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Original Article

Clinical significance of human epididymis protein 4 (HE4), cancer antigen 125 (CA125), the risk of ovarian malignancy algorithm (ROMA), and Copenhagen index (CPH-I) for the diagnosis of endometrial carcinoma

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Abstract

Introduction: Endometrial carcinoma (EC) is the most common gynecological cancer among women, and in more than 90% of cases, the initial manifestation of the disease is postmenopausal bleeding. Unfortunately, despite early diagnosis and treatment, EC often recurs. Among the many serum tumor markers studied, human epididymis protein 4 (HE4) and cancer antigen 125 (CA125) show the most promise as tools for EC diagnosis, prognosis, and monitoring.

Aim: The aim of the current study was to evaluate the clinical usefulness of HE4 and CA125, tested either as single markers or in combination by including them in the Risk of Ovarian Malignancy Algorithms (ROMA) and in Copenhagen index (CPH-I).

Material and methods: In this retrospective study, 1262 women (74 with confirmed EC) were included. The patients with EC had significantly higher values for HE4, CA125, ROMA, and CPH-I ($p<0.001$) than the healthy women and patients with benign diseases. The subgroup analysis based on the histological type of EC revealed that the highest markers and algorithms were recorded in type II EC group.

Results: The ROC curve analysis showed that the best diagnostic performance for detecting EC among patients with benign diseases was the ROMA index (AUC=0.869; 95% CI: 0.818-0.920), followed by CPH-I (AUC=0.822; 95% CI: 0.757-0.887), and HE4 (AUC=0.816; 95% CI: 0.750-0.881). Tested alone, CA125 presented unsatisfactory results for this purpose. Both algorithms proved to have a correlation with the disease stage and progression better than the markers alone (HR=1.046 vs. HR=1.018).

Conclusion: In summary, the ROMA index, CPH-I, and, to a lesser extent, standalone HE4 testing can supplement imaging methods as reliable tools for diagnosing and distinguishing patients with EC from those with benign conditions. They have potential as prognostic markers for advanced disease and could help gynecological oncologists to develop a therapeutic strategy.

Keywords

gynecological malignancies, tumor markers

Introduction

Endometrial carcinoma (EC) is the most common gynecological cancer in women. Over the past 30 years, the number of newly diagnosed cases of EC has increased by over 55%, indicating an increasing trend in its prevalence. Its estimated incidence globally is 8.4/100,000.[1] Risk factors for endometrial carcinoma include obesity, type 2 diabetes, lack of physical activity, use of estrogen after menopause, increased life expectancy, and the pursuit of organ-preserving surgical treatment for benign uterine diseases.[2,3] Usually, the first clinical symptom is bleeding during the postmenopausal period. Clarke and colleagues[4] published data from a meta-analysis encompassing 129 studies with 40,790 women (6,358 of them with EC), according to which in 91% (95% CI, 87%-93%) of EC cases, postmenopausal bleeding was the initial clinical manifestation of the disease. The generalized risk for EC among patients with postmenopausal bleeding was determined to be 9% (95% CI, 8%-11%). This makes it possible to detect it early and achieve an 85% 5-year survival rate. Unfortunately, EC often recurs (in 13%-17% of cases), despite early diagnosis and timely treatment.[5]

Endometrial carcinoma is classified into two categories with different histology and prognosis:

- Type 1 includes the first and second stages of endometrioid endometrial carcinoma. Pathogenetically, it is associated with chronic estrogen stimulation and arises based on atypical hyperplasia. This type of EC is diagnosed relatively early and has a good prognosis.
- Type 2 consists of the third and fourth stages of endometrioid EC and non-endometrioid neoplasms, which develop based on atrophic mucosa and usually have a poorer prognosis – the recurrent EC has a 5-year survival rate of 15%-17%, regardless of treatment.

The diagnostic algorithm for detecting EC includes transvaginal ultrasound examination, endometrial biopsy and, in some cases, hysteroscopy. These examinations demonstrate good sensitivity but have poor specificity (ultrasound examination) or are invasive and painful for patients.[6] Therefore, different proteins, nucleic acids, or genetic expressions are being actively studied to improve the medical management of this disease, even though there are currently no established diagnostic or prognostic blood biomarkers for EC in clinical practice, nor predictive markers for response to systemic treatment or monitoring of recurrence.[7]

Human epididymis protein 4 (HE4) is an acidic whey protein, first isolated from the epithelium of the distal epididymis.[8] Its biological function is not fully understood, but studies report data that it is overexpressed in >90% of EC cases, accelerating tumor proliferation, invasion, and growth.[9,10] HE4 shows better sensitivity and specificity compared to the traditionally used tumor marker cancer antigen (CA125) for detecting EC, and it has been established that its concentration correlates with histopathological markers for disease severity, survival, and recurrence.[11] In a meta-analysis conducted by Li and colleagues[12] on 23 studies, HE4 had a pooled sensitivity of 65%, specificity of 91%, and an area under the curve (AUC) of 0.84 for diagnosing EC compared to a control group of healthy women and patients with benign disease. Similar results are reported by Liu et al. in a meta-analysis of 17 studies with a pooled sensitivity of 65%, specificity of 91%, and an AUC of 0.75.[13] Another meta-analysis by Li et al. that included data from 12 studies showed that HE4 was more capable of diagnosing EC patients than CA125.[14] The ability to make firm recommendations is limited by the substantial data heterogeneity found in all three of the cited meta-analyses.

