Evaluation the Level of Human Epididymal Protein 4 (he4) in Patients of Suspicious Ovarian Mass with Low Serum Level of Cancer Antigen 125 (ca125)

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■ **Abstract:**

Background: Ovarian cancer is one of the three most common malignant tumors in the female reproductive system. Tools currently in use for differentiating between low- and high-risk patients with ovarian cancer are the tumor markers carbohydrate antigen-125 (CA-125) and the human epididymis protein 4 (HE4), as well as the index value of risk of ovarian malignancy algorithm (ROMA).

Objective: to evaluate the role of the HE4 in Cases of suspicious ovarian mass with low serum level of CA125.

Subject: This study included 35 patient with Ovarian mass diagnosed by clinical examination, ultrasonographical, OR/ and Radiological examination. Patient with serum level of CA125 less than 100. No history of chemotherapy or radiotherapy. No history of another malignancy.

Results: There was no significant association between CA125, HE4 and ROMA against pathological findings, LN affection and ascites. There was a significant relation between Family history for cancer and ovarian tumour, history of OCP.

Conclusion: Tumor marker CA125 is low sensitivity and specificity than HE4 in determination of ovarian malignancy. The presence of normal serum level of CA125 does not exclude presence of ovarian malignancy.

■ **Key words:** human epididymal protein 4 (HE4) - suspicious - ovarian mass - serum level of cancer antigen 125

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■ **المستخلص:**

- **الخلفية:** سرطان المبيض هو واحد من أكثر ثلاثة أورام خبيثة شيوعًا في الجهاز التناسلي للأنثى. الوسائل اللانجابية المساعدة حاليًا للتمييز بين مرضى سرطان المبيض منخفض وعالي الخطورة هم مستضد السرطان 125 (CA-125) وبروتين البربخ البشري 4 (HE4) ، بالإضافة إلى قيمة مؤشر خطر الإصابة بالمبيض)خوارزمية الورم الخبيث).

- **الهدف:** تقييم دور HE4 في حالات وجود كتلة مبيض مشبوهة ذات مستوى مصل منخفض من CA125.

- **الموضوع:** تضمنت هذه الدراسة 35 مريضة مصابة بكتلة مبيض تم تشخيصها عن طريق الفحص السريري ، وفحص الموجات فوق الصوتية ، والفحص الإشعاعي. كان جميع المرضى لديهم مستوى CA125 في الدم أقل من 100 وليس لهم تاريخ من العلاج الكيميائي أو العلاج الإشعاعي ولا يوجد تاريخ لورم خبيث آخر.

- **النتائج:** لم يكن هناك ارتباط معنوي بين مستضد السرطان 125 (CA-125) وبروتين البربخ البشري 4 (HE4) ، بالإضافة إلى قيمة مؤشر خطر الإصابة بالمبيض ضد النتائج المرضيه. كانت هناك علاقة ذات دلالة إحصائية بين التاريخ العائلي للسرطان وأورام المبيض، وتاريخ موانع الحمل الفمويه.

- **الخلاصة:** علامة الورم CA125 لها حساسية وخصوصية منخفضة في تحديد ورم المبيض الخبيث. إن وجود مستوى مصل طبيعي من CA125 لا يستبعد وجود ورم خبيث في المبيض.

■ Introduction:

Epithelial ovarian cancer (EOC) has the highest mortality of all gynecological cancers and is the fifth leading cause of mortality due to cancer among women. Despite relatively low incidence (approximately 1/100 000 new cases per year), EOC presents a high case-to-fatality ratio.[1]

That progression of the disease is relatively symptomless makes a significant contribution to the high mortality rates. The 5-year survival rate for EOC is approximately 45%, largely due to the high proportion of cancer cases that are not detected until they have spread beyond the ovary to the pelvis and upper abdomen. Early stages of the disease remain without symptoms, with the first signs typically occurring at an advanced stage. Thus, ovarian cancer is commonly known as a 'silent killer'.[2]

Clinical outcome and survival may be significantly improved by identifying the disease in its early stages without the need for altering surgical or chemotherapeutic approaches. Although certain ovarian cancer screening tests have been shown to decrease mortality rates, the possibility of efficient screening that may be used in everyday practice remains elusive. Measurement of serum CA125 antigen remains the gold standard.[3]

The best-studied serum marker for ovarian cancer, CA125, is elevated in less then half of early stage EOC cases and is not expressed in approximately 20% of ovarian cancers resulting in a decrease of sensitivity.

