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Evaluation of HE4, CA-125, Risk of Ovarian Malignancy Algorithm (ROMA) and Risk of Malignancy Index (RMI) in the Preoperative Assessment of Patients with Adnexal Mass

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ABSTRACT

Objectives: To evaluate the validity and compare the performance of cancer antigen-125 (CA-125), human epididymis protein 4 (HE4), the risk of malignancy index (RMI), and the risk of ovarian malignancy algorithm (ROMA) in the diagnosis of ovarian cancer in patients with ovarian lesions discovered during their preoperative work-up investigations. ***Methods***: This prospective, cross-sectional study looked at patients who attended the gynecology department at the Royal Hospital, Muscat, from 1 March 2014 to 30 April 2015, for the evaluation of an ovarian lesion. The inclusion criteria included women who underwent surgical intervention and who had a preoperative pelvic ultrasound with laboratory investigation for CA-125 and HE4. The study validated the diagnostic performance of CA-125, RMI, HE4, and ROMA using histopathological diagnosis as the gold standard. ***Results:*** The study population had a total of 213 cases of various types of benign (77%) and malignant (23%) ovarian tumors. CA-125 showed the highest sensitivity (79%) when looking at the total patient population. When divided by age, the sensitivity was 67% in premenopausal women. In postmenopausal women, CA-125 had lower sensitivity (89%) compared to RMI, HE4, and ROMA (93% each). A high specificity of 90% was found for HE4 in the total patient population, 93% in premenopausal women and 75% in postmenopausal women. CA-125 had the highest specificity (79%) in postmenopausal women. Both CA-125 and RMI were frequently elevated in benign gynecological conditions particularly in endometriosis when compared to HE4 and ROMA. We also studied modifications of the optimal cut-offs for the four parameters. Both CA-125 and RMI showed a significant increase in their specificity if the cut-off was increased to ≥ 60 U/mL for CA-125 and to ≥ 250 for RMI. For HE4, we noted an improvement in its specificity in postmenopausal women when its cut-off was increased to140 pmol/L. ***Conclusions:*** HE4 and ROMA showed a very high specificity, but were less sensitive than CA-125 and RMI in premenopausal women. However, they were of comparable sensitivity in postmenopausal women and were valuable in distinguishing benign ovarian tumors or endometriosis from ovarian cancer. Modifying the cut-off values of the different markers resulted in a higher accuracy compared to the standard cut-offs, but at the expense of reduced sensitivity.

Ovarian cancer is a common gynecological cancer in women. It is characterized by having a poor prognosis with a five-year survival rate of less than 35%. The majority of cases are diagnosed at an advanced stage.[1] In Oman, ovarian cancer is the seventh most common cancer in women.[2] The Ministry of Health reported in its Cancer Incidence Registry (2011) a crude incidence of 1.8 and age-standardized incidence rate of 3.1 per 100,000, taking into consideration the estimated mid-year Omani population in 2011 of 2,137,807 with sex ratio of 983 females per 1000 males.[2]

Different guidelines are available for the management of different cancers including ovarian cancer. The National Institute for Health and Clinical Excellence (NICE) guidelines on the recognition and initial management of ovarian

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cancer addresses the issue of screening symptomatic women presenting to primary care.[3] Important factors for the early diagnosis of ovarian cancer need health providers and women to be made aware of this disease and primary care physicians to initiate investigations early. Thus, it is crucial to assess certain risk factors for women who present with pelvic masses by optimizing health policies and providing sensitive and specific biomarkers for detecting the disease early; hence, providing early surgical staging procedures followed by appropriate treatment in specialized reference centers helping to stop overburdening these centers with benign manageable conditions.