Despite the promising results to date, the reported sensitivity of HE4 varies significantly between studies. Reasons for this may include a small number of included patients, a wide variety of cut-off values adopted by research teams, and the choice of different control groups in different studies, making comparisons challenging.

There is an intensive search for different diagnostic approaches and the combination of imaging methods with biomarker testing to improve the diagnosis and preoperative staging of EC.[15] There is no definitive answer to the question of whether the simultaneous determination of serum concentrations of CA125 and HE4 would have an advantage over their individual measurement. There are also few studies analyzing the applicability of diagnostic algorithms such as the Risk of Ovarian Malignancy Algorithm (ROMA) and the Copenhagen Index (CPH-I), established in epithelial ovarian carcinoma in patients with EC. Further research is needed to determine whether these or similar models could be validated for use and could have clinical significance in patients with EC.[16]

Aim

The aim of the present study was to assess the diagnostic reliability of the serum tumor markers HE4 and CA125, both individually and in combination, with their inclusion in the algorithms ROMA and CPH-I for the diagnosis of EC.

Materials and methods

Study design

A retrospective analysis was conducted on the demographic, anamnesis, clinical and laboratory indicators extracted from the electronic database of Acibadem City Clinic University Hospital Tokuda for the period 2012-2018. The study was approved by the local Ethics Committee for Scientific Research and was carried out in accordance with the requirements of the Declaration of Helsinki for ethics in science.

Patients

A total of 1,262 women aged 19-79 years were included, divided into the following groups:

- 246 healthy controls (124 premenopausal),
- 942 patients with benign pelvic masses (741 premenopausal),
- 74 patients with confirmed endometrial carcinoma (8 premenopausal).

Participants without complete medical documentation regarding hormonal status, renal function, and those with another malignant disease or inflammatory process at the time of the study were not included.

Quantitative determination of HE4 and CA125

The serum concentrations of HE4 and CA125 were measured using a chemiluminescent microparticle immunoassay (CMIA) on an analytical platform Architect 8200ci (Abbott Laboratories, USA). Blood samples were collected and processed according to the laboratory's standard operating procedure. Biological materials were taken and tested immediately on site; they were neither transported nor stored before analysis. The ROMA index was calculated by specialized software from Abbott Laboratories, integrated into the analytical platform. The CPH-I was calculated retrospectively for the purposes of the study using the calculator validated and published by Karlsen et al. in 2015.[17]

Statistical data processing

Statistical data processing was performed using the SPSS v. 25.0 statistical package. Values at a significance level of $p<0.05$ were considered statistically significant. ROC curves were modeled to assess diagnostic specificity and sensitivity, as well as to calculate positive and negative predictive values for certain tested indicators.

Results

Characteristics of the patient population

The EC group included women with the following histology types (**Fig. 1**):

- Endometrioid carcinoma (N=52),
- Leiomyosarcoma (N=4),
- Serous carcinoma (N=5),
- Clear cell carcinoma (N=2),
- Squamous carcinoma (N=5),
- Carcinoma without histological identification (N=6).

Diagnostic characteristics of the markers and algorithms for detecting EC

The medians and interquartile ranges (IQR) of HE4, CA125, ROMA, and CPH-I in patients with EC, with benign pelvic formations, and healthy controls are shown in **Table 1**.

