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Original Research Article

Diagnostic accuracy of HE4 and risk of ovarian malignancy algorithm in prediction of ovarian cancer in patients with pelvic mass: a regional cancer centre experience

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ABSTRACT

Background: The current study was performed with an objective to evaluate the diagnostic accuracy of HE4 (human epididymis protein) and ROMA in prediction of ovarian cancer in patients with pelvic mass and to compare HE4 and ROMA with CA-125, and RMI (risk of malignancy index) for ovarian cancer prediction in women with pelvic mass.
Methods: This was a diagnostic study enrolling 200 patients with pelvic mass who had been scheduled for Primary surgery. Serum HE4 and CA 125 levels were measured. HE4, CA 125 and ROMA, RMI were evaluated for sensitivity, specificity, positive predictive value and negative predictive value. The receiver operating characteristic (ROC) plots were graphed and area under the curve (AUC) values was calculated to investigate the accuracy of each marker for predicting ovarian malignancy.
Results: Overall, ROMA showed the highest accuracy as it correctly classified 139/200 (69.5%) patients compared with 133/200 (66.5%) in HE4 and 109/200 (54.5%) in CA 125 and RMI. There were more patients with benign tumors being correctly identified by HE4 (89/119, 74.7%) and ROMA (74/119, 62.1%), than CA 125 which identified 39/119 (32.7%) patients. In our study in premenopausal women ROMA and HE4 have comparable sensitivity (80%and 75%) but higher specificity (64% and 65%) and NPV (86% and 83%) as compared to CA125 which has sensitivity of (83%) but very low specificity (46%) in differentiating benign from malignant masses. In postmenopausal women, HE4 had highest specificity (88%) and, CA125 has highest sensitivity (86%) in detecting ovarian malignancy.
Conclusions: HE4 and ROMA showed a high specificity, but were less sensitivity than CA-125 and RMI in premenopausal women. However, ROMA is of comparable sensitivity and HE4 has highest specificity as compared to CA125 in postmenopausal women.

Keywords: Risk of ovarian malignancy algorithm, Risk of malignancy index, CA-125, HE4, Ovarian cancer, Pelvic

INTRODUCTION

Pelvic masses represent a spectrum of conditions from gynecologic and non-gynecologic causes. Gynaecological causes of pelvic mass represent a wide variety of diseases that may arise from ovaries (functional, benign, malignant), fallopian tubes (pelvic inflammatory disease, malignancy, para-ovarian cyst, ectopic pregnancy), and uterus (fibroid, pyometra, haematometra, uterine malignancy, uterine malformations). Ovarian tumors can be functional, benign, or malignant. Ovarian malignancies can be primary or secondary, with primary tumors originating from epithelial cells, sex cords, or germinal cells.[1,2] The largest number of patients with epithelial ovarian cancer is found in the 60-64 years age group.[3] Gynaecological cancers have increased in India

and are estimated to be around 182,602 by the year 2020 constituting about 30% of the total cancers among women in India. Ovarian cancer being contributing about 19.8% of the total cases.[3] There is increasing evidence that outcomes can be improved if cancer patients are managed by trained gynecological oncologists in multidisciplinary teams.[2,4] This depends on the accurate differential diagnosis of adnexal masses and timely referral of patients with malignant masses to cancer centers. The heterogeneous nature of adnexal masses is one of the causes of preoperative difficulties in these tumors.[4,5]

Ovarian cancer (OC) remains the most lethal of all gynecologic malignancies. One of the reasons for the high fatality rate is that more than 70% of women with ovarian cancer are diagnosed with advanced disease. There is a close correlation between stage at presentation and survival; therefore, early detection of ovarian cancer represents the best hope for mortality reduction and long-term disease control. There is preliminary evidence that screening can improve survival, but the impact of screening on mortality from ovarian cancer is still unclear.[6] Epithelial ovarian cancer set by the world health organization (WHO) recognizes eight histological tumor subtypes: serous, mucinous, endometrioid, clear cell, transitional cell, squamous cell, mixed epithelial and undifferentiated.[7] Serous tumors, which carry the poorest prognosis, are the most common form of ovarian carcinoma and make up 30-70% of all diagnoses.[8]