Currently, the standard tools for detecting ovarian cancer are pelvic ultrasonography and measuring serum cancer antigen 125 (also called carbohydrate antigen 125; CA-125) levels, which could be combined with the menopausal status to calculate the risk malignancy index (RMI) and is considered a simple and affordable test.[4] However, 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.[5] HE4, also called whey-acidic-protein (WAP) and four-disulfide core domain protein 2 (WFDC2), was originally described as an epididymis-specific protein that belongs to a four-disulfide core family. This comprises a heterogeneous group of small acid- and heat-stable proteins of divergent function.[6] It is highly over-expressed in epithelial ovarian cancers (EOC) compared to normal ovarian epithelium.[7–9]

Moore et al[10] developed a new numerical score to predict the risk of ovarian malignancy called the Risk of Ovarian Malignancy Algorithm (ROMA), which incorporates the results of HE4, CA-125, and menopausal status. ROMA was studied by many investigators and found to be a promising biomarker for predicting ovarian cancer.[11] HE4 together with CA-125 can improve the accuracy of ovarian cancer detection. Additionally, HE4 is considered a valuable biomarker for discriminating ovarian cancer from ovarian endometriosis making it a more specific marker than CA-125.[12]

The aim of this study was to evaluate the validity of CA-125 as a currently used tumor marker for ovarian cancer and HE4 as a new biomarker for ovarian cancer in a pilot of patients presenting with ovarian lesions during their preoperative workup investigations. We then compared the performance of the four parameters, CA-125, HE4, RMI, and ROMA to determine the best marker to discriminate between benign and malignant ovarian tumors and the appropriate cut-offs of these markers.

METHODS

This prospective, cross-sectional study was done at the Royal Hospital, Muscat, using a sample of 213 patients who attended the gynecology department between 1 March 2014 and 30 April 2015 for the evaluation of an ovarian mass. All patients were examined and assessed using pelvic ultrasonography by specialized gynecologists. Blood specimens from these patients were obtained during their first assessment for laboratory work up. All cases underwent surgical intervention at a later stage to obtain a histopathological diagnosis, which was used as the gold standard test. All clinical and laboratory data were collected using the hospital information system AL Shifa 3 Plus.

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 by a two-step immunoassay using the Architect i2000 SR Immunoassay Analyzer (Abbott Laboratories, Illinois, US), which uses chemiluminescence microparticle immunoassay technology. All manufacturer recommendation for maintenance, calibration, and internal quality assessment were followed for both assays. The between run precisions of CA-125 were 2.8%, 3.2%, and 2.2% for the levels of internal quality control (low, middle, and high concentration of CA-125) materials, respectively. In-house analytical verification of HE4 was performed before it was adopted, as it was a newly introduced test in the Royal Hospital. Within- and between-run imprecision studies for HE4 assay were done by running three levels of internal quality control five

times in the same run and five times on five different days. The within-run precisions of the three levels of internal quality control for the HE4 assay were 1.9%, 2.8%, and 2.2% whereas the between-run precisions were 1.5%, 4.8%, and 5.7%, respectively.

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:

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

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:[10]

1. PI for premenopausal women:

$$PI = -12.0 + 2.38*\ln HE4 + 0.0626*\ln(CA\text{-}125)$$

2. PI for postmenopausal women:

$$PI = -8.09 + 1.04*\ln HE4 + 0.732*\ln(CA\text{-}125)$$

The ROMA score was then obtained using the equation:

$$ROMA\ \% = \exp PI / (1 + \exp PI) \times 100\%$$

$$\text{where } \exp PI = e^{PI}$$

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.[14] The cut-off value for HE4 was 70 pmol/L, and for ROMA for high-risk premenopausal and postmenopausal women was 13.1% and 27.7%, respectively.[10]

A comparison study was done for the four parameters (CA-125, RMI, HE4, and ROMA) and the validity indicators including sensitivity, specificity, positive and negative predictive values (PPV and NPV) and efficiency were calculated. Both the receiver operating characteristic (ROC) curve and area under the curve (AUC) were calculated, and the most valid cut-offs were determined accordingly. For all statistical comparisons, a p-value < 0.050 was accepted as statistically significant. All statistical analysis was done using SPSS Statistics (SPSS Statistics, Chicago, US) version 22.

RESULTS

This prospective study included 213 women who attended the gynecology clinic at the Royal Hospital, Muscat. One-hundred and sixty-two women (76%) were premenopausal, of whom 21 (13%) had a malignant ovarian lesion. Fifty-one (24%) women were postmenopausal, and 27 (53%) of these had malignant ovarian lesion [Table 1].

