Original Article

Are ROMA and HE4 More Accurate than CA-125, in Predicting of Ovarian Epithelial Carcinoma?

Fariba Behnamfar, Aazam Zafarbakhsh, Narges Ahmadian

Department of Obstetrics and Gynecology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background: Evaluation of ovarian tumors based on tumor markers could have high clinical importance. In this study, we aimed to assess the predictive value of HE4 and Risk of Ovarian Malignancy Algorithm (ROMA) compared to CA-125 in the Malignancy of ovarian epithelial masses.

Materials and Methods: This cross-sectional study was performed in 2020–2021 including 203 patients. Serum HE4 and CA-125 levels were checked before surgery. According to the pathology report (benign, borderline, or malignant epithelial mass), the predictive values of the three markers were evaluated.

Results: About 146 cases were benign; 14 cases were borderline and 43 cases were malignant. Most patients (69.8%) in the malignant group were in stage 3. Significantly higher levels of all three markers (CA-125, HE4, and ROMA) were found in patients with malignant tumors compared to benign or borderline tumors ($P < 0.001$ for all). The sensitivity of CA-125 was the highest (90.7%) in pre- and post-menopausal patients but the specificity of HE4 and ROMA were higher than CA-125 (98.1% and 97.5%, respectively, versus 86.9% for CA-125). In post-menopausal patients, both sensitivities of HE4 and ROMA were 90.5% and the specificity and sensitivity of CA-125 were the highest (95.2% and 100%). In premenopausal patients, the sensitivity of ROMA (90.9%) and the specificity of HE4 (100%) were the highest.

Conclusions: HE4 and ROMA are not necessary for postmenopausal patients in low-resource areas and a check of serum CA-125 will be enough. The higher-cost, ROMA, and HE4 checks are recommended in premenopausal people because they are more sensitive.

Keywords: Biomarkers, neoplasms, ovary, tumor

Address for correspondence: Dr. Narges Ahmadian, Department of Obstetrics and Gynecology, School of Medicine, Isfahan University of Medical Sciences, Hezar Jarib St., Isfahan City, Isfahan Province, Iran.
E-mail: Nilufar.Ahmadian2@gmail.com
Submitted: 08-Aug-2022; **Revised:** 16-Nov-2022; **Accepted:** 28-Nov-2022; **Published:** 28-Jun-2023

Introduction

Ovarian cancer is one of the most common female cancers worldwide.[1] Its incidence worldwide is estimated at 222,500 cases per year and about 140,200 people die each year due to this type of malignancy.[2-4] Although ovarian cancer is treatable in the early stages, most patients are diagnosed in the advanced stages of the disease. After diagnosing an ovarian tumor, the primary and most important goal is to determine if it is malignant or benign.[5] Studies have shown that about 5-10% of women with ovarian mass are operated on, of which about 13–21% are diagnosed with malignancy.[6-8] An accurate diagnosis of benign or malignant mass helps the surgeon determine the operation plan because the quality of surgery will significantly impact its prognosis. Primary laparotomy is not only important for determining the extent of tumor spread, but also a good opportunity for maximum treatments.[9,10]

The most used marker is cancer antigen-125 (CA-125), which has increased serum levels in about 80% of ovarian epithelial cancers.[11] However, serum CA-125 levels are nonspecific and should be interpreted in conjunction with clinical signs and

Access this article online

Quick Response Code:

Website: www.advbiores.net

DOI: 10.4103/abr.abr_264_22

How to cite this article: Behnamfar F, Zafarbakhsh A, Ahmadian N. Are ROMA and HE4 more accurate than CA-125, in predicting of ovarian epithelial carcinoma? Adv Biomed Res 2023;12:156.

