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Preoperative Diagnostic Performance of ROMA (Risk of Ovarian Malignancy Algorithm) in Relation to Etiopathogenesis of Epithelial Ovarian Tumors

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Abstract

Background: We studied the usefulness of ROMA for preoperative stratification of patients in relation to the menopausal status, etiopathogenesis of epithelial ovarian tumors and FIGO stage.

Material and methods: The study group (n=214) consisted of 116 premenopausal and 98 postmenopausal patients, including 83 with ovarian cancer and 131 with benign lesions. CA125 and HE4 were determined in each pre- and postmenopausal patient. ROC analysis was done to calculate the sensitivity, specificity, PPV, and NPV and a contingency table was applied to assess the usefulness of ROMA.

Results: ROC analysis identified AUC (area under curve) as the most valuable component of ROMA (0.921) in the study group with respect to CA125 (0.919) and HE4 (0.855). Sensitivity was highest for CA125 (90.4% for the whole group, 85.7% for premenopausal and 91.7% for postmenopausal patients). Specificity was highest for ROMA with cutoff points determined by us (95.4% for the whole group, 96.8% for premenopausal and 91.7% for postmenopausal patients). AUC, sensitivity, specificity, PPV, and NPV calculated from a contingency table demonstrated the superiority of ROMA with our cutoff points in type II cancers (0.979, 93.3%, 95.4%, 87.5%, 97.7%) and advanced cancers (0.980, 95.1%, 95.4%, 90.7%, 97.7%), compared with type I (0.851, 76.3%, 95.4%, 82.9%, 93.3%) not advanced (0.754, 59.1%, 95.4%, 68.4%, 93.3%) cancers.

Conclusions: ROMA is actually a useful diagnostic method for preoperative stratification of patients with a pelvic mass. It performs better in type II and more advanced ovarian cancers. However, its sensitivity, specificity, PPV, and NPV values in type I ovarian cancer make ROMA useful in this group of cancer patients as well.

Keywords: ROMA; HE4; CA125; Ovarian cancer; Diagnosis

Introduction

Thousands of patients with ovarian tumor or cyst are hospitalized and operated all over the world. According to the National Cancer Institute, USA, 13-21% of women are diagnosed with ovarian cancer (EOC) at various clinical stages [1]. Stratification of pelvic mass cases to high- and low-risk groups is important for several reasons. Firstly, recent research has shown that ovarian cancer patients operated at centers specializing in female malignancies have a greater chance of survival [2]. Secondly, the therapeutic decision in cases of ovarian/adnexal tumor relies heavily on the correct diagnostication. Whether the tumor is malignant or benign, the surgeon will choose between laparoscopy or laparotomy, abdominal access (midline or transverse), and extent of surgery. Optimal operative cytoreduction by a skilled surgeon combined with correct staging according to FIGO greatly improves distant results of management in ovarian cancer [3]. Modern imaging techniques and fast progress in laboratory tests have enabled a great step forward in diagnostic algorithms [4-11]. ROMA (Risk of Malignancy Algorithm) based on CA125 and the novel HE4 marker has recently emerged as a promising approach to the preoperative categorization of malignancy risk [12-22]. HE 4 is new marker which was recently proposed for ovarian cancer because of its specificity and high expression in ovarian cancer tissues [23-28]. The diagnostic performance of ROMA was advocated for the first time by Moore et al. [15] who demonstrated that CA125 combined with HE4 reveals the highest sensitivity and specificity among nine markers studied. FDA now recommends ROMA in women over 18 years of age with a pelvic tumor or cyst qualified for surgery, emphasizing that ROMA must always be interpreted against clinical and radiology findings [29]. Currently, several trials are under way using test kits from various manufacturers [13,14,16,19,21,22]. The strategy with ROMA, as well as normal ranges, cutoff points, and interpretation await further optimization.

This work was undertaken to determine the diagnostic performance of ROMA for preoperative stratification of patients with a pelvic mass using cutoff points determined by us and adopt from literature. Additionally we studied usefulness of ROMA algorithm due to recent concepts of etiology of epithelial ovarian malignancies and their categorization to type I and II. We also evaluated the Elecsys HE4

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assay from Roche and the Architect i2000 CA125 assay from Abbott for calculating ROMA.

Material and Methods

We initially studied 248 patients treated at the Department of Gynecologic Surgery and Oncology, Pomeranian Medical University in Stettin, in 2011-2012. At admission, USG or CT scans provided by the patient were reviewed and USG was updated when the time from the scan provided was longer than four weeks. Blood was collected, HE4 and CA125 levels were measured the same day and ROMA was calculated. However, these data were not taken into account when qualifying patients for surgery. The diagnostic performance of ROMA, CA125, and HE4 was studied after histologic verification of the lesion. We did not adopt ROMA for stratification of patients prior to surgery because we decided to calculate cutoff points for our combination of HE4 Elecsys (Roche) and CA125 Architect i2000 (Abbott) assays which were not reported in the literature.

Informed consent to participate in the study was obtained in each case.

Inclusion criteria:

- Ovarian cyst, ovarian tumor, pelvic mass, ascites, or elevated CA125;
- Histopathologic verification obtained.

Exclusion criteria:

- Liver cirrhosis revealed during laparoscopy in patients with ascites and elevated CA125;
- Tumor found not to involve the ovary;
- Qualification for follow-up as functional ovarian cyst;
- Kidney or lung pathology;
- Elevated creatinine without kidney disease.

