.912 | <0.001 |

Note: *p*-values were calculated to test the null hypothesis that the AUC equals 0.50 (no discriminatory ability).
Abbreviations: AUC: Area under the curve; CA-125: Cancer antigen 125; CI: Confidence interval; HE4: Human epididymis protein 4; ROMA: Risk of Ovarian Malignancy Algorithm.

### 3.5. Predictors of adverse postoperative histopathological outcomes

To identify factors associated with malignant postoperative histopathological outcomes, univariable logistic regression analyses were performed using demographic, clinical, ultrasonographic, histopathological, and serum biomarker variables.

Among the evaluated clinical variables, age > 50 years, postmenopausal status, postmenopausal bleeding, obesity (BMI ≥ 30 kg/m$^2$), and endometrial thickness >10 mm were significantly associated with malignant postoperative histopathological outcomes. Preoperative high-risk histopathological findings demonstrated the strongest clinicopathological association, increasing the odds of postoperative malignancy by 16.47–fold (OR = 16.47; 95% CI: 5.60–48.48; $p < 0.001$).

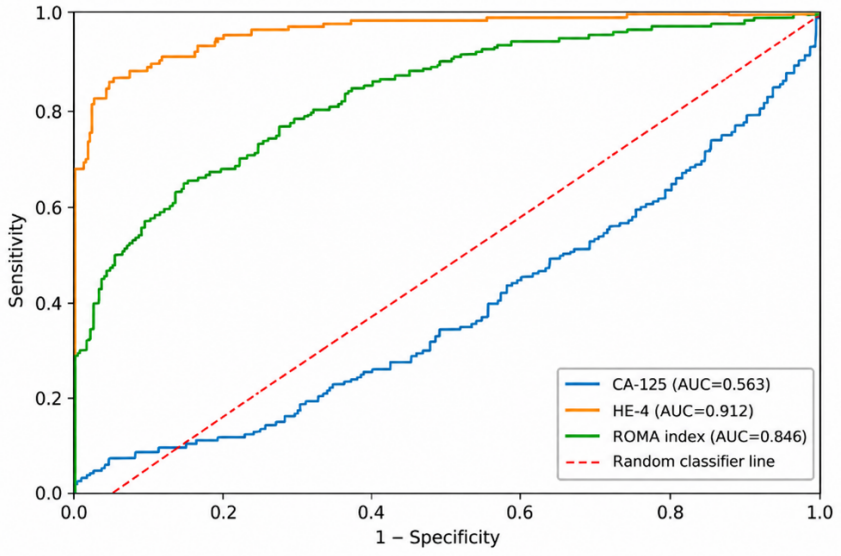



**Figure 1.** Receiver operating characteristic curves of CA-125, HE4, and the ROMA index for predicting malignant postoperative histopathological outcomes.
Abbreviations: CA-125: Cancer antigen 125; HE4: Human epididymis protein 4; ROMA: Risk of Ovarian Malignancy Algorithm.

**Table 5. The cut-off value reported for the ROMA index should be considered exploratory and is specific to the current study population.**

| Biomarker | Optimal cut-off value | Youden index | Sensitivity, % (95% CI) | Specificity, % (95% CI) | PPV, % | NPV, % | Overall accuracy, % |
|---|---|---|---|---|---|---|---|
| CA-125 | ≥25.98 U/mL | 0.162 | 36.2 (24.0–50.5) | 80.0 (68.7–87.9) | 56.7 | 63.4 | 61.6 |
| HE4 | ≥113.80 pmol/L | 0.675 | 76.6 (62.8–86.4) | 90.9 (81.6–95.8) | 85.7 | 84.5 | 85.0 |
| ROMA index | ≥33.36% | 0.594 | 70.2 (56.0–81.3) | 89.2 (79.4–94.7) | 82.5 | 80.6 | 81.3 |

Notes: Optimal cut-off values were established according to the Youden index. The cut-off value reported for the ROMA index should be considered exploratory and is specific to the current study population.
Abbreviations: CA-125: Cancer antigen 125; CI: Confidence interval; HE4: Human epididymis protein 4; NPV: Negative predictive value; PPV: Positive predictive value; ROMA: Risk of Ovarian Malignancy Algorithm.