ultrasound findings.[12] Also, this marker has low sensitivity and specificity in the premenopausal period but has a high diagnostic value in the postmenopausal period. CA-125 susceptibility in ovarian cancers is associated with tumor stage.[12] Increased levels of this marker are seen in 50% of patients with stage I and 90–80% of patients with stage III–IV. In addition, the level of this tumor marker may increase in other conditions, including tumors of non-ovarian origin, benign uterine tumors such as myoma, and endometriosis.[13]

Recent studies have shown that Human Epididymis Protein (HE4), a translation of the WFDC2 gene, increases serum levels in ovarian cancers. These studies showed that HE4 is as sensitive as CA-125 but has more specificity in the diagnosis of ovarian tumors.[14] Recent studies have reported that serum HE4 levels, along with CA-125 and ultrasound, slightly increased the sensitivity and specificity of malignant ovarian tumor diagnosis.[15] It was also shown that serum levels of HE4 and CA-125 were significantly higher in patients with malignant ovarian tumors than in patients with benign ovarian tumors in the control group.[16] Data have reported that serum HE4 levels were higher in patients with ovarian epithelial tumors compared with other ovarian tumors.[17]

Due to the diagnosis of advanced ovarian malignancies and high mortality of patients, having an available and easy, accurate, and reliable test to differentiate malignant ovarian tumors from benign and determine the appropriate surgical plan to increase the prognosis of the patients is necessary. Therefore, further studies on tumor markers and their sensitivity and specificity in diagnosing malignant ovarian masses need to be performed. This study aimed to compare the diagnostic value of HE4 and Risk of Ovarian Malignancy Algorithm (ROMA) with CA-125 in ovarian epithelial malignancies.

Materials and Methods

This study was performed in 2020–2021 in Beheshti and Al-Zahra hospitals in Isfahan on all patients diagnosed with ovarian masses that were referred to our medical centers for surgical operations. The ethics code for this study was IR.MUI.MED.REC.1399.799.

The inclusion criteria were diagnosis of ovarian mass by imaging techniques, primary ovarian masses, candidates of laparotomy surgical procedures, and signing the written informed consent to participate in this study. The exclusion criteria were current pregnancy, previous surgery for adnexal mass, previous malignancy, treatments with chemotherapy, and lack of consent.

According to the pathology report (benign, borderline, or malignant mass), 203 patients with epithelial masses were divided into benign, borderline, and malignant groups. Only those patients with epithelial masses entered this study and other types of ovarian masses did not enter.

Based on the protocols in our medical centers, after the clinical examination and imaging methods (Doppler and B-mode ultrasound) by two experienced gynecologist and radiologist, the diagnosis of adnexal mass was made and the patient was a candidate for laparotomy and was referred to the mentioned centers for surgery. It should be noted that the examiners were blinded to the study aims. At the beginning of the study, we collected patients' demographic data using a checklist. These data were patient age, menstrual status, patient's medications, number of gravid, age of menopause, years after menopause, age of Menarche, past medical history, past social history, history of cancer, polycystic ovary syndrome, past drug history, Fertility Aid Medicine, oral contraceptive pill (OCP) use, alcohol use, cigarettes use, family history of ovarian cancer and history of endometriosis. In this study, menopause was defined as the continuous interruption of menstruation for at least one year.

The amount of 10 ml of venous blood was taken from patients before surgeries and sent to the laboratory to check the HE4 and CA-125 titers. The level of biomarkers was measured by Enzyme immunometric assay (EIA). The patients were then operated on and a sample was sent to the pathology unit to determine the type of tumors.

After determining the serum levels of HE4 and CA-125, the ROMA index was calculated as follows:

ROMA Index (%) =

Premenopausal: (PI): 12 + 2.38 × LN (HE4) + 0.062 6 × LN (CA-125)

Postmenopausal: (PI): 8.09 + 1.04 × LN (HE4) + 0.732 × LN (CA-125)

In addition, the results obtained from the serum level of HE4 and CA-125 of patients and after calculating the ROMA index, sensitivity, specificity, and positive and negative predictive value of each of these indicators were calculated and compared.