Preoperative diagnosis of malignant ovarian neoplasms usually involves pelvic examination followed by transvaginal ultrasonography (TVS) and assessment of the serum tumor marker CA 125. Both serum CA 125 and TVS, when used alone, have high sensitivity but limited specificity for the differential diagnosis of adnexal masses.[9] The risk of malignancy index (RMI) is a standardized index commonly used for clinical evaluation of patients with an adnexal mass.[10] The RMI is defined as the product of menopausal status (M), CA 125 level and ultrasound score (U). At present there are three versions of the RMI, each varying slightly in the method of scoring. The original RMI (RMI1) was described by Jacobs et al.[10] and two modifications (RMI2 and RMI3) have subsequently been described by Tingulstad et al.[11,12] The tumor marker CA125, initially described by Bast et al is widely used for the routine diagnosis of adnexal masses.[13] CA 125 is widely distributed on the surface of both healthy and malignant cells of mesothelial origin, including pleural, pericardial, peritoneal and endometrial cells, as well as in normal genital tract and amniotic membrane. CA 125 also has an important role in differentiating benign and malignant pelvic masses, especially preoperatively, as higher CA 125 levels are considered to correlate with a higher probability of malignancy.[14] However, serum CA 125 levels can be elevated in other malignancies as well as various physiological and benign conditions such as endometriosis, uterine fibroids, pelvic inflammatory disease, early pregnancy, and normal menstruation.[14,15] The positive predictive value of CA 125 for ovarian cancer is high among postmenopausal women (96%) but is associated with a lower specificity among premenopausal women given the various benign conditions that can lead to elevated CA 125 levels.[14,16]

Due to the performance limitations of the standard tools and aims to improve the sensitivity, specificity, and positive predictive value of tumor markers in ovarian cancer, a number of new biomarkers have been studied and evaluated to be used in combination with CA-125.Of these, human epididymis protein 4 (HE4), was identified as a promising marker. HE4, encoded by WFDC2 gene, is a secretory protein highly expressed in the distal human epididymis.[16]

In normal adult tissues, HE4 protein is detected in vas deferens, glandular epithelium of the breast and female genital tract, epithelium of respiratory tract, distal renal tubules, colonic mucosa, and salivary glands.[17] Several different mathematical models and scoring systems have been created, based on clinical features, ultrasound findings, and/or serum level of tumor markers, aimed at increasing the diagnostic performance of each individual parameter.[18] One such model is the risk of ovarian malignancy algorithm (ROMA) created by Moore et al. The ROMA combines the tumor markers CA125 and HE4 using two formulas, taking into account the menopausal status of each patient. The ROMA can classify patients as being at low and high risks for epithelial ovarian cancer (EOC), and 93.8% of cases in Moore et al study were correctly classified under the high-risk category.[19] In 2010, Moore et al. concluded that ROMA achieved higher sensitivity than the risk of malignancy index (RMI) for identifying EOC in a prospective multicenter trial in 457 patients.[20]

METHODS

This, study was done at the Gujarat cancer and research Institute, a regional cancer centre, at Ahmedabad, Gujarat using a sample of 200 patients who attended our department between 1 November 2015 and 31 December 2019 for the evaluation of a pelvic mass. This study was a prospective analytic study approved by the Research Ethics Committee. Women aged above than 18 years, with pelvic mass, scheduled for primary surgery at our hospital were enrolled. Blood specimens from these patients were obtained during their first assessment for laboratory work up. All cases underwent surgery. Final histopathology was used as the gold standard test. The blood samples of the patients were collected during their first assessment, before surgical intervention, using standard serum separator tubes (SST) for different biochemical profiles including tumor markers. The samples were centrifuged immediately after collection to get the sera and then analyzed. The remaining sera were stored at -20°C. After collecting the required number of specimens, serum HE4 was measured. Both CA-125 and

HE4 assays were done (Roche-Cobas machine, using electrochemiluminescence 01 with full caliberation in one step). All manufacturer recommendation for maintenance, calibration, and internal quality assessment were followed for both assays. Patients were grouped according to age (pre- and postmenopausal) and lesion type (benign or malignant). The postmenopausal status was defined as one year or more of amenorrhea or an age of 50 years or more if the woman had undergone a hysterectomy. From the variables collected, the RMI was calculated using the formula:

$$RMI\ 2 = U \times M \times serum\ CA - 125$$

where U is the total ultrasound score, M is the menopausal status and CA-125 value in U/ml.[13]

ROMA was calculated using CA-125 and HE4 results as per the manufacturer's recommendations (Abbott Architect ci8200; Abbott Laboratories, Illinois, US). This was followed as recommended by Moore et al by calculating a predictive index (PI) for premenopausal and postmenopausal patients separately using equation 1 and 2 as follows:[19]