Of the biomarkers examined, HE4 showed the strongest diagnostic performance. Patients with serum HE4 concentrations ≥113.80 pmol/L had 32.73-fold higher odds of malignant postoperative histopathological outcomes (95% CI: 11.15–96.10; $p < 0.001$), whereas a ROMA index ≥33.36% was linked to a 19.53-fold higher risk (95% CI: 7.16–53.24; $p < 0.001$). In contrast, CA-125 was not a significant predictor using either the conventional (>35 U/mL) or the ROC-derived (≥25.98 U/mL) cut-off values.

When analyzed as continuous variables, each 50 pmol/L increase in HE4 was linked to a 4.45-fold higher risk in the odds of malignant postoperative pathology (95% CI: 2.32–8.53; $p < 0.001$), whereas each 10% increase in the ROMA index increased the odds by 2.19-fold (95% CI: 1.64–2.93; $p < 0.001$). CA-125 was not significantly associated with the outcome ($p = 0.082$).

Variables that were statistically significant or clinically relevant in the univariable analyses were selected for inclusion in the multivariable logistic regression model.

In the final multivariable model, preoperative high-risk histopathology remained the strongest independent predictor of malignant postoperative histopathological

outcomes (OR = 31.85; 95% CI: 8.71–116.42; $p < 0.001$), while HE4 also retained independent significance, with each 50 pmol/L increase was linked to a 4.53-fold higher risk in the odds of postoperative malignancy (95% CI: 1.86–11.02; $p = 0.001$). Endometrial thickness >10 mm showed a borderline association ($p = 0.054$), whereas age >50 years and obesity did not remain independently associated with postoperative malignancy after accounting for the other variables

The final prediction model demonstrated excellent discriminatory performance, with an AUC of 0.951, indicating outstanding accuracy for identifying occult endometrial carcinoma (Figure 2A). Calibration analysis showed strong agreement between predicted and observed probabilities across the risk spectrum, supporting good model calibration (Figure 2B). The distribution of predicted probabilities further demonstrated clear separation between patients with non-malignant and malignant postoperative histopathological outcomes, with substantially higher predicted probabilities observed in the malignant group (Figure 2C).

The probability of malignant postoperative histopathological outcomes was estimated using the following logistic regression equation (**Equation 1**):

$$\begin{aligned}\text{Logit}(p) = {} & -6.048 + 0.456 \times (\text{Age} > 50 \text{ years}) \\ & + 0.536 \times (\text{BMI} \geq 30 \text{ kg/m}^2) + 0.981 \\ & \times (\text{endometrial thickness} > 10 \text{ mm}) \\ & + 3.461 \times (\text{Preoperative high-risk} \\ & \text{histopathology}) + 1.511 \times (\text{HE4}/50)\end{aligned} \quad (1)$$

In this equation, $p$ represents the predicted probability of malignant postoperative histopathological outcomes.

### 3.6. Comparative diagnostic performance of serum biomarkers

Among the evaluated serum biomarkers, HE4 consistently demonstrated the strongest diagnostic and predictive performance for identifying occult endometrial carcinoma in women with EIN. HE4 demonstrated excellent discrimination in ROC analysis (AUC = 0.912), a large effect size in group comparisons (rank-biserial correlation = 0.792; $p < 0.001$), and remained independently associated with the outcome after multivariable adjustment. Specifically, every 50 pmol/L increase in serum HE4 concentration was associated with a 4.53-fold increase in the odds of malignant postoperative histopathological outcomes (adjusted OR = 4.53; 95% CI: 1.86–11.02; $p = 0.001$), indicating that HE4 provides clinically meaningful information beyond conventional clinicopathological variables. A comparative summary of the diagnostic and predictive performance of the evaluated serum biomarkers is presented in Table 6. HE4 consistently outperformed both CA-125 and the ROMA index across ROC, effect-size, and regression analyses, whereas CA-125 showed limited discriminatory ability and no independent predictive value. Although the ROMA index also demonstrated good performance, its interpretation should be considered complementary because it incorporates HE4, CA-125, and menopausal status into a composite algorithm (Table 6).