Normal values of HE4, CA-125, and ROMA are presented in Table 1.

The data were analyzed with Statistical Package for Social Sciences (SPSS) software using independent t-tests and Chi-square.

Results

Of the 203 patients with epithelial masses, 146 cases were benign, 14 cases were borderline and 43 cases were

Table 1: Normal ranges for HE4, CA-125, and ROMA

Marker	Normal range
HE4 (pmol/L)	
Premenopausal	<70
Postmenopausal	<140
CA-125 (U/mL)	
Premenopausal	up to 35
Postmenopausal	
ROMA (%)	
Premenopausal	<13.1
Postmenopausal	<27.7

malignant. The most common types of benign masses were serous (26%), endometrioid (25.3%), and mucinous (23.3%), respectively. The most common types of borderline masses were serous (42.9%) and mucinous (35.7%) and the most common types of malignant masses were serous (69.8%). These data are shown in Table 2. Analysis of frequencies of different tumor stages in malignant tumors showed that most patients (69.8%) were in stage 3, 18.6% were in stage 2, 7% of patients were in stage 1 and 4.7% were in stage 4.

In the malignant group, the following data were more frequent compared to the other groups: older age ($P < 0.001$), a higher number of pregnancies ($P = 0.049$), late menopause ($P = 0.006$), younger age of menarche ($P < 0.001$), positive past drug history for comorbidity including hypertension, diabetes mellitus and hypothyroidism ($P = 0.003$). History of OCP use ($P = 0.011$) and history of proven endometriosis (P 0.004) was less frequent in the malignant group [Table 3].

Significantly higher levels of all three markers (CA-125, HE4, and ROMA) were found in patients with malignant tumors compared to benign or borderline tumors ($P < 0.001$ for all) [Table 4].

The sensitivity and specificity of CA-125, HE4, and ROMA in all patients and pre- or post-menopausal patients were assessed. These data showed significant differences in all comparisons ($P < 0.001$ for all). Based on these reports, the sensitivity of CA-125 was the highest (90.7%) in Premenopausal and post-menopausal patients compared with HE4 and ROMA, but the specificity of HE4 and ROMA were higher than CA-125 (98.1% and 97.5%, respectively, versus 86.9% for CA-125). In post-menopausal patients, both sensitivities of HE4 and ROMA were 90.5% and the specificity and sensitivity of CA-125 were the highest (95.2% and 100% respectively). In premenopausal patients, the sensitivity of ROMA (90.9%) and the specificity of HE4 (100%) were the highest. These data are shown in Table 5 and Figure 1.

Table 2: Frequency distribution of mass types in study population

Mass type	Tumor type	Frequency (%)
Benign	Serous	38 (26.00)
	Mucinous	34 (23.30)
	Endometrioid	37 (25.30)
	Clear cell	0 (0.00)
	Brenner	0 (0.00)
	Mixed epithelial	19 (13.00)
	Others	18 (12.30)
Borderline	Serous	6 (42.90)
	Mucinous	5 (35.70)
	Endometrioid	0 (0.00)
	Clear cell	0 (0.00)
	Brenner	0 (0.00)
	Mixed epithelial	3 (21.40)
	Others	0 (0.00)
Malignant	Serous	30 (69.80)
	Mucinous	5 (11.60)
	Endometrioid	1 (2.30)
	Clear cell	1 (2.30)
	Brenner	0 (0.00)
	Mixed epithelial	4 (9.30)
	Others	2 (4.70)