The total number of ovarian specimens was 213, of which 165 (77.5%) were benign, and 48 (22.5%) were malignant tumors. Table 2 shows the histopathology results of all ovarian specimens in pre- and postmenopausal cases. The histopathology classifications of ovarian tumors included surface epithelial-stromal, sex cord stromal, and germ cell tumors. Lesions that did not fit into one of these three groups were termed "others".

Table 1: Patients' demographic characteristics. Data are presented as mean±SD and median (range) unless otherwise indicated.

	All, n = 213			Premenopausal, n = 162			Postmenopausal, n = 51		
	B	**M**	***p*-value**	**B**	**M**	***p*-value**	**B**	**M**	***p*-value**
n (%)	165 (78)	48 (23)		141 (87)	21 (13)		24 (47)	27 (53)	
Age, years	35±14 33 (13–80)	50±18 55 (21–83)	0.001	31±9 31 (13–50)	32±8 33 (21–49)	0.374	61±10 59 (47–80)	64±9 64 (51–83)	0.595
BMI, kg/m^2	28±6 27 (15–48)	27±7 27 (15–45)	0.374	27±6 27 (15–44)	28±7 28 (15–49)	0.767	30±6 29 (22–48)	26±6 23 (19–39)	0.463
Parity, n			0.003			0.148			0.070
Null	80	10		80	8		0	2	
Primi	15	1		15	1		0	0	
Multi	69	28		46	1		23	17	

B: benign; M: malignant; Null: nulliparity; Primi: primi-parity (1 child); Multi: multi-parity (>1 child).

Table 2: Histopathological types of ovarian tumors in the study population.

Tumor	Benign				Malignant			
	Type	All, n = 165	Pre, n = 142	Post, n = 24	Type	All, n = 48	Pre, n = 21	Post, n = 27
Epithelial	Serous cystadenoma	17	12	5	Serous adenocarcinoma	20	5	15
	Mucinous cystadenoma	10	8	2	Mucinous adenocarcinoma	1	1	0
	Endometrial cysts	34	34	0	Endometrial adenocarcinoma	3	1	2
	Sermo-mucinous	1	1	0	Undifferentiated	1	0	1
					Borderline epithelial	7	6	1
	Total, n (%)	**62 (37.6)**	**55 (38.7)**	**7 (29.2)**	**Total, n (%)**	**32 (66.7)**	**13 (62.0)**	**19 (70.4)**
Sex cord	Fibroma	4	3	1	Granulosa	5	4	1
	Thecoma	3	2	1				
	Total, n (%)	**7 (4.2)**	**5 (3.5)**	**2 (8.3)**	**Total, n (%)**	**5 (10.4)**	**4 (19.0)**	**1 (3.7)**
Germ cell	Teratoma	33	29	4	Yolk sac cancer	1	1	0
	Struma ovarri	2	2	0	Immature teratoma	2	2	0
	Total, n (%)	**35 (21.2)**	**31 (21.8)**	**4 (16.7)**	**Total, n (%)**	**3 (6.3)**	**3 (14.3)**	**0 (0.0)**
Others	Simple cyst	9	5	4	Secondaries	7	1	6
	Functional cyst	26	23	3	Lymphoma	1	0	1
	Abscess	7	5	3				
	Para-ovarian cyst	4	4	0				
	Fibroid	9	8	1				
	Normal	6	5	1				
	Total, n (%)	**61 (37.0)**	**50 (35.2)**	**11 (45.8)**	**Total, n (%)**	**8 (16.7)**	**1 (4.8)**	**7 (25.9)**

Pre: pre-menopausal; Post: post-menopausal.

The four variables (CA-125, RMI, HE4, and ROMA) were tested in the study by detailed descriptive analysis within the two main groups of benign and malignant lesions [Table 3]. In this setting, to test for a significant difference, non-parametric *t*-tests were applied (Kruskal-Wallis test and Mann-Whitney U test). All four parameters showed significantly higher median values within the malignant group when compared to the benign group. The distribution of the four variables was also checked through the different histopathology lesions. All showed a significant difference ($p < 0.050$) between benign and malignant groups except for the sex cord tumors in which the four tested variables were not statistically different between the lesion types.