The ROMA index also demonstrated good diagnostic performance (AUC = 0.846) and remained significantly associated with malignant postoperative outcomes in

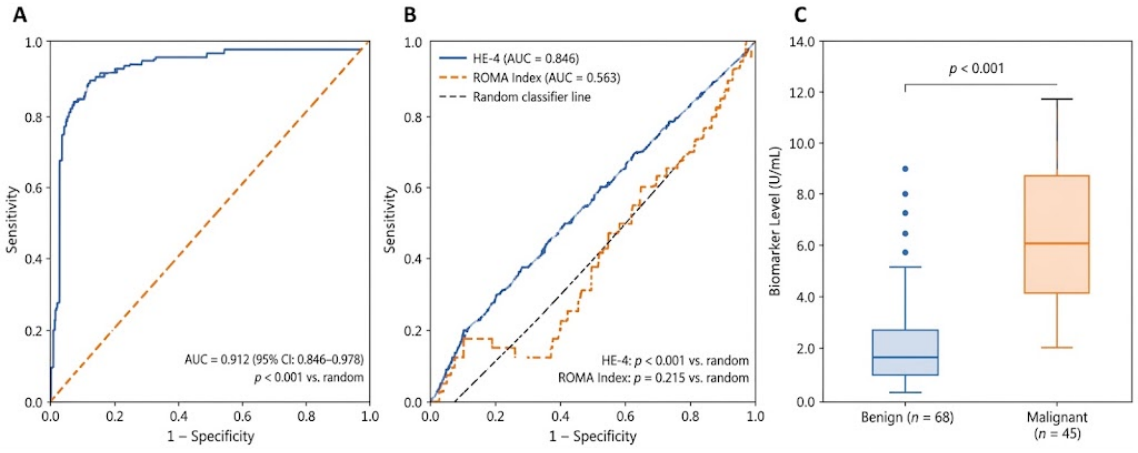



**Figure 2.** Performance of the multivariable HE4-based prediction model. (A) Receiver operating characteristic (ROC) curve. (B) Calibration plot comparing predicted and observed probabilities of occult endometrial carcinoma. (C) Distribution of predicted probabilities according to postoperative histopathological outcome.

Abbreviations: AUC: Area under the curve; CA-125: Cancer antigen 125; CI: Confidence interval; HE4: Human epididymis protein 4; ROMA: Risk of Ovarian Malignancy Algorithm.

both univariable and multivariable analyses. However, because the ROMA index incorporates HE4, CA-125, and menopausal status into a composite algorithm and laboratory-specific calibration is not yet fully standardized, its findings should be considered exploratory.

**Table 6. Comparative diagnostic and predictive performance of serum biomarkers for occult endometrial carcinoma**

| Parameter | CA-125 | HE-4 | ROMA index |
|---|---|---|---|
| Significant difference between postoperative outcome groups | No | Yes | Yes |
| Mann–Whitney *p*-value | 0.369 | <0.001 | <0.001 |
| Rank-biserial correlation (*r*) | 0.100 | 0.792 | 0.661 |
| ROC AUC | 0.563 | 0.912 | 0.846 |
| Diagnostic performance | Poor | Excellent | Good |
| Univariable OR (continuous variable) | 1.20 per 10 U/mL | 4.45 per 50 pmol/L | 2.19 per 10% increase |
| Univariable *p*-value | 0.082 | <0.001 | <0.001 |
| Adjusted OR (multivariable model) | 1.17 per 10 U/mL | 4.53 per 50 pmol/L | 2.02 per 10% increase |
| Multivariable *P* value | 0.367 | 0.001 | <0.001 |
| Incremental value beyond clinical variables | No | Yes | Yes |
| Overall clinical interpretation | Limited utility | Most informative biomarker | Complementary biomarker |

Abbreviations: AUC: Area under the curve; CA-125: Cancer antigen 125; CI: Confidence interval; HE4: Human epididymis protein 4; OR: Odds ratio; ROC: Receiver operating characteristic; ROMA: Risk of Ovarian Malignancy Algorithm.

In contrast, CA-125 showed limited clinical utility in this cohort. It showed no significant differences between postoperative outcome groups ($p$ = 0.369), demonstrated poor discriminatory ability (AUC = 0.563), and was not independently associated with malignant postoperative pathology in either univariable or multivariable analyses. These findings suggest that HE4 is the most informative individual serum biomarker for the preoperative detection of occult endometrial carcinoma among women diagnosed with EIN.