Patients were categorized into two groups of high risks or low risks based on levels of each tumor marker and menopausal status. These risks were compared in different tumor pathology types. Data showed significant differences in all tumor markers in all tumor types ($P < 0.001$ for all). Data demonstrated that in pre-menopausal patients with malignant tumors, most cases (86.4%) had high risks of malignancy based on CA-125. These data were 81.8% and 90.9% for HE4 and ROMA, respectively. In post-menopausal patients, 100% of cases with malignant tumor pathology had high risks for malignancy based on CA-125. These data were 85.7% and 90.5% for HE4 and ROMA, respectively. Considering all patients total, these data were 93%, 83.7%, and 90.7% for CA-125, HE4, and ROMA, respectively. According to these data, in pre-menopausal patients, 16.6% of patients with malignant tumors had normal levels of CA-125, 18.2% of patients had normal levels of HE4 and 9.1% had normal ROMA scores. In post-menopausal patients, these numbers were 0% based on CA-125, 14.3% based on HE4, and 9.5% based on ROMA. About 7% of patients with malignant tumors had normal CA-125 levels, 16.3% had normal HE4 and 9.3% had normal ROMA. These data are shown in Table 6.

There were no significant Pearson's correlations between the tumor markers and tumor staging of the patients with malignant masses ($P > 0.05$ for all) [Table 7].

Discussion

In this study, the prognostic values of CA-125, HE4, and ROMA were compared in 203 patients with epithelial ovarian

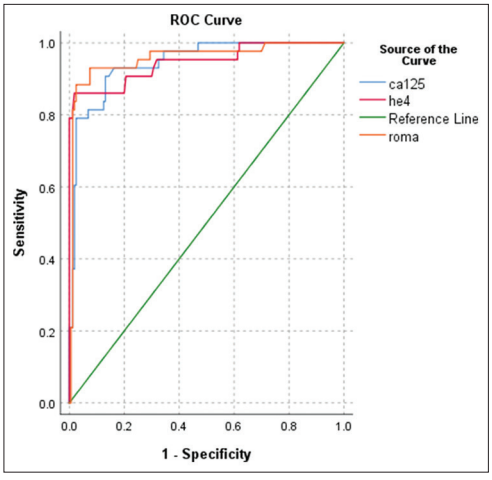

Figure 1: ROC cure for CA-125, HE4, and ROMA

Table 3: Comparison of different characteristics between patients

Variable	Benign *n*=146	Borderline *n*=14	Malignant *n*=43	*P*
Age	42.66±13.93	42.21±11.8	55.14±13.44	<0.0001
Number of gravid	2.68±2.25	2.64±2.68	4±3.18	0.049
Age of Menopause	51.57±2.87	48±4.58	53.36±3.91	0.048
Years after menopause	9.51±7.39	4.6±4.93	12.95±7.47	0.025
Age of Menarche	12.47±1.4	12±1.8	10.86±1.39	<0.0001
Null gravida				
No	116 (79.50)	9 (64.30)	36 (83.70)	0.296
Yes	30 (20.50)	5 (35.70)	7 (16.30)	
Menopausal State				
Premenopausal	107 (74.30)	9 (64.30)	22 (51.20)	0.015
Postmenopausal	37 (25.70)	5 (35.70)	21 (48.80)	
History of Late Menopause				
No	35 (94.60)	5 (100.00)	14 (63.60)	0.006
Yes	2 (5.40)	0 (0.00)	8 (36.40)	
History Of Infertility				
No	136 (93.20)	14 (100.00)	42 (97.70)	0.467
Yes	10 (6.80)	0 (0.00)	1 (2.30)	
PMH				
No	79 (54.20)	7 (50.00)	13 (30.20)	0.057
Yes	67 (45.90)	7 (50.00)	30 (69.80)	
PSH				
No	80 (54.80)	9 (64.30)	30 (69.70)	
Yes	66 (45.20)	5 (35.70)	13 (30.20)	
History of cancer				
No	145 (99.30)	14 (100.00)	43 (100.00)	1.000
Yes	1 (0.70)	0 (0.00)	0 (0.00)	
Polycystic ovary syndrome				
No	130 (89.00)	14 (100.00)	41 (95.30)	0.310
Yes	16 (11.00)	0 (0.00)	2 (4.70)	
Past drug history				
No	86 (58.90)	9 (64.30)	13 (30.20)	0.003
Yes	60 (41.10)	5 (35.70)	30 (69.80)	
Fertility Aid Medicine				
No	142 (97.30)	14 (100.00)	41 (95.30)	0.754
Yes	4 (2.70)	0 (0.00)	2 (4.70)	
OCP use				
No	101 (69.20)	13 (92.90)	38 (88.40)	0.011
Yes	45 (30.80)	1 (7.10)	5 (11.60)	
Alcohol use				
No	146 (100.00)	14 (100.00)	43 (100.00)	-
Yes	0 (0.00)	0 (0.00)	0 (0.00)	
Cigarettes use				
No	146 (100.00)	14 (100.00)	43 (100.00)	-
Yes	0 (0.00)	0 (0.00)	0 (0.00)	
Family History of ovarian cancer				
No	138 (94.50)	12 (85.70)	39 (90.70)	0.213
Yes	8 (5.50)	2 (14.30)	4 (9.30)	
History of endometriosis				
No	121 (82.90)	14 (100.00)	43 (100.00)	0.004
Yes	25 (17.10)	0 (0.00)	0 (0.00)	