Table 3: CA-125, RMI, HE4, and ROMA values in all, pre-menopausal (pre) and post-menopausal (post) patient groups at their standard cut-offs. Data presented as mean ± SD and median (range).

Variable	All		Pre		Post	
	Benign	Malignant	Benign	Malignant	Benign	Malignant
CA-125, U/mL	62±132 23(1–978)	1039±2326 261 (7–14507)	67±141 24 (4–2296)	927±3153 65 (7–14507)	31±40 20 (5–199)	1125±1454 458 (8–5733)
RMI	189±427 45 (4–3184)	10751±19543 1777 (7–91728)	164 ±374 40 (4–2296)	3640±12631 260 (7–58028)	336±651 140 (20–3184)	15961±22332 7264 (128–91728)
HE4, pmol/L	65.8±210.8 43 (18–2677)	688.8±1122.4 207 (27–5932)	42.3±43.8 41.8 (18–537)	387.8±1280.8 66.9 (27–5932)	180.3±537.8 51.0 (24–2677)	923.0±941.2 7264 (128–91728)
ROMA, %	8.9±13.1 6 (1–96)	59.4±40.2 77.0 (2–100)	6.9±9.0 5.0 (1–96)	28.2±32.8 16.6 (2–100)	21.0±23.6 12.5 (4–94)	83.6±26.4 96 (12–100)

The p-value is < 0.001 for all variables (CA-125, RMI, HE4, and ROMA) between benign and malignant tumor in all, pre- and postmenopausal women.

Table 4: Validity indicators of the tested parameters in all, pre-menopausal (pre) and post-menopausal (post) patient groups at their standard cut-offs.

Indicators	Age group	CA-125 ≥35 U/mL	RMI ≥200	HE4 ≥70 pmol/L	ROMA pre ≥13.1 post ≥27.7
Sensitivity	All	79	77	71	75
	Pre	67	57	57	52
	Post	89	93	93	93
Specificity	All	62	82	90	88
	Pre	60	85	93	90
	Post	79	67	75	78
NPV	All	91	93	91	92
	Pre	92	93	94	93
	Post	86	89	90	90
PPV	All	38	56	68	65
	Pre	20	36	55	44
	Post	83	76	81	83
Efficiency	All	71	80	81	82
	Pre	63	71	75	71
	Post	84	80	84	85
AUC	All	0.809	0.853	0.824	0.837
	Pre	0.673	0.724	0.674	0.680
	Post	0.938	0.941	0.897	0.944

Using the proposed cut-offs for the four tested variables, the validity indicators for the four parameters including their sensitivity, specificity, NPV, PPV, efficiency, and AUC are shown in Table 4.

Table 5: Comparison of the tested four parameters among patients with endometriosis and other benign ovarian lesions. Data are presented as mean ± SD and median (range).

Tested parameters	Endometriosis, n = 34	Other benign lesions, n = 132	*p*-value
CA-125, U/mL	133±197	43±102	<0.001
	64 (9–973)	19 (1–978)	
RMI	327±557	153±381	<0.001
	111 (26–2296)	36 (4–3184)	
HE4, pmol/L	43.6±14.1	71.6±236.3	0.845
	41.1 (21–78)	42.8 (18–2677)	
ROMA, %	6.9±5.6	9.4±14.4	0.462
	5.3 (1.0–22.3)	5.6 (0.7–96.1)	

Out of the 48 ovarian cancer cases, CA-125 detected 38 cases while HE4 detected 34. The four parameters were able to detect the various types of ovarian cancer except for sex cord/granulosa tumors in which these tools detected one out of five cases. The four parameters detected most epithelial tumors except for borderline lesions. CA-125 was able to detect four out of seven cases, and HE4 was able to detect two of seven cases only. The validity indicators for the four variables were also tested in EOC lesions alone and were compared to all cases of ovarian cancers. The highest calculated sensitivity was for CA-125 (88% in EOC vs. 79% in all) followed by RMI (84% in EOC vs. 77% in all) and ROMA (84% in EOC vs. 75% in all). HE4 measured the least sensitivity (78% in EOC vs. 71% in all).