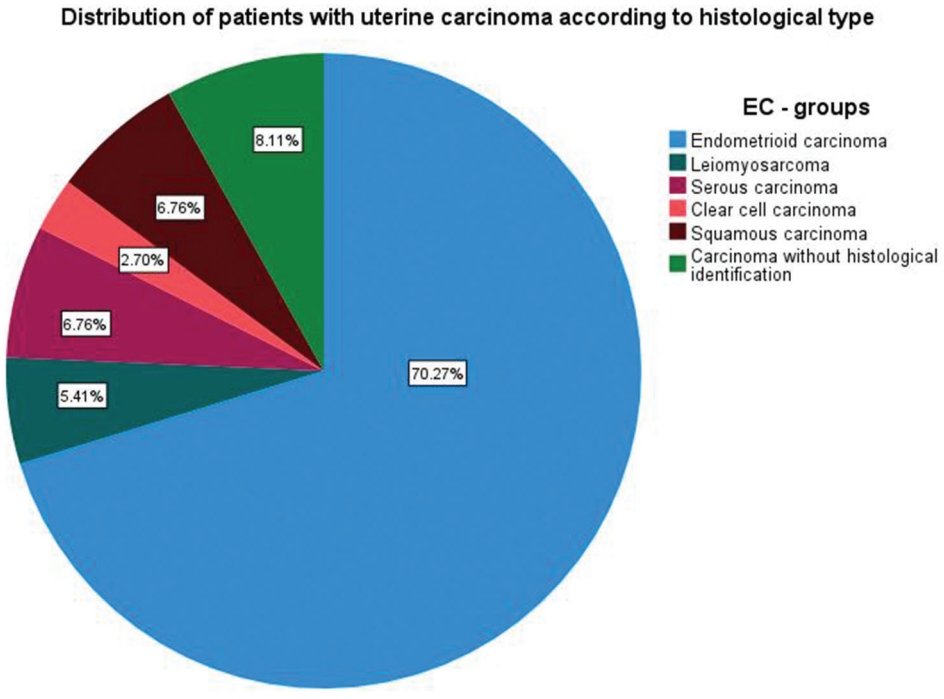

Figure 1. Distribution of patients with EC by histological type.

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Table 1. Median and IQR of HE4, CA125, ROMA, CPH-I in patients with EC, benign pelvic formations, and healthy control

Group	N	HE4 pmol/L	CA125 U/mL	ROMA %	CPH-I %
		Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
EC	74	98.8 (51.68-195.99)	30.25 (16.2-57.15)	29.53 (13.99-57.9)	8.81 (2.46-36.02)
Benign formations	942	42.35 (35.00-52.7)	18.10 (11.58-36.53)	5.76 (3.63-9.67)	1.03 (0.59-1.918)
Healthy controls	246	38.90 (33.50-47.43)	12.00 (8.25-17.05)	4.94 (3.27-7.39)	0.60 (0.39-1.00)

Patients with EC had significantly higher values of HE4 compared to the control group (98.80 vs. 38.90 pmol/L), U=2745.00, $p<0.001$, $r=-0.509$, and compared to patients with benign diseases (98.80 vs. 42.35 pmol/L), U=12855.00, $p<0.001$, $r=-0.284$ (**Table 1**). Like HE4, patients with EC had significantly higher values of CA125 compared to the control group (30.25 vs. 12.00 U/mL), U=2550.00, $p<0.001$, $r=-0.512$, and compared to patients with benign diseases (30.25 vs. 18.10 U/mL), U=25023.00, $p<0.001$, $r=-0.127$.

The values of the ROMA index in the EC group were significantly higher compared to the control group (29.53% vs. 4.94%), U=1393.50, $p<0.001$, $r=-0.623$, and compared to patients with benign diseases (29.53% vs. 5.76%), U=9148.00, $p<0.001$, $r=-0.332$. Similar results were observed for CPH-I – significantly higher in the EC cases compared to the control group (8.81% vs. 0.60%), U=1760.00, $p<0.001$, $r=-0.587$, and compared to patients with benign diseases (8.81% vs. 1.03%), U=12399.00, $p<0.001$, $r=-0.290$.

In a subgroup analysis according to the histological type of EC, the highest concentrations of biomarkers and algorithms were measured in the group of serous carcinomas (**Table 2**).

Patients with EC are usually categorized into one of two types – type I (endometrioid carcinoma in stages I and II) and type II (endometrioid carcinoma in stages III and IV and non-endometrioid carcinoma). We conducted such subgroup analysis in our patient cohort. The results are shown in **Table 3**.

The differences in HE4 values between type I and type II EC were statistically significant: U=232.00, $p=0.036$, $r=-0.269$. Patients with types I and II EC had significantly higher HE4 values compared to the control group (100.00 vs. 38.90 pmol/L), U=2032.00, $p<0.001$, $r=-0.503$, with statistical significance maintained in the subgroups: type I and type II – (78.30 vs. 38.90 pmol/L), U=1359.50, $p<0.001$, $r=-0.472$ and (240.95 vs. 38.90 pmol/L), U=673.00, $p<0.001$, $r=-0.272$.

