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Comparison of Human Epididymal Protien 4(He4), Cancer Antigen 125(Ca125) and Risk of Ovarian Malignancy Algorithm (Roma) As Diagnostic Tests In Ovarian Tumour

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ABSTRACT
OBJECTIVE: Comparison of the efficacy of CA125, HE4 and ROMA for diagnosis of ovarian tumours and to differentiate benign from malignant ovarian tumours preoperatively in premenopausal and postmenopausal women.
METHODS: All patients who were diagnosed as ovarian tumour by Ultrasonography, Computed-tomography or Magnetic resonance (n=72) were included and underwent surgery or biopsy. The definitive diagnosis and typing of tumour however was based histopathological study (WHO Criteria). The diagnostic efficacy of serum HE4 , CA 125 and ROMA were than calculated. The sensitivity and specificity of each parameter were analysed. The receiver operating curves and the area under the curve(AUC) were calculated for the accuracy of each marker for prediction of ovarian malignancy.
RESULTS: For the diagnosis of ovarian malignancy, HE4 and ROMA showed the highest AUC value of 0.938 in overall patients whereas ROMA showed highest AUC value of 0.927 in premenopausal women. When the optimal cutoff values were applied, the sensitivity of CA125, HE4 and ROMA were 84.3%,84.5% and 87.5% respectively while the specificities were 92.5%,95% and 92.5% respectively in overall patients. PPV and NPV of CA125, HE4 and ROMA 90 and 88.1, 93.1 and 88.4 and 90.3 and 90.2 respectively.
CONCLUSION: The overall and premenopausal specificity was highest of HE4 in differentiating benign from malignant ovarian tumor. However, in postmenopausal women sensitivity of CA125 was found to be highest and specificity of HE4 and ROMA was found to be highest in detecting ovarian malignancy.
KEYWORDS: CA125, HE4, ROMA, Tumour marker, ovarian malignancy, sensitivity and specificity.

I. INTRODUCTION

About 90% of the ovarian cancers are epithelial and out of these the most common being serous carcinoma. According to the population based cancer registration in India, ovarian cancer is the third leading cancer among women next to cervix and breast cancer and comprising up to 8.7% of cancer in different parts of country.[1,2]Unfortunately, the common symptoms of ovarian cancer are vague and non specific similar to those observed in other benign conditions and most of the patients are diagnosed at advanced stages and thus resulting in late presentation of the patient.[3,4,5]

There are lots of diagnostic methods for ovarian tumour evaluation including the clinical examination, imaging modalities and serum biomarkers in clinical practice.[7] Carbohydrate Antigen 125 (CA 125) is the most widely used tumors marker in ovarian cancers and has been used since 1983 by Bast et al for monitoring of ovarian cancer, diagnosis, effective evaluation and recurrence.[8] In women with epithelial ovarian cancer ; 80% have CA125 levels >35 U/L, with elevations of 50-60% in clinically detected stage 1 disease, 90% in stage 2 and >90% in stage 3 and 4.[6] Its levels are raised in approximately 80% of all the epithelial ovarian cancers (EOC) and in only 50% of stage 1 EOC.[10] Thus the SN and SP of CA125 are not high enough for population screening for the detection of early stage ovarian carcinoma.[11]

A new tumour marker Human Epididymal Protein 4 (HE4), also known as WAP-type four disulphide core 2 (WFDC2) has emerged as one of the good biomarkers for the diagnosis of ovarian epithelial cancers. The sensitivity was similar to that of CA125 but with higher specificity.[9] Moreover serum expression of HE4 in non gynaecological carcinoma has not been reported. HE4 has the highest sensitivity of 72.9% and specificity of 95%.[12]

In order to utilise the value of existing detection and to further improve the accuracy of

early diagnosis of ovarian cancer while simultaneously assessing the risk of ovarian cancer and combining the research results and the relevant statistical analysis, the ROMA (Risk of ovarian malignancy algorithm) index value has been introduced.[13] The ROMA index value is an algorithm that takes into account the levels of CA125 and HE4 together with menopausal status using quantitative and objective parameters.[14] In 2011 a combination of CA125 ,HE4 and risk of ovarian malignancy algorithm (ROMA) score was approved for the differential diagnosis and malignancy assessment in women with pelvic mass.[15] Research demonstrates that examining levels of CA125 and HE4 using ROMA algorithm shows highest accuracy in determining ovarian carcinoma risk in pre and post menopausal women with an ovarian mass. The morbidity and mortality are markedly increased in advanced stages and this makes early detection and diagnosis very important. The ovarian tumour has the highest fatality-to-case ratio to all the gynecologic cancers.[19] The early diagnosis of ovarian malignant tumour becomes a key factor in improving the survival rate of patients.