PI for premenopausal women:

$$PI = -12.0 + 2.38 * lnHE4 + 0.0626 * ln\,(CA - 125)$$

PI for postmenopausal women:

$$PI = -8.09 + 1.04 * lnHE4 + 0.732 * ln\,(CA - 125)$$

The ROMA score was then obtained using the equation:

$$ROMA\,\% = exp\ PI\ /\ (1 + exp\ PI) \times 100\%$$
$$where\ Exp\ PI = ePI$$

The cut-off value for CA-125 was 35 U/ml as recommended by the manufacturer and the cut-off value for RMI was 200 as proposed by Jacobs et al.[9] The HE4 positive cut-off values for premenopausal and postmenopausal women were >70pmol/l and >140pmol/l respectively. The ROMA score was calculated automatically by the computer program with a standard formula. According to the indications of the manufacturer, an index of ROMA ≥11.4 and ≥29.9% indicates a high risk for the presence of epithelial ovarian cancer in pre- and postmenopausal women, respectively. The risk of ovarian malignancy algorithm (ROMA) score corresponds to predicted probability and is expressed by a percentage rate.[20] Based on the immunoassay for CA125 and HE4, the thresholds may differ to categorize patients in a low or high-risk group.[21] Matching these values to postoperative histopathology resulted in the preoperative prediction values. A comparison study was done for the four parameters (HE4, ROMA,CA-125, and RMI) and the validity indicators including sensitivity, specificity, positive and negative predictive values (PPV and NPV) and efficiency were calculated for two groups separately (premenopausal and menopausal).

RESULTS

Of the 200 women, 106 were premenopausal (age: median: 37, range: 18-55) and 94 postmenopausal (age: median: 56, range: 37-92). Among 200 women with pelvic mass, 81 were malignant & 119 were benign. Histopathology results of all specimens are shown in (Table 1-2).

Table 1: Histopathology results of specimens in the study population (benign, n=119).

Variables	N		N
Epithelial ovarian tumour	1	Mucinous cystadenoma	27
	2	Serous cystadenoma	18
	3	Seromucinous	3
	4	Brenner tumour	4
Germ cell tumours		Dermoid cyst	3
Sex cord stromal tumours	1	Fibroma	5
	2	Thecoma	2
	3	Fibrothecoma	8
Others			
Endometriois	7		
Leiomyoma	16		
Simple cyst	13		
Haemorrhagic cyst	7		
Hydrosalpinx	4		
Ectopic	2		
Total	119		

Table 2: Histopathology results of specimens in study population (malignant, n=81).

Variables	N		N
Epithelial ovarian tumour	1	Serous adenocarcinoma	23
	2	Mucinous Adenocarcinoma	14
	3	Endometroid adenocarcinoma	2
	4	Clear cell carcinoma	2
	5	Borderline tumors (12-Serous, 4-Mucinous)	16
Germ cell tumours	1	Immature teratoma	1
	2	Yolk cell tumour	2
Sex cord stromal tumours	1	Granulosa cell tumurs	15
	2	Sertoli leydig cell tumour	1
Malignant mixed mullerian tumour of ovary			1
Metastatic			4
Total			81

The histopathological classification of ovarian tumours included surface epithelial, sex-cord stromal and germ cell tumours. Lesion that did not fit into any of these groups was termed as "others". In our study mucinous cystadenoma (N=17) was the most common benign tumour in the postmenopausal women while in

premenopausal women leiomyoma (N=13) was more common tumour (Table 3).

Table 3: Distribution of benign tumors in the study according to menopausal status.

Distribution of benign tumors in the study (n=119)			
Menopause (M)	**N**	**Premenopause (PM)**	**N**
Mucinous cystadenoma	17	Leiomyoma	13
Serous cystadenoma	8	Serous cystadenoma	10
Fibroma/ fibrothecoma	9	Mucinous cystadenoma	10
Dermoid cyst	1	Seromucinous	3
Endometriois	1	Fibroma/fibrothecoma	6
Leiomyoma	3	Endometriois	6
Simple cyst	4	Dermoid cyst	2
Haemorrhagic cyst	2	Simple cyst	9
Hydrosalpinx	1	Haemorrhagic cyst	5
Brenner tumour	4	Hydrosalpinx	3
Total	50	Ectopic	2
		Total	69

Serous adenocarcinoma is the most common ovarian malignancy in both pre and post menopausal women (Table 4). CA-125, RMI, HE4, and ROMA values in all patient groups at their standard cut-offs is shown in (Table 5). Data presented as mean (SD) and median (range).