### 3.7. Performance of the final prediction model

The final HE4-based multivariable prediction model demonstrated excellent diagnostic performance for identifying occult endometrial carcinoma in women with EIN. The model yielded an area under the ROC curve (AUC) of 0.950, reflecting excellent discriminatory performance. Using the optimal probability threshold, sensitivity was 84.8%, and specificity was 97.0%, with a positive predictive value of 95.1%, a negative predictive value of 90.3%, and overall diagnostic accuracy of 92.0%. The calibration analysis showed strong agreement between predicted and observed probabilities. In addition, the predicted probability distributions showed clear differentiation between patients with malignant and non-malignant postoperative histopathological outcomes. Collectively, these findings indicate that the final prediction model provides excellent discrimination and reliable preoperative risk stratification for occult endometrial carcinoma.

## 4. Discussion

The present study evaluated the diagnostic value of serum HE4 for preoperative identification of occult endometrial carcinoma in women with EIN and developed a multivariable prediction model incorporating clinical, ultrasonographic, histopathological, and biomarker variables. The findings demonstrate that occult endometrial carcinoma is common among women with EIN and that serum HE4 provides superior diagnostic performance compared with CA-125 and the ROMA index. Furthermore, elevated HE4 concentrations and high-risk preoperative histopathological findings were identified as the strongest independent predictors of concurrent carcinoma. Integrating these variables into a multivariable prediction model yielded excellent diagnostic accuracy, supporting the clinical utility of this approach for individualized preoperative risk assessment and surgical decision-making.

Our results provide further evidence that a substantial proportion of women diagnosed with EIN or atypical endometrial hyperplasia have concurrent endometrial carcinoma identified at hysterectomy. Consequently, recent clinical recommendations emphasize careful preoperative assessment to exclude occult carcinoma before selecting surgical or fertility-sparing management.[22-24]

Our findings further demonstrated that obesity and increased endometrial thickness were associated with occult endometrial carcinoma in women with EIN, particularly in univariable analysis. This observation aligns with evidence that obesity plays a central role in the development and progression of endometrial neoplasia through endocrine, inflammatory, and metabolic

mechanisms, including chronic hyperestrogenism, insulin resistance, and adipokine dysregulation, all of which promote endometrial carcinogenesis. Obesity is among the most consistently reported risk factors for endometrial hyperplasia and carcinoma, with increasing BMI associated with progressively greater cancer risk.[25-27] In addition, increased endometrial thickness is an important ultrasonographic marker of malignant endometrial pathology. Recent studies based on the International Endometrial Tumor Analysis consensus have emphasized the value of standardized ultrasound assessment for improving the preoperative identification of high-risk endometrial lesions and supporting surgical planning.[28-30] The present findings therefore reinforce the importance of incorporating both BMI and endometrial thickness into comprehensive preoperative risk assessment models for women with EIN.

The superior performance of HE4 observed in the present study is in agreement with previous systematic reviews and meta-analyses demonstrating that HE4 has higher diagnostic specificity than CA-125 for endometrial carcinoma.[31,32] Elevated serum HE4 levels have been identified as an independent predictor of poorer recurrence-free and overall survival. HE4 may also provide greater sensitivity than CA-125 for detecting disease recurrence during follow-up, particularly in patients with high-risk uterine cancer who have a greater propensity for distant metastasis.[33-35] A comprehensive review by Bignotti *et al.*[36] concluded that HE4 is currently the most promising serum biomarker for endometrial cancer because it correlates with tumor stage, myometrial invasion, lymphovascular invasion, lymph node metastasis, and disease recurrence. Similarly, pooled analyses consistently report high specificity (approximately 90%) but only moderate sensitivity, supporting HE4 as an adjunct rather than a replacement for histopathological evaluation.[36]

Several recent studies have consistently shown that serum HE4 has greater diagnostic accuracy than CA-125 for detecting and preoperatively assessing endometrial carcinoma. In their comprehensive review, Behrouzi *et al.*[12] summarized evidence indicating that HE4 is a promising biomarker for identifying endometrial cancer and is associated with adverse clinicopathological features, including deep myometrial invasion, advanced International Federation of Gynecology and Obstetrics stage, lymph node involvement, and poorer prognosis. The authors further emphasized that HE4 may provide additional clinical value when interpreted alongside established clinicopathological and imaging findings rather than as a standalone biomarker.[12] Consistent with these observations, our study showed that HE4 provided the highest diagnostic performance among the biomarkers assessed and retained its independent predictive value for occult endometrial carcinoma in the multivariable model, supporting its incorporation into comprehensive preoperative risk assessment in women with EIN.[14]