II. MATERIALS AND METHODS

This was a prospective study conducted on patients coming to the Department of Obstetrics and Gynaecology of Kamla Nehru state hospital for mother and child, IGMC Shimla after approval from hospital ethical committee and after taking written informed consents between 1st august 2019 to 31st july 2020. A total of 77 patients between the age of 20 and 65 years were included in this study.

INCLUSION CRITERIA –

All the patients diagnosed as a case of ovarian tumour through imaging analysis and scheduled for surgical intervention.

EXCLUSION CRITERIA-

1)Pregnancy 2)Received cytotoxic chemotherapy or hormonal therapy 3)Serious debilitating heart, liver ,kidney disorders or diabetes mellitus 4)Previously diagnosed disease commonly associated with increase in CA 125.

III. METHODOLOGY-

All the patients who were diagnosed as ovarian tumour by Ultrasonography(USG), Computed-tomography(CT) or Magnetic resonance(MR) were included in this study. Blood sample for CA 125 and HE4 were taken prior to surgery or biopsy. The post menopausal patients were considered to be those who had not experienced menses for at least one year. All the patients in the study underwent surgery or imaging-guided biopsy(when they presented with signs of carcinomatosis) following which specimen were sent for histopathology.CA 125 and HE4 assay were done two days prior to surgery or imaging guided biopsy two blood samples (2 ml each) were withdrawn and centrifuged within 30 minutes of collection to obtain serum. The serum was stored at a controlled and monitored temperature of 2-8 degree C (4 days) and -20 degree C (more than 4 days) in case of HE4 and 2-8 degree C(7 days) and -20 degree C (more than 7 days) in case of CA 125. Serum samples were tested using chemiluminescent microparticle immunoassay (CMIA). The cut off values by this method for HE4 in premenopausal women is <70 pmol/ml and for postmenopausal women is <140 pmol/ml and for CA 125 the cut off is <2.0-35.0U/ml.

ROMA INDEX CALCULATION- From this , a predictive index (PI) was calculated :

Premenopausal – PI= $12+2.38\times LN[HE4] + 0.0626\times LN[CA\ 125]$

Postmenopausal-PI= $8.09+1.04\times LN[HE4] +0.732\times LN[CA\ 125]$

LN=natural logarithm Predicted probability (PP)=exp(PI)/[1+ exp(PI)×100 where , exp(PI) = ePI.

All patients than underwent surgery or biopsy. The definitive diagnosis and typing of tumour however was based histopathological study (WHO Criteria). The diagnostic efficacy of serum HE4 , CA 125 and ROMA were than calculated.

IV. STATISTICAL ANALYSIS

SPSS 22.0 Statistical software (SPSS 22.0 V,inc.,Chicago, IL,USA) was used for statistical analysis. HE4 , CA 125, ROMA index and other non-normal measurement data were shown as quartile interval. The sensitivity and specificity analysis was done using MedCalc Version 19.6.4 (Acacialaan 22 8400 Ostend Belgium). By use of Binary Logistic regression and Pearson's chi-square test, data were statistically analysed. $P<0.05$ was considered to indicate a statistically significant difference.

V. RESULTS

Out of 77 patients, five patients were excluded from this study due to following reasons: technical problems were encountered for two patients, two patients had a subserous leiomyoma instead of an ovarian tumour and one patient had mesenteric cyst.The characteristics of the studied population, including age, parity, menopausal status, family history of other gynaecological cancers and other demographic characteristics are

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shown in Table 1. Histological types for both benign and malignant tumours are shown in Table 2. Low malignant potential tumours were included in the benign group during analysis.

Table 1: Demographic characteristics of the patients.