masses. About 146 cases were benign, 14 cases were borderline and 43 cases were malignant. Analysis of frequencies of different tumor stages in malignant tumors showed that most patients (69.8%) were in stage 3 and 18.6% were in stage 2.

There have been previous data on using of these markers in ovarian masses. In 2016, a study was performed by Wei and colleagues on 158 individuals having ovarian cancer, benign tumor, or no masses. The results of this survey showed that

levels of HE4, CA-125, and ROMA in the sera of the ovarian cancer group were significantly higher than those of the ovarian benign tumor and control groups, regardless of pre- or postmenopausal status.[18]

The clinical importance of these data is high yield and physicians could utilize the combinations of all these three markers in patients with ovarian masses. The early diagnosis of malignant ovarian masses could have significant beneficial effects on the prognosis of patients. In another study by Huy and colleagues in 2018, they conducted a descriptive study on 277 patients with ovarian masses. They reported that serum CA-125 and HE4 levels and ROMA have good validity in diagnosing ovarian carcinoma and ROMA had the highest specificity.[19] Dochez[20] and others in a review also mentioned that CA-125, ROMA, and HE4 have proved to be highly efficient in the diagnosis of malignant ovarian masses and ROMA had the highest sensitivity in post-menopausal masses. In these cases, HE4 and CA-125 had the highest specificity. Our results were consistent with these findings emphasizing the clinical value of these three tumor markers.

Some previous studies have also shown the importance of CA-125, HE4, and ROMA index measurements in diagnosing malignant ovarian masses but there seem to be differences in the sensitivity and specificity of these markers according to patient's characteristics.[21,22] These studies have suggested that further studies on larger populations should be conducted.[23] An important point of this study was that we compared the three markers in ovarian masses for the first time in our region.

Table 4: Levels of the evaluated markers based on tumor types

Variable	Benign *n*=146	Borderline *n*=14	Malignant *n*=43	*P*
CA-125	38.83±73.94	22.92±15	440.42±640.29	<0.0001
HE4	44.38±18.02	50.73±22.34	515.16±584.7	<0.0001
ROMA	12.91±50.26	9.69±5.87	77.88±46.26	<0.0001

According to our data, in pre-menopausal patients, 16.6% of patients with malignant tumors had normal levels of CA-125, 18.2% of patients had normal levels of HE4 and 9.1% had normal ROMA scores. In post-menopausal patients, these numbers were 0% based on CA-125, 14.3% based on HE4, and 9.5% based on ROMA. 7% of patients with malignant tumors had normal CA-125 levels, 16.3% had normal HE4 and 9.3% had normal ROMA. Therefore, it is believed that there is a chance of missing patients with malignant tumors. This issue highlights other complementary diagnostic methods in patients with ovarian masses.