The lack of specificity of CA125 is secondary to its levels being elevated in a number of benign gynecological and non-gynecological conditions.

As such, in recent years over 45 new or already known substances have been verified as ovarian cancer biomarkers, such as human epididymis protein 4 (HE4) and soluble mesothelin-related protein (SMRP). Novel biomarkers alone or combined with CA125 potentially increase the sensitivity and specificity of CA125.[4]

HE4 protein was first identified in the epithelium of the distal epididymis and was predicted to be involved in sperm maturation as a protease inhibitor. This protein has a WAP-type four-disulphide core (WFDC) domain and is encoded by the WFDC2 gene. In malignant ovarian neoplasms upregulation of that gene was observed. In patients with ovarian tumors, sensitivity of the HE4 protein is similar to CA125 but specificity for malignancy was increased as compared to benign disease.[5]

HE4 level were found increased with age and smoking status, HE4 is a novel serum marker which is more sensitive in prediction of risk of ovarian malignancy than CA125 alone in patient with ovarian mass.[6]

■ Aim of the work:

The aim of the present study was to Evaluate the Role of the HE4 in Cases of Suspicious Ovarian Mass with Low Serum Level of CA125.

■ Patients:

The study was carried on (35) patients reruited from gynecological oncology clinic at El-Shatby Matetnity University Hospital were presenting with suspicious ovarian masses about 10cm or more as being detected clinically

and\or by two –dimensional ultrasonic examination and low or normal serum level of CA125.

■ **Inclusion criteria including: -** *No history of chemotherapy or radiotherapy, - No history of another malignancy and patients with suspicious adnexal mass*

The criteria of suspicious mass were: *Including the adnexa; Bilateral; Fixed or adherent to other organs; Solid or variable in consistency by ultrasound; Cystic or presence of papillae by ultrasound; Ascites*

Exclusion criteria: - *Another malignant disease. Exposure to Radiotherapy or chemotherapy.*

Methods:

Patients recruitment and sample collection were performed within the guidelines of protocol approved by institutional review boards. After approval of local Ethics committee, a written informed consent was obtained from all subjects.

The study included (35) females recruited from El-Shatby Maternity University Hospital.

All cases were subjected to:

A. At booking:

• Comprehensive history taken:

• Full examination (general & gynecological):

General examination: general signs of malignancy (anemia, manifestation of metastasis) edema and ascities.

Abdominal and pelvic clinical examination to determine site, size, unilateral or bi lateral and mobility of mass.

· **Ultrasonographic scanning:**

Using transvaginal probe or/ and trans abdominal probe to assess size, shape, papillae and borders of ovarian mass, present ascitis.

B. pre-operative blood sample for:

• CBC, liver functions, kidney functions.

- Serum level of CA125` were done using immune assay (normal level<34 U/ml).

C. **pre-operative imaging procedures:**

- *Chest X-ray.*
- *CT–scan and / or MRI chest, abdomen and pelvis in patients with ultrasonographical suspicious mass for:*

1. Metastatic disease.

2. Nodal involvement.

3. Tumor bulk.

D. pre-operative serum sample from all patients were obtained, and analyzed for level s of HE4:*(normal level<150picomoles/L)*

(Blood (20 ml) was collected, clotted for 60 min and centrifuged. The serum fraction was removed and stored at −70°C until use. Serum level of, HE4 were measured using bead-based immunoassay kits from commercial suppliers according to manufacturers' instructions.)

Method for calculation of the ROMA:[8]

In pre menopausal woman:

ROMA=-12.0+2.38*LN(HE4)+0.0626*LN(CA125)

In post menopausal woman:

ROMA=-8.09+1.04*LN(HE4)+0.732*LN(CA125)

Also it could be calculated by special soft ware. ROMA calculates arisk of finding ovarian cancer during surgery.