The differences in the CA125 values between type I and type II EC were also statistically significant: U=180.50, $p=0.003$, $r=-0.377$. Compared to the control group, patients with types I and II EC had significantly higher CA125 val-

Table 2. Median and IQR of HE4, CA125, ROMA, CPH-I in histologically differentiated groups with endometrial cancer

Histology	N	HE4 (pmol/L)	CA125 (U/mL)	ROMA (%)	CPH-I (%)
		Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
Healthy controls	246	38.90 (33.50-47.43)	12.00 (8.25-17.05)	4.94 (3.27-7.39)	0.60 (0.39-1.00)
Endometrioid carcinoma	52	72.35 (47.90-160.85)	23.90 (14.95-45.37)	22.02 (12.30-46.27)	5.02 (1.73-27.97)
Leiomyosarcoma	4	100.75 (96.70-234.70)	105.75 (22.60-172.70)	35.74 (24.35-72.88)	17.96 (8.06-52.29)
Serous carcinoma	5	542.70 (105.00-1267.00)	429.70 (220.85-1154.55)	95.80 (56.58-98.01)	94.07 (29.82-98.19)
Clear cell carcinoma	2	29.10 (*)	11.75 (*)	3.27 (*)	0.40 (*)
Squamous carcinoma	5	170.50 (117.20-312.50)	48.60 (32.75-81.10)	52.30 (43.90-67.17)	27.09 (15.75-52.55)
Without histology	6	261.55 (88.50-437.80)	28.00 (19.43-122.18)	61.90 (24.52-69.45)	37.33 (5.72-45.40)

Table 3. Median and IQR of HE4, CA125, ROMA, CPH-I in patients with EC types I and II

Group	N	HE4 pmol/L	CA125 U/mL	ROMA %	CPH-I %
		Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
EC type I+ type II	61	100 (56.6-200.55)	30.75 (16.9-61.95)	31.37 (14.22-58.27)	9.6 (2.52-38.01)
EC type I	45	78.3 (53.65-154.5)	29.6 (16.1-44.55)	23.01 (13.79-44.6)	5.31 (2.42-23.29)
EC type II	16	240.95 (94.38-452.83)	81.1 (30.5-387.38)	71.7 (47.55-84.52)	44.63 (16.76-75.39)
Healthy controls	246	38.90 (33.50-47.43)	12.00 (8.25-17.05)	4.94 (3.27-7.39)	0.60 (0.39-1.00)

ues (30.75 vs. 12.0 U/mL), U=1831.50, $p<0.001$, $r=-0.517$, with statistical significance maintained in the subgroups: type I and type II – (29.60 vs. 12.0 U/mL), U=1537.00, $p<0.001$, $r=-0.446$ and (81.1 vs. 12.0 U/mL), U=294.00, $p<0.001$, $r=-0.365$.

When analyzing the algorithms, the data is similar. The differences in ROMA index values between type I and type II EC were statistically significant: U=166.00, $p=0.001$, $r=-0.407$. Compared to the control group, patients with types I and II EC had significantly higher ROMA index values (31.37% vs. 4.94%), U=1150.00, $p<0.001$, $r=-0.592$, with statistical significance maintained in the subgroups: type I and type II – (23.01% vs. 4.94%), U=784.00, $p<0.001$, $r=-0.549$ and (71.7% vs. 4.94%), U=366.00, $p<0.001$, $r=-0.346$.

The differences in the CPH-I values between type I and type II EC were statistically significant: U=183.00, $p=0.004$, $r=-0.372$. Compared to the control group, patients with types I and II EC had significantly higher CPH-I values (9.60 vs. 0.60%), U=910.00, $p<0.001$, $r=-0.619$, with statistical significance maintained in the subgroups: type I and type II – (5.31% vs. 0.60%), U=522.00, $p<0.001$, $r=-0.568$ and (44.6% vs. 0.60%), U=388.00, $p<0.001$, $r=-0.340$.

Diagnostic significance of biomarkers and algorithms for differentiating EC from benign pelvic formations

The ROC analysis showed that the standalone application of HE4 demonstrated very good diagnostic performance for detecting patients with EC among patients with benign diseases with an AUC-ROC of 0.816 (95% CI: 0.750-0.881). At a cut-off value of HE4 of 69.90 pmol/L, the test has a diagnostic sensitivity of 64.9% and specificity of 91.7%, positive and negative likelihood ratios – LR+ 7.82 and LR- 0.382, as well as positive and negative predictive values of 38.1% and 97.1% (**Fig. 2**).

The ROC analysis also revealed that CA125, used alone, had unsatisfactory diagnostic effectiveness for detecting patients with uterine carcinoma among those with benign diseases with an AUC-ROC of 0.641.

When combining the markers into diagnostic algorithms, the ROC analysis showed that the ROMA index demonstrates very good diagnostic performance for detecting patients with endometrial carcinoma among patients with benign diseases with an AUC-ROC of 0.869 (95% CI: 0.818-0.920). At a cut-off value of the ROMA index of 13.70 (corresponding to the upper reference limit in postmenopausal women), the test showed a diagnostic sensitivity of 75.7% and specificity of 85.7%, with positive and negative likelihood ratios – LR+ 5.29 and LR– 0.284, as well as positive and negative predictive values of 29.3% and 97.8%, respectively, for distinguishing patients with uterine carcinoma from those with benign diseases.