Evaluation of benign tumors showed that the most common tumor types were serous (26%), endometrioid (25.3%), and mucinous (23.3%). It was observed that the ROMA score was lowest (12.91 ± 50.26) compared to other markers ($P < 0.001$). According to the results of Table 6, in pre-menopausal women, HE4 and ROMA had shown low-risk results in 97.2% and 96.3% of patients respectively. In postmenopausal women, HE4 and ROMA showed 100% and 97.3% low-risk results, respectively, and in total, HE4 and ROMA showed 97.9% and 96.5% low-risk results respectively.

Another issue that was shown by this study was the levels of the three markers in patients with benign masses. Based on our results, the levels of ROMA were significantly lower than other markers and HE4 was higher than ROMA and CA-125. It could be determined that the levels of these markers could also be practical in the diagnosis of benign masses. It is suggested that further studies should be conducted on this issue.

The limitations of this study were the restricted study population and not evaluating the sensitivity and specificity of these markers based on pathologic types of tumors. However, based on the results of this study and previous studies, the use of HE4, ROMA, and CA-125 could have significant efficacy in the diagnosis of malignant masses. We recommend that gynecologists and oncologists pay more attention to the values of these markers.

Table 5: Comparison of sensitivity and specificity of the three markers

	Sensitivity	Specificity	PPV	NPV	LR+	LR-	AUC	*P*
total								
CA-125	0.907 (0.777, 0.968)	0.869 (0.807, 0.913)	0.650	0.972	6.910	0.107	0.945 (0.911, 0.98)	<0.0001
He4	0.86 (0.722, 0.937)	0.981 (0.943, 0.996)	0.925	0.963	45.891	0.142	0.947 (0.902, 0.991)	<0.0001
ROMA	0.884 (0.749, 0.953)	0.975 (0.935, 0.992)	0.905	0.969	35.349	0.119	0.957 (0.918, 0.996)	<0.0001
Post menopause								
CA-125	1 (0.814, 1)	0.952 (0.832, 0.994)	0.913	1.000	21.000	< 0.0001	0.994 (0.985, 1)	<0.0001
He4	0.905 (0.696, 0.984)	1 (0.898, 1)	1.000	0.955	NA	0.095	0.947 (0.87, 1)	<0.0001
ROMA	0.905 (0.696, 0.984)	1 (0.898, 1)	1.000	0.955	NA	0.095	0.964 (0.91, 1)	<0.0001
Pre menopause								
CA-125	0.773 (0.56, 0.901)	0.966 (0.911, 0.989)	0.810	0.957	22.409	0.235	0.915 (0.853, 0.978)	<0.0001
He4	0.818 (0.607, 0.931)	1 (0.96, 1)	1.000	0.967	NA	0.182	0.944 (0.885, 1)	<0.0001
ROMA	0.909 (0.707, 0.985)	0.966 (0.911, 0.989)	0.833	0.982	26.364	0.094	0.948 (0.887, 1)	<0.0001