E. Operative procedure:

- *Comprehensive surgical staging plus total abdominal hysterectomy and bilateral salpingo oophorectomy and pelvic lymphadenctomy, omentectomy in suspicouses malignant mass depended (Stage of malignant, age and parity).*
- *Adnexectomy or TAH with BSO (menopausal women) for benign cases predicted by vaginal ultrasound examination or other Radiological examination.*

D. **Histopathological examination for all cases and recording data.**

■ RESULTS:

The basic demographic data showed that the age ranged between 17-70 with the mean of 46.59±15.08 years, most of the studied patients more than 45 years (71.4%). Post menopause was found in 42.9%, menstruated was found in 57.1%. Most of the studied patients (94.3%) were married and only 5.7% of the studied patients were single (Virgins), 57.1% of the studied patients were life in urban and 42.9% were life in rural. The body mass index, demonstrated that, normal weight were found in 40.0%, over weight were found in 45.7% and obese were found in 14.3% of the studied patients.

The Maternal history of the studied groups showed that Gravidity were found in most of the studied patients 31 (88.6%) of the studied sample. It ranged between 0-13 with the mean of 4.03±3.22. Parity ranged between 0-8 with the mean of 3.5±2.37, most of them (88.6%). Abortion ranged between 0-9 with the mean of 0.64±2.06.

The past medical history showed that, most of the studied patients don't have any medical history (negative), 28.6% with DM and 28.6% with hypertension. While the past surgical history was negative in most of the studied patients (71.4%), C/S were found in 14.3, and sub total abdominal hysterectomy (STAH) were found in 8.6%.

The family history showed that the studied patients (60.0%) negative family history and (40.0%) were positive.

The history of oral contraceptive pill (OCP) was as follows, 51.4% of the studied patients negative for history of OCP, while 17% were positive.

Clinical symptoms was *lower abdominal in 34.3%, abdominal distention in 42.9%, abnormal bleeding in 20.0% and dysparonia were found in 17.1%, notes that more than one complain in the same patients.*

Clinical data:

Positive LN were found in 37.1% of the studied patients and negative were found in only 62.9 of the studied patients. Ascites were found in 12 (34.3%) of the studied patients and mild degree were found in 28.6%, moderate in 25.7% and severe were found in 5.7%.

Histopathological type of patients

The histopathological type of patients, Malignant degree were found in 34.3% of the patients including: 8.6% serous adenocarcinoma, 5.7% mucinous adenocarcinoma, 11.4% endometroid adenocarcinoma, 2.9% immature

terotoma, and 5.7% clear cell carcinoma. Benign degree were found in 28.6% of the studied patients including: 8.6% mature terotoma, 14.3% fibroma, 5.7% chronic abscess. Border line were found in 37.1% of the studied patients, including: 20.0% border line mucinous adenocarcinoma, and 17.1% border line serous adenocarcinoma.

■ **Staging**

The staging, was 7 (20.0%) of the patients were staging (2), 6 (17.1%) of the patients were staging 1, 4 (11.4%) of the patients were staging (4).

Relation between HE4, ROMA and CA 125 in relation to pathological finding

Relation between HE4, ROMA and CA 125 in relation to pathological finding were presented in table (1), it showed that, there were no statistical significant relation between HE4, ROMA, CA 125 with pathological finding.

Relation between HE4, ROMA and CA 125 in relation to LN affection

Relation between HE4, ROMA and CA 125 in relation to LN affection were presented in table (2), it showed that, there were no statistical significant relation between HE4, ROMA, CA 125 with LN affection.

Relation between HE4, ROMA and CA 125 in relation to ascites in patients

Relation between HE4, ROMA and CA 125 in relation to ascites were presented in table (3), it showed that, there were no statistical significant relation between HE4, ROMA, CA 125 with ascites

Table (1): Relation between HE4, ROMA and CA125 in relation to pathological findings.