In contrast, the false positive rates in different benign lesions were similar in most lesions except for endometriosis, teratoma, and fibroid lesions in which CA-125 level was raised in 27/34, 7/33, and 6/9 of cases respectively, compared to the HE4 level that was raised only in 3/34, 0/33 and 3/9 of cases, respectively. Two cases of fibroid lesions had Chronic Kidney Disease (CKD) stage 5 and one fibroid case had ascites, which are known to contribute to the false positive results.[15,16]

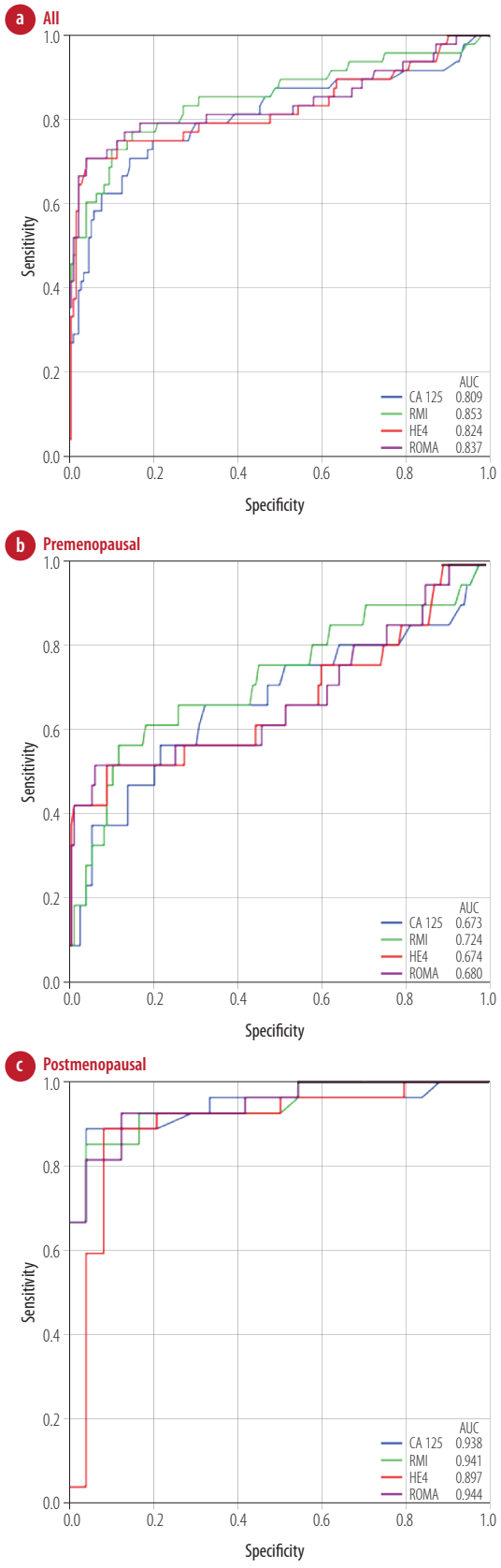

Figure 1: The receiver operating characteristic (ROC) curve and area under the curve (AUC) of CA-125, RMI, HE4, and ROMA for **(a)** all, **(b)** premenopausal, and **(c)** postmenopausal patients.

To compare endometriosis with other benign ovarian lesions, the medians of the four parameters were calculated in both groups as shown in Table 5. Both HE4 and ROMA showed no significant difference between the two types of lesions whereas for CA-125 and RMI the medians revealed significantly higher levels in the endometriosis lesion group.

Figure 1 shows the ROC curve of the four parameters in all, premenopausal, and postmenopausal groups. RMI showed a slightly higher AUC than the other parameters in all (0.853) and the premenopausal (0.724) women. However, all tested parameters were slightly better than CA-125 in these groups. ROMA and RMI had a slightly higher AUC in the postmenopausal group (0.944 and 0.941, respectively) and the AUC of HE4 was the lowest in this group (0.897). Using the ROC curve, different cut-offs were investigated to determine the optimal cut-off to get the appropriate sensitivity and specificity [Table 6].