The ROC analysis showed that CPH-I demonstrated very good diagnostic performance for detecting patients with EC among patients with benign diseases with an AUC-ROC of 0.822 (95% CI: 0.757-0.887). At a cut-off value of CPH-I of 3.33% (corresponding to the upper reference limit in postmenopausal women), the test showed a diagnostic sensitivity and specificity of 67.6% and 86.6%, respectively, positive and negative likelihood ratios – LR+ 5.05 and LR– 0.374, as well as positive and negative predic-

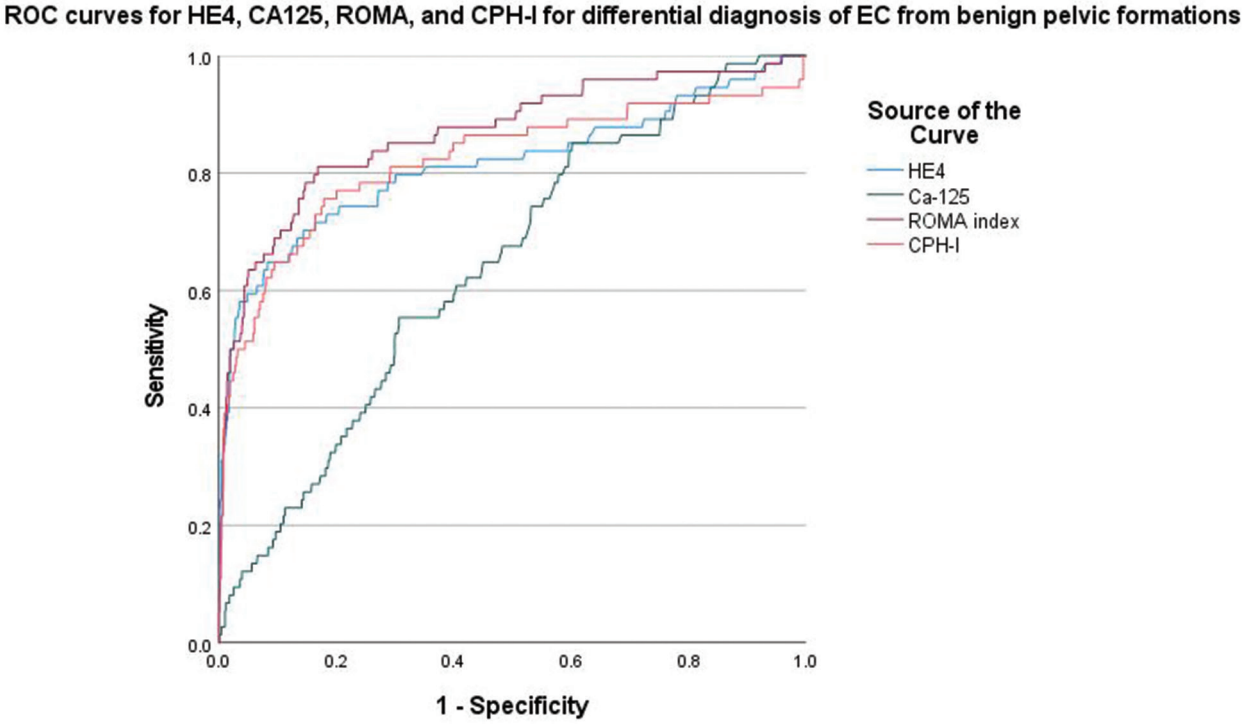

Figure 2. ROC curves for HE4, CA125, ROMA, and CPH-I for differential diagnosis of EC from benign pelvic formations.

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tive values – 28.4% and 97.1% for distinguishing patients with uterine carcinoma from those with benign diseases.

To assess the ability of HE4 to predict the progression of EC, a logistic regression analysis was conducted. The standalone use of HE4 statistically significantly predicts the distribution of patients into type I and type II subgroups (χ^2=8.878, df=1, p=0.003), with the marker contributing significantly to the correct distribution of patients in the two groups. The model explains between 14% (Cox & Snell R^2) and 20% (Nagelkerke R^2) of the variance and correctly classifies 77% of patients with EC in the defined groups. The exponent of the regression coefficient Exp(B) (HR) shows that an increase in HE4 by 1 pmol/L in patients with EC in stage I or stage II increases the chance of disease progression by 1.004 times (95% CI: 1.001-1.008).