Characteristics	**Total(n=72)**
AGE IN YEARS, n(%)	
<35	13(18.1)
35-55	46(63.9)
>55	13(18.1)
PARITY, n(%)	
NULLIPAROUS	18(25)
MULTIPAROUS	54(75)
MENOPAUSAL STATUS, n(%)	
PREMENOPAUSAL	49(68.1)
POSTMENOPAUSAL	23(31.9)
FAMILY HISTORY OF OTHER GYNAECOLOGICAL CANCERS, n (%)	
SIGNIFICANT	1(1.4)
NON SIGNIFICANT	71(98.6)
PERSONAL HISTORY, n(%)	
SMOKER	3(4.1)
NON SMOKER	69(95.9)

Table 2: Histological types of ovarian tumours(WHO)

Histology	**n(%)**
EPITHELIAL TUMOUR	46(63.9)
Serous	17(23.6)
Mucinous	16(22.2)
Endometroid	1(1.4)
Clear cell	3(4.2)
Mixed epithelial	5(6.9)
Undifferentiated ca	1(1.4)
Brenner tumour	3(4.2)
SEX CORD STROMAL TUMOUR	3(4.2)
GERM CELL TUMOUR	11(15.3)
SECONDARY METASTATIC TUMOUR	3(4.2)
TUMOUR LIKE CONDITIONS	9(12.5)

In the epithelial tumour group, 17(63.9%) were serous, 17(23.6%) were mucinous and only 1(1.4%) was endometroid whereas 3(4.2%) were clear cell, sex cord stomal and brenner tumour each. Tumour like coditions 9(12.5%) included tuboovarian masses, parovarian cysts, hydrosalpinx and endometriomas.

Each of the serum CA125, HE4 and ROMA cut-offs were evaluated individually. The sensitivity, specificity, PPV and NPV from the ROC curve analysis using the default cutoff and optimal cutoff of each tumour marker are presented in Table 3. This shows that CA125 have a suggested cutoff of 61.6U/ml for overall patients and premenopausal group is similar that is 61.6U/ml whereas it falls to 28.6U/ml in postmenopausal women. Similarly HE4 had a suggested cutoff of 63.8pmol/L in overall cases similar to premenopausal women that is 60.40pmol/L but rises to 110.0pmol/L in postmenopausal women. ROMA had a suggested cutoff of 14.1% in overall cases same as premenopausal women but rises to 57.6% in postmenopausal women.

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Table 3: Comparison of sensitivity, specificity, PPV and NPV of CA125, HE4 and ROMA in predicting ovarian malignancy

	Markers	Conventional cutoffs	Suggested cutoffs	Sensitivity(%)	Specificity(%)	PPV	NPV
A	**OVERALL**						
	CA 125(U/ml)	35.00	61.60	84.37	92.50	90.00	88.10
	HE4(pmol/L)	72.20	68.30	84.37	95.00	93.10	88.40
	ROMA	22.20	14.10	87.50	92.50	90.30	90.20
B	**Pre Menopausal**						
	CA 125(U/ml)	83.80	61.60	77.78	93.55	87.50	87.90
	HE4(pmol/L)	66.00	60.40	83.33	95.55	88.20	90.60
	ROMA	16.60	14.10	83.33	86.77	93.80	90.90
C	**Post menopausal**						
	CA 125(U/ml)	51.20	28.60	100.00	88.89	93.30	100.00
	HE4(pmol/L)	74.20	110.00	92.86	100.00	100.00	90.00
	ROMA	35.90	57.60	85.71	100.00	100.00	81.80

Also, the median values and interquartile range of CA125, HE4 and ROMA were calculated for malignant tumours as shown in Table 4. Median value for CA125 for malignant tumor were serous carcinoma 1000, mixed epithelial carcinoma 84.80 , undifferentiated carcinoma 576.05 and secondary metastatic tumor 125.80.The median value for HE4 for malignant tumor were serous carcinoma 713, mixed epithelial carcinoma 57.00 , undifferentiated carcinoma 327.40 and secondary metastatic tumor 110.80.The median value for ROMA for malignant tumor were serous carcinoma 98.30, mixed epithelial carcinoma 10.60 , undifferentiated carcinoma 98.95 and secondary metastatic tumor 37.90.

Table 4: Serum CA125, HE4 and ROMA levels according to histopathological findings suggesting malignancy.