	Pathological findings			F	p
	Benign	Malignant	Border line		
Pre operative CA125	*29.84±30.39*	*46.30±28.03*	*28.55±17.68*	*1.517*	*0.235*
Preoperative HE4	*32.14±24.61*	*34.69±20.60*	*38.60±18.32*	*0.136*	*0.873*
ROMA	*67.33±59.16*	*73.17±39.78*	*81.68±44.11*	*0.151*	*0.860*

Table (2): Relation between HE4, ROMA and CA125 in relation to LN affection.

	LN affection		F	p
	No	Yes		
Pre operative CA125	*30.50±3.54*	*41.08±28.58*	*0.266*	*0.609*
Preoperative HE4	*22.50±7.78*	*35.48±20.96*	*0.743*	*0.395*
ROMA	*43.45±18.74*	*75.02±44.00*	*0.995*	*0.326*

Table (3): Relation between HE4, ROMA and CA125 in relation to ascites in patients.

	Ascites		F	p
	Yes	No		
Pre operative CA125	*43.20±29.59*	*36.38±25.51*	*0.496*	*0.486*
Preoperative HE4	*31.05±20.57*	*40.29±20.11*	*1.724*	*0.198*
ROMA	*67.12±44.51*	*82.36±41.71*	*1.033*	*0.317*

Relation between family history for cancer and ovarian tumour

Table (4) shows relation between family history for cancer and ovarian tumour, it demonstrated that, there were statistical significant relation between positive family history with ovarian tumour. (P=0.001).

Table (4): Relation between Family history for cancer and ovarian tumour.

	Positive family history		Negative family history		Total
	.No	%	.No	%	
Benign	*8*	*57.1*	*4*	*19.0*	*12*
Malignant	*1*	*7.1*	*9*	*42.9*	*10*
Border line	*5*	*35.7*	*8*	*38.1*	*13*
Total	*14*		*21*		
X^2	*12.65*				
p	**0.001*				

Relation between body mass index and ovarian tumour

Table (5) shows relation between body mass index and ovarian tumour, it demonstrated that, there were no statistical significant relation between body mass index with ovarian tumour. (P>0.05).

Table (5): Relation between body mass index and ovarian tumour.

	Normal weight		Over weight		Obese		Total
	No.	*%*	*No.*	*%*	*No.*	*%*	
Benign	*6*	*42.9*	*5*	*33.3*	*1*	*20.0*	*12*
Malignant	*4*	*28.6*	*3*	*20.0*	*3*	*60.0*	*10*
Border line	*4*	*28.6*	*7*	*46.7*	*2*	*40.0*	*13*
Total	*14*		*15*		*5*		
X^2	*1.98*						
p	*0.452*						

Relation between history of OCP and ovarian tumour

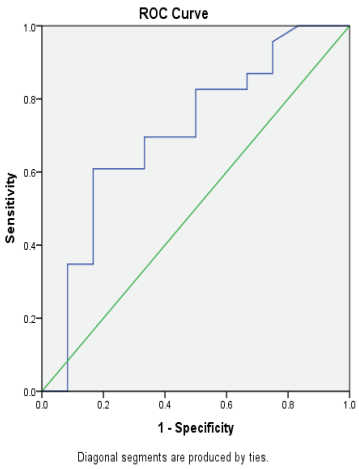
Table (6) shows relation between history of OCP and ovarian tumour, it illustrated that, there were statistical significant relation between positive history of OCP and ovarian tumour. (P=0.0166).

Table (6): Relation between History of OCP and ovarian tumour.