Table 4: Distribution of malignant tumors according to menopausal status.

Menopause	N	Premenopause	N
Serous adenocarcinoma	15	Serous adenocarcinoma	8
Mucinous Adenocarcinoma	10	Mucinous adenocarcinoma	4
Granulosa cell tumour	8	Granulosa cell tumour	8
Borderline (4-serous, mucinous-2)	6	Borderline (8-serous, mucinous-2)	10
Malignant mixed mullerian tumour of ovary	1	Endometroid carcinoma	1
Metastatic	3	Clear cell carcinoma	2
Endometroid carcinoma	1	Immature teratoma	1
Total	44	Yolk sac tumour of ovary	2
		Metastatic	1
		Total	37

Median value of CA-125 (93.37), HE-4 (100) RMI (378) and ROMA (43) were high in women with malignant tumors (Table 5).

In premenopausal women ROMA and HE4 have comparable sensitivity (80%and 75%) but higher specificity (64% and 65%) and NPV (86%and 83%) as compared to CA125 which has sensitivity of (83%) but very low specificity (46%) in differentiating benign from malignant masses. Out of 37malignancies in premenopausal women CA-125 detected 31.CA-125was falsely high in 48 benign masses. Thus CA-125 in premenopausal women has sensitivity of 83% and specificity of 46%. In postmenopausal women, HE4 had highest specificity (88%) and, CA125 has highest sensitivity (86%) in predicting ovarian malignancy (Table 7). ROC curves of CA 125, HE4 and ROMA and RMI in predicting EOC were plotted. The AUC for CA 125, HE4 and ROMA and RMI for premenopausal women was 0.692(95% CI 0.563-0.820), 0.706 (95% CI 0.590-0.823) 0.552 (95% CI 0.416-0.687) and 0.490 (95% CI 0.345-0.634) respectively are shown in (Table 8). Values for menopausal women were 0.557 (0.429-0.685) for CA125, 0.660(0.429-0.685) for HE4, 0.597 (0.469-0.725) for ROMA and 0.517 (0.389- 0.644) for RMI. ROC curve analysis suggested a better prediction of ovarian malignancy when the CA 125 optimal cutoff was increased to 38 U/ml in premenopausal and decreased to 24 U/ml in postmenopausal women. RMI cut off was 137 for premenopausal women and 37 for postmenopausal women.HE4 cut-off was appropriate for premenopausal women (70.18pmol/l) and post-menopausal women (139pmol/l). The recalculated ROMA cut-off for premenopausal women was 6.05% which was less than the cut-off of 11.4% suggested by the manufacturer. For postmenopausal women, the optimal ROMA cut-off of 23.1% performed slightly better as compared to the manufacturers recommended cut-off of 29.9%.

DISCUSSION

In this study, we aimed to prospectively assess whether preoperatively measured serum concentration of HE4 and ROMA score is superior to CA125 and RMI score in the detection of ovarian cancer in women with a pelvic mass. We evaluated the diagnostic performance of HE4, ROMA CA-125, and RMI in women with pelvic mass. The diagnostic value includes sensitivity, specificity, NPV, and PPV. Results were sub grouped into premenopausal and menopausal as HE4value and ROMA score were different in these two groups. Our results indicate that the tumor marker HE4 and ROMA score are useful methods for differentiating pelvic masses according to whether they are associated with a high or low risk for developing into ovarian cancer, and this type of assessment which will ultimately optimize the referral of patients to reference centers. In our study we included all type of malignancies in measurement of diagnostic performance. Overall, ROMA showed the highest accuracy as it correctly classified 139/200 (69.5%) patients compared with 133/200 (66.5%) in HE4 and 109/200 (54.5%) in CA 125 and RMI.

Table 5: CA-125, RMI, HE4, and ROMA values in all patient groups at their standard cut-offs. Data presented as mean (SD) and median (range).