	CA125		**HE4**		**ROMA**	
	Median	IR	Median	IR	Median	IR
HPE findings - MALIGNANT						
Serous carcinoma	1000	255.40-1214.00	713	130.85 - 1571.50	98.3	72.30 - 99.45
Endometroid carcinoma	--	--	--	--	--	--
Clear cell carcinoma	--	--	--	--	--	--
Mixed epithelial carcinoma	84.8	31.03-1557.20	57	27.60 - 953.48	10.6	2.53 - 78.45
Undifferentiated carcinoma	576.05	45.53-3011.10	327.4	57.18 - 1485.00	98.95	15.35 - 99.85
Secondary metastatic tumor	125.8	124.10-584.90	110.8	93.10 - 211.40	37.9	28.80 - 67.00

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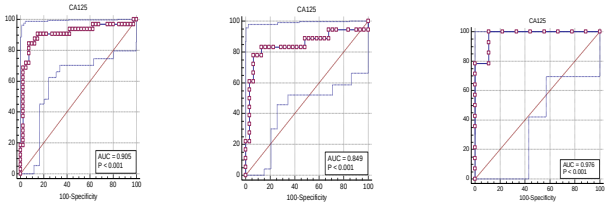
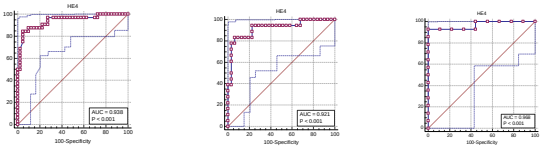
The diagnostic performance of serum CA125, HE4 and ROMA in discriminating ovarian malignancy from benign ovarian tumours was verified using the ROC analysis together with the AUC calculation for each marker depicted in Figure 1. AUC of HE4 and ROMA were 0.938 which was better than CA125 with value of 0.905 for overall patients. similarly AUC of premenopausal women of HE4 and ROMA were0.921 and 0.938 respectively which was better than AUC of CA125 which was 0.849. AUC of CA125 was better in postmenopausal women with a value of 0.976 which was better than HE4 and ROMA which were0.968 and 0.952 respectively. All values were statistically significant with p value of <0.001.

FIGURE 1: ROC Curves for CA125, HE4 and ROMA

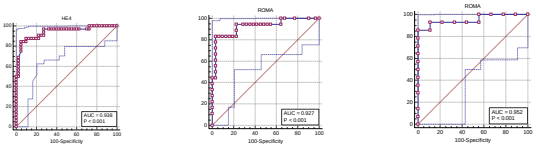
ROC CURVES FOR CA125 - OVERALL, PREMENOPAUSAL AND POSTMENOPAUSAL



ROC CURVES FOR HE4- OVERALL, PREMENOPAUSAL AND POSTMENOPAUSAL



ROC CURVES FOR ROMA- OVERALL, PREMENOPAUSAL AND POSTMENOPAUSAL



VI. DISCUSSION

The present study evaluated the serum levels of CA125 and HE4 in pre and postmenopausal women and combined their values via ROMA for predicting the malignancy status of ovarian/adnexal mass. The optimum diagnosis of the malignant status of masses is important as it facilitates the selection of patients with malignant masses who need urgent referral to gynaecological oncology centres and consequently improves the overall survival rate of patients with ovarian cancer.[16]

In present study, we included the low malignant potential tumour in the benign group as the performance of CA125 and HE4 were not affected despite the inclusion of LMP tumours into the benign group and these tumours are generally managed as benign.[18] We used the cutoff values proposed by manufacturer of 35U/ml for CA125, 140pmol/L for HE4 and 11.4%(premenopausal) and 29.9%(postmenopausal) for ROMA to assess the performance of each marker in evaluation of ovarian tumours.

In present study, overall sensitivity of CA125 was found to be 84.3% which was similar to studies done by T Van Gorp et al 79.5% and Teh et al 88.9%. Sensitivity was found to be less in study done by Anton C et al 61.6% due to heterogeneity of histologic types.Premenopausal sensitivity of CA125 was found to be 77.78% which was similar to studies done by T Van Gorp et al 75% , Anton C et al 77.8% and Teh et al 85.7% [15], [17], [18]. Postmenopausal sensitivity of CA125 was found to be 100% in my study comparable to study done by Teh et al 100% and T Van Gorp et al 90.9% because of less variation in histology and small study group [18], [15]. Specificity of CA125 overall was found to be 92.5%, premenopausal 93.5% and postmenopausal 88.8% which were similar to results by T Van Gorp et al with overall specificity of 81.6%, premenopausal 80.1% and postmenopausal 83.7%, Anton C et al with overall specificity of 86.4%,