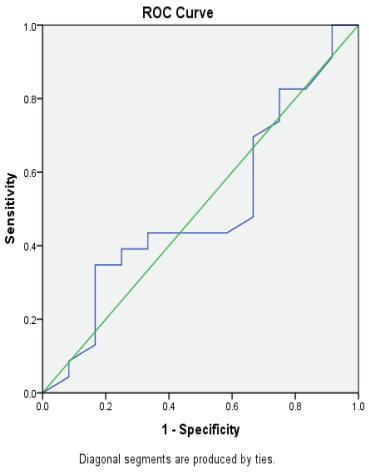
	Positive history of OCP		Negative history of OCP		Total
	.No	*%*	*.No*	*%*	
Benign	*10*	*55.6*	*2*	*11.8*	*12*
Malignant	*3*	*16.7*	*7*	*41.2*	*10*
Border line	*5*	*27.8*	*8*	*47.1*	*13*
Total	*18*		*17*		
X^2	*10.68*				
p	**0.0166*				

Table (7): Area Under the Curve; Test Result Variable(s): pre operative CA125, HE4 and ROMA

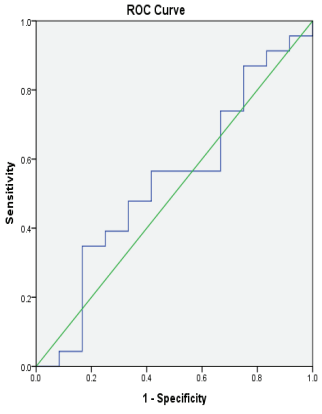
	Area	Cut off value	P value	Sensitivity	1 - Specificity	Asymptotic 95% Confidence Interval	
						Lower Bound	Upper Bound
CA125	*0.705*	*≥35.80*	*0.050*	*0.522*	*0.167*	*0.514*	*0.895*
HE4	*0.504*	*≥40.5*	*0.972*	*0.391*	*0.333*	*0.298*	*0.710*
ROMA	*0.536*	*≥70.70*	*0.728*	*0.565*	*0.667*	*0.328*	*0.744*



CA125



HE4



ROMA

Figure (1): ROC curve to determine the sensitivity, specificity of CA 125, HE4 and ROMA in predict the pathological findings.

■ Discussion:

Results of operative findings and histopathological findings were compared to findings of serum level of CA125 and HE4 to find out the accurancy and sensitivity of two tumor markers in the diagnosis of the nature of ovarian masses before surgery. The mean age of our studied patients was 45 years, fifteen patients (42.9%) patients were post menopausal while twenty patients (57.1%) were menstruating. The mean age and menstrual agreed with the mean age and menstrual status of the most published series.

Mansour T, 2020, carried out a study to compared three –dimensional ultrasound and magnetic resonance imaging techniques in diagnosis of nature of ovarian masses in 40patients.the mean age of his studied was 47years withSD±46. 18 patients (45%) were postmenopausal while 22patients (55%) were menstruating.[9]

In our study, gravidity were found in most of the studied patients 31 (88.6%) of the studied sample. It ranged between 0-13 with the mean of 4.03±3.22. Parity ranged between 0-8 with the mean of 3.5±2.37, most of them Abortion ranged between 0-9 with the mean of 0.64±2.06.

Yeoh, M, 2015, studied 60 cases with malignant ovarian tumor by two-dimensional ultrasound and computed tomography, and found that 48 cases (80%) were in low parous patients.[10]

In this study, it was found the Most of the studied patients don't have any medical history (negative), 28.6% with DM and 28.6% with hypertension. Negative were found in most of the studied patients (71.4%), C/S were found in 14.3%. Most of the studied patients (60.0%) negative family history and (40.0%) were positive. 51.4% of the studied patients negative for history of OCP, while 17% were positive. Normal weight were found in 40.0%, over weight were found in 45.7% and obese were found in 14.3% of the studied patients.

In this study, it was found the highest percentage of patients (15) complaining of abdominal distention (42.9 %),12cases (34.4%) were asymptomatic, one case (3,1%) of bleeding respectively. There was5 cases (16%) complained of lower abdominal pain, one case (3.1%) were complained dysparonia, and one case (3.1%) complained of infertility

Sharadha et al, 2015, reported that the most common presenting symptoms

of malignant ovarian tumors were abdominal distention, abdominal pain, and menstrual irregularities. At the end of the work,32cases were malignant of them 16 cases (50%) complained of abdominal distention, 5cases (15.6%) complained of abdominal pain,4cases (12.5%) complained of bleeding, 4cases (12.5%) complained of weight loss.3cases (9.4%) were asymptomatic.[11]

In our study, most of the studied patients don't have any medical history (negative), 28.6% with DM and 28.6% with hypertension. Negative were found in most of the studied patients (71.4%), C/S were found in 14.3%. Most of the studied patients (60.0%) negative family history and (40.0%) were positive. 51.4% of the studied patients negative for history of OCP, while 17% were positive.