DISCUSSION

CA-125 in this study had the highest sensitivity (79%) in the total study population and the premenopausal group (67%) compared to the other markers. However, in the postmenopausal group, CA-125 had a sensitivity of 89%, lower than the 93% sensitivity of the other three markers. In contrast, a high specificity of 90% was found for HE4 in the total study population. This was 93% in the premenopausal group and 75% in the postmenopausal group. CA-125 had the highest specificity of 79% in the postmenopausal group, compared to 78% for ROMA, 75% for HE4 and 67% for RMI. Hence, HE4, and ROMA showed a high specificity, and although they were less sensitive than CA-125 and RMI in premenopausal women, they were of comparable sensitivity in postmenopausal women in addition to their higher specificity.

All epithelial tumors were detected by one or more of the four markers except the borderline lesions. Of the seven cases with borderline epithelial lesions, CA-125 was the best marker for their detection. CA-125 detected four out of seven of cases, RMI and ROMA detected three out of seven of cases, and HE4 detected two of seven of cases. The four markers detected only one of five cases of sex cord/granulosa tumor.

Table 6: Sensitivity and specificity of the four parameters for premenopausal and postmenopausal patients at the standard cut-offs and optimal identified cut-offs.

Parameter	Group	Standard cut-offs			Optimal cut-offs		
		Cut-off	Sensitivity	Specificity	Cut-off	Sensitivity	Specificity
CA-125, U/mL	All	35	79	62	82	71	86
	Pre	35	67	60	60	57	78
	Post	35	89	79	71	89	96
RMI	All	200	77	82	348	73	90
	Pre	200	57	85	240	57	88
	Post	200	93	67	944	85	96
HE4, pmol/L	All	70	71	90	77.5	71	96
	Pre	70	57	93	63.6	91	52
	Post	70	93	75	137.9	89	92
ROMA, %	All	-	75	88	22.7	71	96
	Pre	13.1	52	90	16.4	52	94
	Post	27.7	93	78	28.4	93	88

Ferraro et al[5] reported in their meta-analysis overlapped sensitivity of 79% for HE4 and CA-125, but a significantly higher specificity for HE4 (93%) compared to CA-125 (78%). Similarly, Anastasi et al[12] reported a higher sensitivity for CA-125 (90%) compared to HE4 (87%) and a lower specificity for CA-125 (70%) compared to HE4 (100%) in the diagnosis of EOC. A prospective study by Richards et al[17] noted that HE4 had a better specificity than CA-125 for the diagnosis of ovarian cancer in all women as well as in premenopausal women in addition to the higher ROC-AUC for HE4 compared to CA-125 in all women. ROMA was not inferior to the RMI calculation in their study population.

We reported that both CA-125 and HE4 were not sensitive to diagnose borderline ovarian cancer. To increase their sensitivity and specificity in this setting, it was suggested to perform serials of CA-125 and HE4 measurements along with ultrasound assessment.[18] Also, CA-125 was reported as a poor marker for detecting granulosa cell tumors.[19] When analyzing the false positive rates in different benign lesions, CA-125 was frequently elevated in patients with benign gynecological conditions particularly in premenopausal women compared to HE4 (38% vs. 10%, respectively). Some cases (mainly endometriosis) were found to have high levels of CA-125 and RMI compared to HE4 and ROMA. The medians of HE4 and ROMA values showed no significant difference between benign ovarian lesions and endometriosis, whereas the results of CA-125 and RMI revealed significantly higher levels in endometriosis. HE4 and ROMA can be useful markers when CA-125 levels are falsely elevated particularly in cases of endometriosis. Others also reported that measuring HE4 can be a valuable approach for distinguishing patients with ovarian endometrioma or other benign adnexal masses from those with ovarian malignancy, which may reduce other costs by reducing expensive diagnostic procedures.[12] Similar to CA-125, HE4 values were noted to be falsely raised in the two cases with CKD stage 5 and one case with ascites, which has been previously reported for both markers.[16]

In this study, RMI appears to be comparable to ROMA, but a critical inspection may be needed in this setting since in our patient series the RMI score was calculated using an objective ultrasound assessment, which depends solely on the experience of the gynecologist. The calculated RMI value may be affected if ultrasound examination is performed by non-trained personnel including primary health care clinicians. Anton et al[20] and Moore et al[21] assessed the impact of using advanced computed tomography or magnetic resonance imaging on RMI score and its outcome. They found that the performance was not affected by these modifications, and no differences were noted in the accuracy of the four parameters for differentiating between the types of ovarian masses.