Variables		All patients(n=200)			
		CA-125 U/l	He-4 pmol/l	RMI	ROMA (%)
Benign N=119	Mean	112.77	74.89	447.83	20.71
	Median	30.05	60.03	76.00	12.20
	SD	226.86	42.50	1301.76	19.92
	Range	1245.00	309.71	9990.00	87.20
Malignant N=81	Mean	403.49	231.68	2342.30	51.52
	Median	93.37	100.00	378.00	43.20
	SD	226.60	309.06	6390.49	31.64
	Range	1245.00	1446.00	46575.00	95.00
	Range	368.84	826.00	1233.00	94.20

Table 6: Validity indicators of the tested parameters in premenopausal patient group at their standard cut-offs for discriminating between benign ovarian diseases and malignant ovarian tumors.

Variables	HE4 (%) (95% CI)	ROMA (%) (95% CI)	CA-125 (%) (95% CI)	RMI (%) (95% CI)
Sensitivity	75 (58.80 to 88.23)	80 (63.98 to 91.81)	83 (67.99 to 93.81)	48 (31.92 to 65.60)
Specificity	65 (52.79 to 76.29)	64 (51.93 to 75.39)	46 (34.28 to 58.80)	78 (66.69 to 87.29)
PPV (positive predictive value)	53 (44.60 to 62.84)	54 (44.91 to 62.28)	45 (39.22 to 52.11)	54 (40.75 to 67.68)
NPV (negative predictive value)	83 (73.41 to 90.05)	86 (76.37 to 92.75)	84 (71.07 to 92.05)	73 (66.98 to 79.93)
Accuracy	68 (59.14 to 77.51)	69 (60.13 to 78.35)	59 (49.46 to 68.87)	67 (58.16 to 76.66)

Table 7: Validity indicators of the tested parameters in menopausal patient group at their standard cut-offs for discriminating between benign ovarian diseases and malignant ovarian tumors.

Variables	HE4 (%) (95% CI)	ROMA (%) (95% CI)	CA-125 (%) (95% CI)	RMI (%) (95% CI)
Sensitivity	38 (22.98 to 53.27)	81 (67.29 to 91.81)	86 (73.21 to 94.95)	81 (67.29 to 91.81)
Specificity	88 (75.69 to 95.47)	58 (43.21 to 71.81)	66 (51.23 to 78.79)	72 (57.51 to 83.77)
PPV	73 (53.39 to 86.13)	63 (54.61 to 70.96)	69 (60.53 to 77.44)	72 (61.74 to 80.38)
NPV	61 (55.89 to 67.70)	78 (64.98 to 87.63)	84 (71.78 to 92.24)	81 (70.14 to 89.61)
Accuracy	64 (53.91 to 74.17)	69 (58.78 to 78.27)	75 (65.92 to 83.99)	76.60 (66.74 to 84.71)

Table 8: ROC curves and AUC values of CA 125, HE4 and ROMA and RMI for the diagnosis of epithelial ovarian malignancy in patients with pelvic masses.

Variables	HE4	ROMA	CA125	RMI
PM	0.706 (0.590-0.823)	0.552 (0.416-0.687)	0.692 (0.563-0.820)	0.490(0.345-0.634)
M	0.660 (0.429- 0.685)	0.597 (0.469- 0.725)	0.557 (0.429-0.685)	0.517 (0.389- 0.644)

There were more patients with benign tumors being correctly identified by HE4 (89/119, 74.7%) and ROMA (74/119, 62.1%), than CA 125 which identified 39/119 (32.7%) patients. On the other hand, CA 125 (70/81, 86.4%) and ROMA (65/81, 80.2%) each correctly identified patients with malignant tumors while HE4 (44/81, 54.3%) and RMI (54/81, 66.6%) identified much fewer patients. In premenopausal women ROMA correctly diagnosed benign tumors in 45/69 (69%), HE4 in 45/69 (69%), RMI in 19/69 (27%) and CA-125 in 21/69 (30%).In our study in benign tumors CA125 was falsely elevated in 37 of premenopausal women (mucinous cystadenoma=4, endometriosis=6, fibroma/fibrothecoma=4, simplecyst=7, leiomyoma=6, haemorrhagiccyst=4, hydrsalpinx=2, dermoid cyst=2, ectopic=2). In the same group HE4 was normal in 26 women and ROMA was low risk in 23 women. This observation is of clinical relevance as CA125 is falsely elevated in many benign conditions in premenopausal women like fibroid, endometriosis etc. In our studyCA125 was raised in 6/7 patients of

endometriosis.HE4 was normal and ROMA was low risk in 5/7 women with endometriosis. We can conclude if CA-125 is raised and ROMA is low risk and HE4 is normal chances of malignancy on final histopathology is low. The increased specificity of HE4 for the differentiation between endometriosis and ovarian cancer is in agreement with two recently published studies suggesting that the use of both markers together can improve this type of evaluation.[22,23]