PPV: positive predictive value, NPV: negative predictive value

Table 6: Risk assessments of the three markers based on tumor pathology

Variable	Pathology			*P*
	Benign	borderline	malignant	
Pre-menopause				
CA-125				
Low risk	71 (66.40)	8 (88.90)	3 (16.60)	<0.0001
High risk	36 (33.60)	1 (11.10)	19 (86.40)	
He4				
Low risk	104 (97.20)	9 (100.00)	4 (18.20)	<0.0001
High risk	3 (2.80)	0 (0.00)	18 (81.80)	
ROMA				
Low risk	103 (96.30)	9 (100.00)	2 (9.10)	<0.0001
High risk	4 (3.70)	0 (0.00)	20 (90.90)	
Post-menopause				
CA-125				
Low risk	28 (75.70)	5 (100.00)	0 (0.00)	<0.0001
High risk	9 (24.30)	0 (0.00)	21 (100.00)	
He4				
Low risk	37 (100.00)	5 (100.00)	3 (14.30)	<0.0001
High risk	0 (0.00)	0 (0.00)	18 (85.70)	
ROMA				
Low risk	36 (97.30)	5 (100.00)	2 (9.50)	<0.0001
High risk	1 (2.70)	0 (0.00)	19 (90.50)	
Total				
CA-125				
Low risk	101 (69.20)	13 (92.90)	3 (7.00)	<0.0001
High risk	45 (30.80)	1 (7.10)	40 (93.00)	
He4				
Low risk	141 (97.90)	14 (100.00)	7 (16.30)	<0.0001
High risk	3 (2.10)	0 (0.00)	36 (83.70)	
ROMA				
Low risk	139 (96.50)	14 (100.00)	4 (9.30)	<0.0001
High risk	5 (3.50)	0 (0.00)	39 (90.70)	

Table 7: Correlations of the three markers with tumor staging in patients with malignant masses

Variable	CA-125	He4	ROMA
Pre-menopause			
Pearson Correlations	0.096	0.109	0.104
P	0.67	0.631	0.645
Post-menopause			
Pearson Correlations	0.207	0.207	0.12
P	0.367	0.367	0.605
Total			
Pearson Correlations	0.122	0.129	0.036
P	0.436	0.409	0.817

Conclusion

The main goal of this study was to assess the requirement of evaluating HE4 and ROMA index associated with CA-125 in patients with an ovarian mass. This issue has high clinical importance because each of these tests is related to extra costs for the healthcare system. Based on this data, the sensitivity of CA-125 was the highest (90.7%) in Premenopausal and post-menopausal patients compared with HE4 and ROMA but the specificity of HE4 and ROMA was higher than CA-125 (98.1% and 97.5% respectively, versus 86.9% for CA-125) in both groups. In post-menopausal patients, both sensitivities of HE4 and ROMA were 90.5% and the specificity and sensitivity of CA-125 were the highest (95.2% and 100% respectively) in these cases. In premenopausal patients, the sensitivity of ROMA (90.9%) and the specificity of HE4 (100%) were the highest. These data could reveal that HE4 and ROMA are not necessary for postmenopausal patients in low-resource areas and a check of serum CA-125 will be enough. Despite the higher cost, ROMA and HE4 checks are recommended in premenopausal people because they are more sensitive.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

This study was granted by the Isfahan University of Medical Sciences.

Conflicts of interest

There are no conflicts of interest.

References

1. Matulonis UA, Sood AK, Fallowfield L, Howitt BE, Sehouli J, Karlan BY. Ovarian cancer. Nat Rev Dis Prim 2016;2:1-22.
2. Stewart C, Ralyea C, Lockwood S, editors. Ovarian cancer: An integrated review. Semin Oncol Nurs 2019;35:151-6.
3. Reid BM, Permuth JB, Sellers TA. Epidemiology of ovarian cancer: A review. Cancer Biol Med 2017;14:9.
4. Zadeh AR, Farrokhi M, Etemadifar M, Beni AA. Prevalence of benign tumors among patients with multiple sclerosis. Am J Exp Clin Res 2015;2:127-32.
5. Cortez AJ, Tudrej P, Kujawa KA, Lisowska KM. Advances in ovarian cancer therapy. Cancer Chemother Pharmacol 2018;81:17-38.
6. Doubeni CA, Doubeni AR, Myers AE. Diagnosis and management of ovarian cancer. Am Fam Physician 2016;93:937-44.
7. Momenimovahed Z, Tiznobaik A, Taheri S, Salehiniya H. Ovarian cancer in the world: epidemiology and risk factors. Int J Womens Health 2019;11:287-99.
8. Rafiee Zadeh A, Ghadimi K, Mohammadi B, Hatamian H, Naghibi SN, Danaeiniya A. Effects of estrogen and progesterone on different immune cells related to multiple sclerosis. Casp J Neurol Sci 2018;4:83-90.
9. Banerjee S, Tian T, Wei Z, Shih N, Feldman MD, Alwine JC, *et al*. The ovarian cancer oncobiome. Oncotarget 2017;8:36225.
10. Orr B, Edwards RP. Diagnosis and treatment of ovarian cancer. Hematol Oncol Clin North Am 2018;32:943-64.
11. Charkhchi P, Cybulski C, Gronwald J, Wong FO, Narod SA, Akbari MR. CA125 and ovarian cancer: A comprehensive review. Cancers 2020;12:3730.
12. Zhang M, Cheng S, Jin Y, Zhao Y, Wang Y. Roles of CA125 in diagnosis, prediction, and oncogenesis of ovarian cancer. Biochim Biophys Acta Rev Cancer 2021;1875:188503.