The standalone use of CA125 statistically significantly predicts the distribution of patients in type I and type II subgroups (χ^2=20.357, df=1, p<0.001), with the marker contributing significantly to the correct distribution of patients in the two groups. The model explains between 28% (Cox & Snell R^2) and 42% (Nagelkerke R^2) of the variance and correctly classifies 85% of patients with EC in the defined groups. The exponent of the regression coefficient Exp(B) (HR) shows that an increase in CA125 by 1 U/mL in patients with EC in stage I or stage II increases the chance of disease progression by 1.018 times (95% CI: 1.003-1.034).

Logistic regression analysis of the ROMA index statistically significantly predicts the distribution of patients in type I and type II subgroups (χ^2=15.614, df=1, p<0.001), with the algorithm contributing significantly to the correct distribution of patients in the two groups. The model explains between 23% (Cox & Snell R^2) and 33% (Nagelkerke R^2) of the variance and correctly classifies 85% of patients with EC in the defined groups. The exponent of the regression coefficient Exp(B) (HR) shows that an increase in the ROMA index by 1 in patients with EC in stage I or stage II increases the chance of disease progression by 1.046 times (95% CI: 1.020-1.073).

The regression analysis performed for CPH-I also statistically significantly predicted the distribution of patients in the subgroups type I and type II (χ^2=15.878, df=1, p<0.001), with the marker contributing significantly to the correct distribution of patients in the two groups. The model explains between 23% (Cox & Snell R^2) and 34% (Nagelkerke R^2) of the variance and correctly classifies 79% of patients with EC in the defined groups. The exponent of the regression coefficient Exp(B) (HR) shows that an increase in CPH-I by 1% in patients with EC in stage I or stage II increases the chance of disease progression by 1.046 times (95% CI: 1.019-1.074).

Table 4 presents summarized data on the diagnostic effectiveness of biomarkers and algorithms for diagnosing EC.

The data shows that the ROMA index and CPH-I outperform the standalone use of HE4 and CA125 in diagnosing EC. The ROMA index demonstrates the highest diagnostic performance in distinguishing EC from benign diseases – 85%. Both algorithms (ROMA index and CPH-I) correlate with disease stage and progression. An increase in their values by 1 in patients with EC stage I or stage II increases the chance of disease progression to stage III or IV by 1.046 times.

Discussion

Endometrial carcinoma is the most common gynecological cancer, and although it is diagnosed at an early stage in a large percentage of cases, it recurs in 15-17% of patients. The ability to make a timely diagnosis, as well as to build a prognosis regarding disease stage and risk of recurrence or progression, are the reasons for the intensive search for new or already established diagnostic modalities for other localizations.

The ROMA index is a calculator initially created and validated to differentiate ovarian carcinoma from benign diseases by combining CA125, HE4, and menopausal status.[18,19] CA125 is an established serum tumor marker in the diagnosis and follow-up of patients with epithelial ovarian carcinoma. Subsequently, it is often applied as a marker for EC detection. Studies have reported its elevation in

Table 4. Diagnostic performance of HE4, CA125, ROMA index, and CPH-I in the diagnosis of EC

Diagnostic performance	HE-4		Ca-125		ROMA		CPH-I	
	cut-off	AUC-ROC (Cl 95)	cut-off	AUC-ROC (Cl 95)	cut-off	AUC-ROC (Cl 95)	cut-off	AUC-ROC (Cl 95)
Differentiation of EC in benign diseases	69.90 pmol/L	0.816 (0.750-0.881)	Not enough diagnostic effectiveness		13.70	0.869 (0.818-0.920)	3.33%	0.822 (0.757-0.887)
Differentiation according to histological type of EC	Not enough DE		Not enough DE		Not enough DE		Not enough DE	
Staging of EC – Stages I/II and Stages III/IV	HR – 1.004		HR – 1.018		HR – 1.046		HR – 1.046	

EC: endometrial carcinoma; BD: benign diseases; DE: diagnostic effectiveness

24.6% of patients with EC but only in 10% of patients with early-stage disease.[20] In recent years, HE4 increasingly stands out as a promising biomarker for early detection, diagnosis, prognosis building, and recurrence monitoring in ovarian and endometrial carcinoma.[21] Its advantage over CA125 is that benign pelvic tumor masses, inflammation, endometriosis, adenomyosis, and pregnancy have less of an impact on its serum concentration.

CPH-I was validated later than the ROMA index in patients with ovarian carcinoma, again using serum concentrations of HE4 and CA125 but considering the patient's age instead of menopausal status.[17] Publications from recent years report its superiority over the ROMA index and its implementation in diagnostic nomograms.[22] In any case, however, to date, there are very few studies reporting data on the application of the ROMA index and/or CPH-I in diagnosing patients with EC.