For CA-125 and RMI, we observed a significant increase in their specificity if the cut-off was increased to ≥ 60 U/mL for CA-125 and to ≥ 250 for RMI.

For HE4, we noted an improvement in its specificity in the postmenopausal group when its cut-off was increased to 140 pmol/L. No significant change in the performance of ROMA was noted when its cut-off was altered for any groups. Winarto et al[22] reported a better prediction of ovarian malignancy when using modified cut-offs for the different markers compared to the standard cut-offs, which resulted in higher specificity and accuracy but at the expense of reduced sensitivity. They reported that at modified cut-off values of CA-125 (165.2 U/mL), HE4 (103.4 pmol/L), RMI (368.7) and ROMA (28/54), the sensitivity and specificity was 67% and 75.4% for CA-125; 73.1% and 85.2% for HE4; 73.1% and 80.3% for RMI; and 77.6% and 86.9% for ROMA. When compared to the standard cut-off values, the sensitivity and specificity was 91% and 24.6% for CA-125; 83.6% and 65% for HE4; 80.6% and 65.6% for RMI; and 91.0% and 42.6% for ROMA.

Moszynski et al[23] studied the usefulness of HE4 as a second-line test in the assessment of women with suspicious ovarian tumors. They concluded that HE4 had a higher specificity, accuracy, and positive predictive value than CA-125. However, the two markers are complementary and may be useful in situations when less experienced sonographers perform a pelvic ultrasound. This may suggest that HE4 is a more reliable test than RMI since the latter is dependent on ultrasound score. Therefore, taking into account the high sensitivity of CA-125 and high specificity of HE4, a panel of both tests using algorithms such as ROMA appears to be advantageous. Moore et al[10,24] reported a sensitivity of 94.3% and specificity of 75% in one study and a sensitivity of 76.5% and specificity of 95% in another study when both were combined to differentiate benign from malignant ovarian lesions. The authors also reported a sensitivity of 93.8%, a specificity of 74.9% and a negative predictive value of 99% when using both markers in a ROMA.[25] The combined panel has the advantage of being less likely to be elevated in benign tumors compared to CA-125, particularly in differentiating endometriosis from malignant ovarian tumors.

Recently a novel diagnostic index combining HE4, CA-125, and age was reported as a simple index that could be used to speed up the referral of women with suspected ovarian cancer and was independent of ultrasound and menopausal status.[26] Additionally, there are genetic algorithms for risk assessment of ovarian cancer screening that have been recently described by applying classic genetic pedigree with a panel of biomarkers that identify both phenotypic and genotypic expression of high-risk markers followed by conventional and advanced ultrasonography. This approach might improve the screening process of asymptomatic high-risk women using this technology in specialized centers in the future.[27] However, the inclusion of HE4 and use of algorithms in the workup investigations has to consider its cost-effectiveness and impact on the total budgetary expenditure of the overall service balanced by the additional advantages of its use, whether alone or in combination with CA-125 that allows calculation of the ROMA. This includes the number of patients' referrals to gyne-oncology clinics as the available evidence still support CA-125 with lowered cut-off as a cost-effective strategy.[28]

CONCLUSION

Our study indicates that CA-125 and HE4, as well as ROMA and RMI values, are useful tools to differentiate between benign and malignant ovarian tumors. Although HE4 and ROMA were less sensitive than CA-125 and RMI in premenopausal women, they were of comparable sensitivity in postmenopausal women in addition to their higher specificity. HE4 and ROMA were more useful in distinguishing other benign ovarian tumors or endometriosis from ovarian cancer. HE4 can be a useful marker in situations where pelvic ultrasonography is performed by less experienced sonographers as in a primary care setting to triage further women presenting with adnexal lesions.

Disclosure

The authors declared no conflicts of interest. No funding was received for this study.

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