These results also align with recent meta-analyses evaluating the diagnostic accuracy of HE4 in endometrial cancer. A 2024 systematic review of more than 9,000 women reported that HE4 achieved a pooled specificity of approximately **93%**, whereas sensitivity remained moderate, confirming that HE4 is particularly useful for identifying women at high risk of malignancy rather than excluding disease. Earlier meta-analyses reached similar conclusions, reporting pooled AUCs of 0.75 to 0.84 and consistently showing HE4's superior diagnostic performance compared with CA-125.[37]

The independent association between HE4 and occult endometrial carcinoma observed in the present study suggests that this biomarker provides clinically relevant information beyond conventional demographic, ultrasonographic, and histopathological variables. Further external validation and prospective evaluation are needed before biomarker-based approaches can be routinely implemented in clinical practice.[38] Importantly, integrating HE4 into a multivariable prediction model substantially improved the discrimination of patients at increased risk of concurrent carcinoma relative to the use of individual biomarkers These results are in line with increasing evidence that optimal preoperative risk assessment should rely on multimodal prediction models incorporating biochemical, clinical, and imaging parameters rather than isolated serum biomarkers.[12,13] Recent studies have examined different approaches to predicting concurrent or occult endometrial carcinoma before surgery in women with EIN or atypical endometrial hyperplasia. Lou *et al.*[13] developed a nomogram based on HE4, BMI, and menopausal status, while Zeevi *et al.*[39] developed a predictive model specifically for women with EIN using clinical and ultrasonographic variables. More recently, Wolff *et al.*[11] reported a model for occult carcinoma in women with atypical hyperplasia, in which age, obesity, hyperlipidemia, and biopsy-related factors were associated with the risk of carcinoma. Previous studies have incorporated clinical and ultrasonographic parameters, including endometrial thickness, into preoperative risk assessment in women with EIN.[40,41] In our study, these parameters were also associated with postoperative pathology in univariable analysis, while HE4 remained an independent predictor in the multivariable model. By integrating these clinical, ultrasonographic, histopathological, and biomarker variables, our model achieved good discriminatory

performance, with an AUC of 0.951. Such an approach may facilitate more individualized surgical planning, improve patient counseling, and support appropriate referral to gynecologic oncology services, particularly in women with EIN who are at increased risk of occult malignancy.

The study should be interpreted in light of several limitations. First, the investigation was performed at a single tertiary referral center and involved a relatively small cohort, which may limit the extent to which the results can be generalized to other patient populations. Second, external validation of the prediction model was not performed; therefore, the diagnostic performance should be confirmed in independent multicenter cohorts. Third, although ROMA demonstrated good diagnostic performance, it was excluded from the final multivariable model because of its mathematical dependence on HE4 and CA-125, which could introduce multicollinearity. Finally, serum biomarker concentrations were measured only before surgery, and longitudinal changes were not evaluated.

## 5. Conclusion

Serum HE4 showed good diagnostic performance for identifying occult endometrial carcinoma in women with EIN and performed better than CA-125. Preoperative high-risk histopathology and elevated HE4 were the strongest independent predictors of malignant postoperative histopathological outcomes. The final multivariable model combined age, BMI, endometrial thickness, preoperative histopathology, and HE4 to estimate the preoperative probability of occult carcinoma. In clinical practice, applying this model to routinely available preoperative data may help identify patients at increased risk of occult carcinoma, support surgical planning, and facilitate appropriate referral to a gynecologic oncology team when indicated. Before routine clinical use, the model should undergo external validation in larger, multicenter cohorts.

## Acknowledgments

None.

## Funding

None.

## Conflict of interest

The authors declare that they have no competing interests.

## Author contributions

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## Ethics approval and consent to participate

The research was conducted in accordance with the Declaration of Helsinki and the ethical requirements of the institutional research committee. Approval was obtained from the Ethics Committee of the Oncology Clinic of Azerbaijan Medical University (Protocol No. 8, dated 2022).

## Consent for publication

Not applicable.

## Availability of data

Data underlying the findings of this study can be obtained from the corresponding author upon reasonable request.

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