13. Funston G, Hamilton W, Abel G, Crosbie EJ, Rous B, Walter FM. The diagnostic performance of CA125 for the detection of ovarian and non-ovarian cancer in primary care: A population-based cohort study. PLoS Med 2020;17:e1003295.
14. Scaletta G, Plotti F, Luvero D, Capriglione S, Montera R, Miranda A, *et al*. The role of novel biomarker HE4 in the diagnosis, prognosis and follow-up of ovarian cancer: A systematic review. Expert Rev Anticancer Ther 2017;17:827-39.
15. Capriglione S, Luvero D, Plotti F, Terranova C, Montera R, Scaletta G, *et al*. Ovarian cancer recurrence and early detection: may HE4 play a key role in this open challenge? A systematic review of literature. Med Oncol 2017;34:1-5.
16. Zheng X, Chen S, Li L, Liu X, Liu X, Dai S, *et al*. Evaluation of HE4 and TTR for diagnosis of ovarian cancer: comparison with CA-125. J Gynecol Obstet and Hum Reprod 2018;47:227-30.
17. Romagnolo C, Leon AE, Fabricio AS, Taborelli M, Polesel J, Del Pup L, *et al*. HE4, CA125 and risk of ovarian malignancy algorithm (ROMA) as diagnostic tools for ovarian cancer in patients with a pelvic mass: an Italian multicenter study. Gynecol Oncol 2016;141:303-11.
18. Wei S, Li H, Zhang B. The diagnostic value of serum HE4 and CA-125 and ROMA index in ovarian cancer. Biomed Rep 2016;5:41-4.
19. Huy NVQ, Van Khoa V, Vinh TQ, Tung NS, Thanh CN, Chuang L. Standard and optimal cut-off values of serum ca-125, HE4 and ROMA in preoperative prediction of ovarian cancer in Vietnam. Gynecol Oncol Rep 2018;25:110-4.
20. Dochez V, Caillon H, Vaucel E, Dimet J, Winer N, Ducarme G. Biomarkers and algorithms for diagnosis of ovarian cancer: CA125, HE4, RMI and ROMA, a review. J Ovarian Res 2019;12:1-9.
21. Shen F, Lu S, Peng Y, Yang F, Chen Y, Lin Y, *et al*. Performance of ROMA based on architect CA 125 II and HE4 values in Chinese women presenting with a pelvic mass: A multicenter prospective study. Clin Chim Acta 2017;471:119-25.
22. Oranratanaphan S, Wanishpongpan S, Termrungruanglert W, Triratanachat S. Assessment of diagnostic values among CA-125, RMI, HE4, and ROMA for cancer prediction in women with nonfunctional ovarian cysts. Obstet Gynecol Int 2018;2018:7821574.
23. Choi H-J, Lee Y-Y, Sohn I, Kim Y-M, Kim J-W, Kang S, *et al*. Comparison of CA 125 alone and risk of ovarian malignancy algorithm (ROMA) in patients with adnexal mass: A multicenter study. Current Problems in Cancer 2020;44:100508.