Barnard et al, 2023, reported that there is a18 folds increased risk among women who had a mother or sister with epithelial ovarian cancer.[12] *Deng et al, 2022, reported that women with an initial primary malignancy of the breast, endometrium, or colon have two to four times greater risk of developing a subsequent ovarian cancer than women of comparable age and race having no malignancies.*[13]

Qian et al, 2023,found that 40% of benign ovarian masses, 74% of border line tumors and 100% of epithelial ovarian carcinoma had abnormal levels of CA125.[14]

Charkhchi et al, 2020,found that the serum CA125 levels was abnormal in 85.1% in epithelial ovarian carcinoma pre operatively while the other 15.9% had a normal levels. The stated that the serum levels of CA125 were elevated in 75% of grade I ovarian malignancy.[15]

Ascites were found in 12 (34.3%) of the studied patients and mild degree were found in 28.6%, moderate in 25.7% and severe were found in 5.7%. this was agreement Ibrahim et al., Haller et al, and Sladkevicius P et al, found that ascites was present in 32%,65.9%,and 28.6% of patients with ovarian cancer. also in our study ascites was absent in patients with benign adnexal masses. this was agreement with Sladkeviccius et al.[16,17,18]

In our study malignant changes were common in mixed adnexal lesions than in cystic lesions, and this was agreement with Sladkevicius P et al,[18]

In our study presence of papillae were associated with malignant changes (70% of patients with papillae were with malignant lesions) and absent in

benign lesion. this was agreement with Boyacıoğlu et al., and Hassen Ket al, they found that papillae were present in 33% of malignantadnexal masses and absent in benign masses.[19]

In our study malignant masses werelarger in sizes than benign masses. and this was agreement with Sladkevicius et al.[18]

In our study, malignant mass were found in 34.3% of the patients including:11.4% serious adenocarcinoma, 5.7% mucinous adenocarcinoma, 8.6% endometroid adenocarcinoma, 2.9% immature terotoma, and 5.7% clear cell carcinoma. Benign degree were found in 28.6% of the studied patients including: 8.6% mature terotoma, 14.3% fibroma, 5.7% chronic abcess. Border line were found in 37.1% of the studied patients, including: 20.0% border line mucinous adenocarcinoma, and 17.1% border line serous adenocarcinoma.

This was agreement with Pelayo et al, and Abdullah LS et al, where benign adnexal masses were present in (53%,72.8%), where malignant masses were present in (45%,22%), and border line lesions were present (2%,5.2%) respectively.[20,21]

Serous adenocarcinomas were the commonest ovarian cancer subtype followed by endometroid, mucinous, teratoma and clear cell carcinoma this was agreement with McCluggage, they found that serous sub type is the commonest (43.3%, 33.3%, 67.6%, 42.4%, 11.3%, 41.5% respectively). This was not agreement with Gilks R et al while endometrioid subtype was the commonest subtype, present 34.4% of cases.[22,23]

Kadija, et al., (2012), determine the diagnostic potential of human epididymal protein 4 (HE4), the combination of HE4+CA125, and the Risk of Ovarian Malignancy Algorithm (ROMA) for patients with pelvic mass, particularly in differentiating endometriosis from carcinoma. A prospective cross-sectional study was conducted at the Clinic for Gynecology and Obstetrics, Clinical Center of Serbia. Serum samples were obtained preoperatively from 108 women undergoing surgery for pelvic mass; 29 of them had ovarian carcinoma, and 79 had a nonmalignant ovarian disease (39 with benign tumor, 20 with endometriosis, 20 healthy controls). Sera were analyzed for the levels of HE4 and CA125 and were then compared with the final pathologic results. The diagnostic performance of HE4 and CA125 was estimated using receiver operating characteristic curve and area under the receiver operating