The current study analyzed the diagnostic potential of two serum tumor markers – HE4 and CA125 – and their combination in the algorithms ROMA and CPH-I. The results demonstrated the best diagnostic performance of the ROMA index (AUC=0.869), followed by CPH-I (AUC=0.822) and HE4 (AUC=0.816) for distinguishing benign processes from EC. Unlike its significance in epithelial ovarian carcinoma, CA125 has no diagnostic effectiveness in EC and cannot independently distinguish benign from oncological disease. Its addition to HE4, however, enhances its clinical significance.

Our data confirm the results from meta-analyses by Li et al., Liu et al., and Li J et al.[12-14] regarding the diagnostic performance of HE4 in detecting EC. HE4 has good specificity, allowing it to discriminate EC from benign diseases. Unfortunately, the diagnostic sensitivity is not sufficient (65%-71%), limiting its application in early stages. Our data confirm the results from meta-analyses regarding the lack of diagnostic effectiveness of standalone application of CA125 in EC (AUC=0.64 in our study, AUC=0.58 in Li et al.'s meta-analysis).

In conducting the subgroup analysis, our study did not prove sufficient potential of the markers, neither individually nor in combination, to distinguish the histological type of EC, although higher values were found in the group of non-endometrioid carcinoma (mainly in patients with serous type carcinoma). Similar data are reported by Sun et al.[23] In their study, HE4 is significantly higher in papillary serous carcinoma of the endometrium compared to patients with endometrioid carcinoma of the uterus.

When the relationship between their elevation and disease stage was examined, HE4 and the combination of the two markers showed a good correlation with EC advancement.[24] This opens a horizon for building prognosis and prediction before treatment initiation. Currently, staging is performed according to FIGO criteria based on postoperative pathological assessment, and about 15%-20% of patients are clinically staged as earlier stage before treatment.[25] Therefore, proper preoperative evaluation is extremely important, especially in cases of women where fertility preservation is aimed or in inoperable patients. Additionally, proper preoperative staging can help in decision-making regarding neoadjuvant chemotherapy or the inability to map sentinel lymph nodes in advanced disease.

In our patient cohort, both the standalone use of markers HE4 and CA125, and even more explicitly the calculated indices with the addition of multivariate parameters such as age or menopausal status (ROMA and CPH-I), demonstrate potential as prognostic markers in terms of discrimination between early and late disease stage, as well as risk of progression.

To date, there are few scientific reports regarding the applicability of the ROMA index and CPH-I algorithms in patients with EC. The study published by Wang et al. in 2022 regarding the predictive significance of the ROMA index for advanced EC before surgical treatment compares biomarker data with several other variables such as age, body mass index, presence of type II diabetes, hormonal status, hypertension, tumor size, and degree of invasion.[26] The authors conclude that the ROMA index, as a standard, reliable, easily measurable laboratory test, could be used by gynecologic oncologists as a tool to select an appropriate therapeutic plan for patients with advanced EC before surgical treatment.

Our study also established the superiority of the ROMA index, determined preoperatively, over the standalone determination of HE4 and CA125. The results regarding CPH-I show comparable diagnostic significance to that of the ROMA index. The advantage of using CPH-I should be sought in its independence from the hormonal status of patients (especially in the perimenopausal age group) and its closer correlation with HE4 values. The relationship of HE4 with age and the increase in its values, especially after 60 years of age, when the peak incidence of EC occurs, is known. Another advantage of CPH-I would be its ability to be easily implemented in the laboratory information system and automated result generation.

At the time of this publication, we did not find any reported data from another study evaluating the application of CPH-I in a cohort of patients with EC. For this reason, although highly optimistic, our results require validation of the algorithm in a larger group of patients in a prospective study design.

Conclusion

In summary, the ROMA index, CPH-I, and to a lesser extent, the standalone testing of HE4 can complement imaging methods as a reliable means of diagnosing patients with EC and distinguishing them from benign diseases. They have potential as prognostic markers regarding advanced disease and could assist gynecological oncologists in developing a therapeutic strategy.