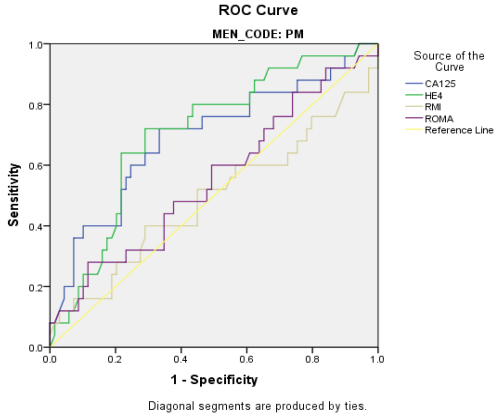

Figure 1: Premenopause ROC curves and AUC values of CA 125, HE4 and ROMA and RMI for the diagnosis of epithelial ovarian malignancy in patients with pelvic masses.

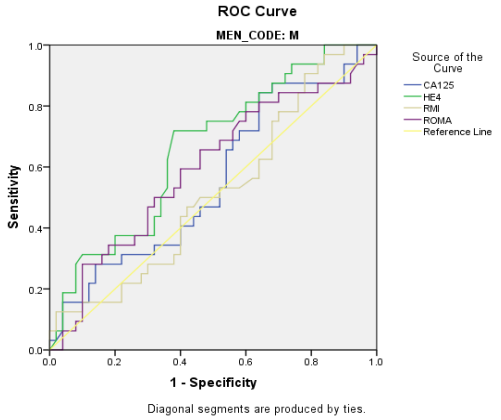

Figure 2: Menopause ROC curves and AUC values of CA 125, HE4 and ROMA and RMI for the diagnosis of epithelial ovarian malignancy in patients with pelvic masses.

In our study in premenopausal women ROMA and HE4 have comparable sensitivity (80%and 75%) but higher specificity (64% and 65%) and NPV (86%and 83%) as compared to CA125 which has sensitivity of (83%) but very low specificity (46%) in differentiating benign from malignant masses. Regarding detecting EOC (epithelial ovarian cancer N=25) in premenopausal women ROMA and HE4 diagnosed EOC in 22/25, CA125 in 21/25 and RMI in 12/25. In menopausal women HE4 correctly identified women having benign tumors in 44/50, RMI in 36/50, CA125in 33/50, and ROMA in 29/50.In the same group ROMA has sensitivity of 81% and NPV of 78%, HE4 has specificity of 88% as compared to CA125 which has sensitivity of 86% and NPV of 84% in differentiating benign from malignant pelvic masses. Among epithelial ovarian cancers ROMA correctly classified 53/57 (92.9%) into high risk. It was low risk in 4/57(mucinous=1, serous borderline=1, endometroid=1, serous carcinoma=1). CA125 also correctly identified malignancy in 53/57(92.9%). CA125 was less than normal in 4/57 (serous carcinoma=1, mucinous carcinoma=3). HE4 identified 38/57 and RMI detected 41/57. Among borderline ovarian tumors CA-125 was raised in all 16 borderline ovarian tumours and ROMA was high risk in all except in one serous borderline ovarian malignancy. Regarding granulosa cell tumours ROMA was high risk in 6/16 (37%), and CA125 was raised in 8/16 (50%). Ferraro et al. conducted a meta-analysis on 16 original articles published from 2009 to 2012, covering 1342 ovarian cancer patients and 2516 controls. The meta-analysis revealed an overall sensitivity of 79% (95% confidence interval (CI: 76-81%) and a specificity of 93% (95% CI: 92-94%) for HE4 and an overall sensitivity of 79% (95% CI: 77-82%) and a specificity of 78% (95% CI: 76-80%) for CA125, respectively. The significantly higher specificity of HE4 than that of CA125 indicated that the former is less likely interfered by factors other than the malignancy itself.[24] A meta-analysis by Dayyani et al in 2016 analyzed five studies incorporating 1975 patients with adnexal masses. On the basis of the AUC (95% confidence interval) data for all patients, the authors concluded that the ROMA (0.921; 0.855-0.960) showed a numerically greater diagnostic performance than CA125 (0.883; 0.771-0.950) and HE4 (0.899; 0.835-0.943). Similar results were shown in each of the subgroup populations, in particular, postmenopausal patients and patients with early OC.[25] Shin Oranratanaphan et al did study on 283 women with ovarian cyst. They concluded that compared to CA-125, HE4 had lower sensitivity (53.4% vs. 87.9%) and NPV (89% vs. 93.6%) but higher specificity (97.8% vs. 46.2%) and PPV (86.1% vs. 29.8%) for differentiating between benign and malignant ovarian tumor.[26] Lycke M et al validated, in a multicenter clinical trial, the performance of biomarkers and algorithms for differential diagnosis in a population of women diagnosed with an unknown ovarian cyst or pelvic tumor. In postmenopausal women, RMI (>200), ROMA (≥ 29.9), CA125 (>35 U/ml), and HE4 (>140 pmol/l) showed sensitivity of 89%, 91%, 92%, and 72%, respectively, and specificity of 80%, 77%, 80%, and 92%. In premenopausal women, sensitivity of RMI, ROMA (≥11.6), CA125, and HE4 (>70 pmol/l) was 87%, 87%, 96%, and 83%, respectively, and specificity was 90%, 81%, 60%, 91%. This study confirms prior results from single-center studies and suggests the implementation of HE4 measurement in daily practice.[27] Consistent with previous studies our study showed that ROMA and HE4 had a superior specificity and comparable sensitivity than CA 125 in predicting ovarian malignancy among