premenopausal 82.8% and postmenopausal 86.5% [15], [17]. Suggested cutoff of CA125 was found to be 61.6 overall, 60.4 premenopausal and 28.6 postmenopausal which were similar to results of studies by T Van Gorp et al (62.5 overall, 83.8 premenopausal, 51.2 postmenopausal), Anton C et al (59 overall, 24 postmenopausal) and Teh et al (60 overall, 60 premenopausal and 38 postmenopausal) [15], [17], [18].

Sensitivity, specificity and suggested cut off of HE4 was found to be 84.3%, 95% and 68.3 overall , 83.3%, 95.5% and 60.4 premenopausal and 92.6%, 100% and 110 postmenopausal respectively which were similar to results of studies by T Van Gorp et al (74.5%, 83.3% and 72.2 overall, 67.5%, 90.8% and 66 premenopausal and 77.3%, 66.3% ,74.2 postmenopausal), Anton C et al (75.9%,77.3%,87 overall, 72.2%,82.8%,96 premenopausal and 75%,78.4%,104 for postmenopausal women) and Teh et al (51.9%, 95.1%,70 overall , 50%, 97.7%,70 premenopausal and 53.8%,78.6% , 114 postmenopausal) [15], [17], [18].

Sensitivity, specificity and suggested cut off of ROMA was found to be 87.5%, 92.5% and 14.1 overall , 83.3%, 86.7% and 14.1 premenopausal and 85.71%, 100% and 57.6 postmenopausal respectively which were similar to results of studies by T Van Gorp et al (84.9%, 79.7% and 14.4 overall, 67.5%, 67.5%, 87.9% and 16.6 premenopausal and 90.9%, 91.9% and 35.9 postmenopausal), Anton C et al (75.9%, 81.8% and 13.3 overall, 77.8%, 79.3% and 13.9 premenopausal and 63.9%, 97.3% and 39.7 for postmenopausal women) and Teh et al (88.9%, 89.2% and 11.4 overall , 78.6%, 92% and 10 premenopausal and 100%, 71.4% and 40 postmenopausal) [15], [17], [18].

Our further analysis suggested a better prediction of ovarian malignancy when the CA125 optimal cutoff was increased to 61.6U/ml. The present study showed that the HE4 cutoff of 140pmol/L recommend by the manufacturer may be too high. Reduction of the HE4 cutoff to 68pmol/L increased the specificity to 95.5% in premenopausal and 100% in postmenopausal women. The ROMA cutoff for premenopausal women was 14.1% which was almost same as the value suggested by the manufacturer that is 11.4% but for postmenopausal women, the recalculated ROMA cutoff of 57.6% was higher as compared to the manufacturer's recommended cutoff of 29.9%.

Given these small variations, all the three markers which were used to differentiate adnexal/ovarian masses (CA125,HE4 and ROMA) demonstrated similar levels of accuracy. In present study, we found that the overall and premenopausal specificity was highest of HE4 in differentiating benign from malignant ovarian tumour. However, in postmenopausal women sensitivity of CA125 was found to be highest and specificity of HE4 and ROMA was found to be highest in detecting ovarian malignancy.

VII. CONCLUSION

Ovarian cancer is one of the three most common malignant tumours of female reproductive tract. The common symptoms of ovarian cancer are vague and non specific similar to those observed in other benign conditions and most of the patients are diagnosed at advanced stages and thus resulting in late presentation of the patient. Hence, preoperative diagnosis of ovarian cancer is of utmost importance as it helps in deciding the modality of treatment. When ovarian cancer is detected at an early stage, where the disease is still contained within the ovaries (stage 1) , 5 year survival rate can approach 90% with optimal surgery and currently available combination chemotherapy. Preoperative Diagnosis of epithelial ovarian cancer is also important as it facilitates the selection of patients with malignant masses who need urgent referral to gynecological oncology centres and consequently improves the overall survival rate of patients with ovarian cancer. Histopathological study of the ovarian tumors reveals a wide variety, early evaluation of which will help us to plan for successful management by implementation of alternative procedures to avoid radical surgeries so that women receives maximum benefits with least morbidity.

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