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References

1. Uterine Cancer Statistics. Available from: https://www.wcrf.org/preventing-cancer/cancer-statistics/endometrial-cancer-statistics/ (accessed on 07 January 2025).
2. Calle EE, Kaaks R. Overweight, obesity and cancer: Epidemiological evidence and proposed mechanisms. Nat Rev Cancer 2004; 4:579–91. doi: org/10.1038/nrc1408
3. Crosbie E, Morrison J. The emerging epidemic of endometrial cancer: Time to take action. Cochrane Database Syst Rev 2014; 12:ED000095.
4. Clarke MA, Long BJ, Morillo ADM, et al. Association of endometrial cancer risk with postmenopausal bleeding in women. JAMA Intern Med 2018; 178:1210–22.
5. Banz-Jansen C, Helweg LP, Kaltschmidt B. Endometrial cancer stem cells: where do we stand and where should we go? Int J Mol Sci 2022; 23:3412. doi: 10.3390/ijms23063412
6. Jones ER, O'Flynn H, Njoku K, et al. Detecting endometrial cancer. Obstet Gynaecol 2021; 23:103–12.
7. Concin N, Creutzberg CL, Vergote I, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Virchows Arch 2021; 478(2):153–90. doi: 10.1007/s00428-020-03007-z
8. Kirchhoff C, Habben I, Ivell R, et al. A major human epididymis-specific cDNA encodes a protein with sequence homology to extracellular proteinase inhibitors. Biol Reprod 1991; 45:350–7.
9. Li J, Chen H, Mariani A, et al. HE4 (WFDC2) promotes tumor growth in endometrial cancer cell lines. Int J Mol Sci 2013; 14:6026.
10. Lu Q, Chen H, Senkowski C, et al. Recombinant HE4 protein promotes proliferation of pancreatic and endometrial cancer cell lines. Oncol Rep 2015; 35:163–70.
11. Degez M, Caillon H, Chauviré-Drouard A, et al. Endometrial cancer: A systematic review of HE4, REM and REM-B. Clin Chim Acta 2021; 515:27–36.
12. Li L-M, Zhu Y, Zhong Y, et al. Human epididymis protein 4 in endometrial cancer: A meta-analysis. Clin Chim Acta 2018; 482:215–23.
13. Liu J, Han L, Sun Q, et al. Meta-analysis of the diagnostic accuracy of HE4 for endometrial carcinoma. Eur J Obstet Gynecol Reprod Biol 2020; 252:404–11.
14. Li J, Wang X, Qu W, et al. Comparison of serum human epididymis protein 4 and CA125 on endometrial cancer detection: A meta-analysis. Clin Chim Acta 2019; 488:215–20.
15. Torok P, Krasznai Z, Molnar S, et al. Preoperative assessment of endometrial cancer. Translational Cancer Research 2020; 9(12):7746–58. doi: 10.21037/tcr-20-2068.
16. Barr CE, Njoku K, Jones ER, et al. Serum CA125 and HE4 as biomarkers for the detection of endometrial cancer and associated high-risk features. Diagnostics 2022; 12:2834. doi: 10.3390/diagnostics12112834
17. Karlsen MA, Hogdall EV, Christensen IJ, et al. A novel diagnostic index combining HE4, CA125 and age may improve triage of women with suspected ovarian cancer – an international multicenter study in women with ovarian mass. Gynecol Oncol 2015; 138:640–6.
18. Dochez V, Caillon H, Vaucel E, et al. Biomarkers and algorithms for diagnosis of ovarian cancer: CA125, HE4, RMI and ROMA, a review. J Ovar Res 2019; 12(1):28. doi: 10.1186/s13048-019-0503-7.
19. Zhang R, Siu MKY, Ngan HYS, et al. Molecular biomarkers for the early detection of ovarian cancer. Int J Mol Sci 2022; 23(19):12041. doi: 10.3390/ijms231912041
20. Capriglione S, Plotti F, Miranda A, et al. Further insight into prognostic factors in endometrial cancer: the new serum biomarker HE4. Expert Rev Anticancer Ther 2017; 17(1):9–18. doi: 10.1080/14737140.2017.1266263
21. Behrouzi R, Barr CE, Crosbie EJ. HE4 as a biomarker for endometrial cancer. Cancers 2021; 13(19):4764. doi: 10.3390/cancers13194764
22. Song Z, Wang X, Fu J, et al. Copenhagen index (CPH-I) is more favorable than CA125, HE4, and risk of ovarian malignancy algorithm (ROMA): Nomogram prediction models with clinical- ultrasonographic feature for diagnosing ovarian neoplasms. Front Surg 2023; 9:1068492. doi: 10.3389/fsurg.2022.1068492
23. Sun Y, Liu X, Zhao F, et al. Value of detection of serum human epididymis secretory protein 4 and carbohydrate antigen 125 in diagnosis of early endometrial cancer of different pathological subtypes. OncoTargets Ther 2015; 8:1239–43.
24. Behrouzi R, Barr CE, Crosbie EJ. HE4 as a biomarker for endometrial cancer. Cancers 2021; 13(19):4764. doi: 10.3390/cancers13194764.
25. Jamaluddin MF, Ko YA, Ghosh A, et al. Proteomic and functional characterization of intra-tumor heterogeneity in human endometrial cancer. Cell Reports Medicine 2022; 3(9):100738. doi: 10.1016/j.xcrm.2022.100738
26. Wang J, Xu P, Zou G, et al. ROMA index is an effective predictor for advanced endometrial cancer before surgery. Dis Markers 2022; 22:7409368. doi: 10.1155/2022/7409368.