premenopausal women.[28,29] This was due to the fact that serum HE4 is not elevated whereas serum CA 125 is falsely elevated in patients with benign ovarian cyst and endometriosis. NPV of ROMA and HE4 were high in same age group. In postmenopausal women, HE4 had highest specificity (88%) and, CA 125 has highest sensitivity (86%) in detecting ovarian malignancy. CA125 (84%) has highest negative predictive value in the same age group. Previous studies had demonstrated conflicting results. Van Gorp et al and Chan et al. reported that ROMA and HE4 were not superior to CA 125 in detection of ovarian malignancy among the postmenopausal women.[29,30] Montagnana et al and Sandri et al. demonstrated that ROMA exhibited excellent diagnostic performance in postmenopausal women.[31,32] Our further analysis suggested a better prediction of ovarian malignancy when the CA 125 optimal cutoff was increased to 38 U/ml in premenopausal and decreased to 24 U/ml in postmenopausal women. RMI cut off was 137 for premenopausal women and 37 for postmenopausal women.HE4 cut-off was appropriate for premenopausal women (70.18 pmol/l) and post-menopausal women (139 pmol/l). The recalculated ROMA cut-off for premenopausal women was 6.05% which was less than the cut-off of 11.4% suggested by the manufacturer. For postmenopausal women, the optimal ROMA cut-off of 23.1% performed slightly better as compared to the manufacturers recommended cut-off of 29.9%. Anton et al. demonstrated that this HE4 cut-off was appropriate for premenopausal women with a sensitivity of 72.2-79.6% and specificity 82.5–82.8%.[28] Other studies seemed agreeable to the manufacturer recommended ROMA cut-off for postmenopausal women with the cut-off ranging between 25.3% and 27.7%.[9,28-30]

Limitations

One of the major limitations of current study was that it was a single centre study.

CONCLUSION

From our study we can conclude that in premenopausal women, if the HE4 is low and ROMA low risk (high negative predictive value in our study) then it is unlikely that the pelvic mass would be malignant and therefore surgery may be carried out by a general gynaecologist. However, if the HE4 levels are high and ROMA high risk surgery should be performed by a gynaecological oncologist. HE4 and ROMA were more useful in distinguishing other benign ovarian tumors or endometriosis from ovarian cancer. In the postmenopausal group, a low ROMA score, low Ca125 (high negative predictive value) levels may preclude malignancy but a high score and raised CA125 levels (high sensitivity) would almost always indicate malignancy. This may potentially reduce unnecessary referrals of a low risk pelvic mass to a higher centre and many more surgeries can be performed by a general gynaecologist in peripheral hospitals as the current local practice is only to routinely take CA 125 into consideration and to refer all patients with high CA 125 regardless of age or menopausal status to a tertiary hospital. Further ROMA and HE 4 does not include ultrasound criteria, so they can be used to triage pelvic masses at district hospitals in which ultrasound expertise is less widely available.

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