characteristic curve. They found that, the level of HE4 and CA125 was significantly higher among the patients with malignant tumors, compared with patients with nonmalignant disease. At the predefined specificity of 95%, HE4 and CA125 showed sensitivity of 65.5% and 58.6%, respectively, whereas the combination of HE4+CA125 reached 68.9% at the same specificity. Importantly, the level of HE4 did not differ significantly between the patients with endometriosis and with other nonmalignant diseases (which was not the case with CA125). Risk of Ovarian Malignancy Algorithm classified 96% of benign premenopausal cases as at low risk for ovarian cancer.[24]

Wei, et al., (2016), demonstrated that, the early diagnosis of ovarian malignancies is one of the key factors for improving the survival rate of patients[125]*. CA-125 has been used as a tumor marker for the diagnosis and monitoring of ovarian cancer for 30 years, and is also used for efficacy evaluation and monitoring of recurrence. Data have shown that the serum levels of CA-125, HE4 and ROMA in ovarian cancer patients were significantly higher than those of the patients with ovarian benign disease and healthy women. The specificity and positive predictive value of HE4 for ovarian cancer was the highest, and the sensitivity of ROMA index was the highest.*[25]

In their study, the 158 cases were divided into the premenopausal and postmenopausal group to evaluate the three indicators in the diagnostic value of ovarian cancer. The ROMA index demonstrated the highest sensitivity and negative predictive value for ovarian cancer. HE4 had the highest specificity and positive predictive value.

The specificity of HE4 for ovarian cancer was higher in the postmenopausal women, as reported elsewhere.[26]

In this study, there were no statistical significant relation between HE4, ROMA, CA 125 with LN affection and ascites.

The sensitivity, specificity, positive predictive value and negative predictive value of the ROMA index in ovarian cancer were the highest (91.89, 96.97, 97.14 and 91.45%), respectively. CA-125 and HE4 were significantly different from the ROMA index, and the ROMA index was significantly better than CA-125 and HE4 in the diagnosis of ovarian cancer.

In addition, the ROC curve drawn in this study for the benign tumor of ovary and healthy control groups, identified that the area under the ROC

curve of CA-125, HE4 and ROMA index was increased by 0.941, 0.990 and 0.994, respectively. This result confirmed the clinical diagnostic value of the ROMA index [113]. It also showed that detection of ROMA index in the diagnosis of ovarian cancer was higher than CA125 and HE4.

Fujiwara, et al., (2015) evaluated HE4 levels and ROMA as diagnostic tools of type I and type II EOC in Japanese women. They found that, no obvious linear trend was noted and the Pearson correlation coefficient was 0.14 (p = 0.19). When CA125 and HE4 levels in premenopausal patients with endometriotic cyst were evaluated, the CA125 level was elevated to above the cutoff value (35 U/mL) in 80 % (24/30) of cases, whereas the HE4 level was not elevated.[27]

■ **Conclusions:**

The main challenge for gynecologist is to differentiate benign from malignant ovarian masses. The clinical evaluation, including detailed history, abdominal and pelvic examinations, alone, is ineffective method of determination of nature of the ovarian masses as it lacks sufficient sensitivity and specificity. Despite of these limitations, it is important as it directs us to do further investigations in presence of abnormal clinical findings.

Tumor marker CA125 is low sensitivity and specificity in determination of ovarian malignancy. The presence of normal serum level of CA125 does not exclude presence of ovarian malignancy.

■ **Recommendations:**

■ **The study recommends:**

· Making randomized controlled studies based on large sample sizes to test HE4 and ROMA as markers for screening and diagnosis of ovarian cancer.

- Studying the relation between HE4&ROMA and different gynecological cancers.
- Further studies to set HE4 level as prognostic factors or indicator for survival in patients with ovarian cancer and as indicators for chemotherapy response in patients with advanced ovarian cancer.
- Study HE4 levels in relations to para aortic LN affection in patients with ovarian cancer.

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