We finally enrolled 214 patients and assigned them to two groups:

I. Benign ovarian lesions (n=131; endometrioid cyst (n=27); dermoid cyst (n=20); benign epithelial tumor (n=37); other benign lesion (n=47; serous cystadenoma, hemorrhagic cyst, inflammatory tumor, paraovarian cyst);

II. Ovarian cancers (n=83); serous (n=67), mucinous (n=4), clear-cell (n=5), endometrioid (n=7).

Group II was categorized depending on:

- Tumor stage (FIGO I and II (non advanced) vs. FIGO III and IV (advanced);
- Cancer type (type I, n=38; type II, n=45) according to Kurman and Shih [30].

Women were considered to be postmenopausal when last menstrual period was >1 year before our study.

Sensitivity, specificity, PPV, and NPV were calculated with the following cutoff points: 35 U/ml for CA125 and 70 pmol/L for HE4; and ROMA: 13.1% for premenopausal and 27.7% for postmenopausal patients. We determined our cutoff points at the 95th percentile level in group I and recalculated the aforementioned parameters.

The study was approved by the Local Ethics Committee.

Laboratory methods

Assays were performed at the Central Laboratory of the Independent Public Hospital, Pomeranian Medical University. CA125 was determined with the Architect i2000 assay from Abbott Diagnostics (Abbott Park, Il, USA). Serum HE4 concentrations were measured with the Elecsys ECLIA assay from Roche running on the cobas e 601 analyzer. The measurement range was 15.0-1500 pmol/L. Samples exceeding the upper range were diluted 1:20 with Elecsys Diluent Multiassay. Manufacturer's instructions were followed and control samples were within the normal range.

Predictive probability calculations

The predictive index (PI) was calculated according to the following equations:

Premenopause PI = – 12.0 + 2.38*ln(HE4) + 0.0626*ln(CA125);

Postmenopause PI = – 8.09 + 1.04*ln(HE4) + 0.732*ln(CA125);

where ln is the natural logarithm. ROMA was determined using the following equation:

ROMA (%) = exp(PI)/[1 – exp(PI)]*100. We adopted 13.1% and 27.7% as the cutoff points for pre- and postmenopausal patients, respectively. Additionally, we calculated our cutoff points (ROMA1) at the 95th percentile level in group I (benign lesions).

Statistics

The following contingency table was used to evaluate the diagnostic performance of CA125, HE4, and ROMA (Table 1).

Sensitivity = TP/TP+FN

Specificity = TN/FP+TN

Positive Predictive Value (PPV) = TP/TP+FP

Negative Predictive Value (NPV) = TN/FN+TN

The diagnostic performance was studied with ROC (Receiver Operating Characteristic) curves based on continuous variables. HE4, CA125, and ROMA represented diagnostic variables acting as stimulants which increase the probability of ovarian cancer proportionally to their rising value. The area under curve (AUC), standard error (SE_{AUC}), and confidence interval (CI_{AUC}) for AUC were calculated according to the nonparametric method of DeLong et al. [31]. We used this method to compare AUCs considering the fact that measurements of HE4, CA125, and ROMA were done for the same objects (group of patients). The level of significance was taken as $p<0.05$.

Results

Patient characteristics are given in table 2. The diagnostic performance of ROMA for the stratification of ovarian cancer patients was analyzed by us with ROC curves (Figures 1 and 2) and a contingency table presenting sensitivity, specificity, PPV, and NPV. AUCs for

		CANCER	NO CANCER	Total
ROMA or HE4 or CA125	HIGH	TP	FP	TP+FP
	LOW	FN	TN	FN+TN
	Total	TP+FN	FP+TN	TP+FN+FP+TN

TP – True Positive; FP – False Positive; TN – True Negative; FN – False Negative

Table 1: Table of contingency.

	n/age [mean (range)] **All PM and M** **PM | M**
All patients	214 / 46.5 (18-90) 116 / 33.9 (18-52) | 98 / 61.9 (50-90)
Benign ovarian lesions	131 / 39.5 (18-88) 96/ 30.3 (18-53) | 35/ 60.9 (52-88)
• Endometrioid cyst	27 / 35.6 (18-58) 24 / 33.5 (18-53) | 3 / 53 (58-60)
• Dermoid cyst	20 / 29.6 (18-64) 18 / 25.4 (18-42) | 2 / 63 (62-64)
• Benign epithelial tumor	37 / 49.5 (18-88) 15 / 29.6 (18-48) | 22 / 63.9 (52-88)
• Other	47 / 38.2 (18-77) 39 / 32.9 (18-40) | 8 / 63.8 (53-77)
Ovarian cancers	83 / 57.8 (32-90) 21 / 43.5 (32-52) | 62 / 62.3 (48-90)
• Type I	38 / 56.3 (32-90) 12 / 40 (32-48) | 26 / 62.1 (48-90)
• Type II	45 / 58.2 (45-89) 11 / 46.7 (42-52) | 34 / 62.3 (52-89)
• Advanced	61 / 58.8 (34-90) 14 / 44.4 (34-50) | 47 / 62.4 (48-90)
• Not advanced	22 / 53.2 (32-80) 14 / 42.3 (32-52) | 9 / 60.8 (51-80)

PM- Premenopause, M- Postmenopause

Table 2: Patient characteristics.

ROMA, HE4, and CA125 were 0.921, 0.855, and 0.919, respectively, for the whole group, 0.944, 0.862 and 0.941 for postmenopausal, and 0.818, 0.814, and 0.917 for premenopausal patients (Figure 1). ROMA performed better in postmenopausal and CA125 in premenopausal patients. ROMA demonstrated the greatest AUC, irrespectively of menopausal status. Basing on the nonparametric method of DeLong et al. [31], we disclosed a significant difference in AUCs between ROMA and HE4 in the whole group (p=0.0036). In postmenopausal patients, significant differences were noted between ROMA and HE4 (p=0.0052) and HE4 and CA125 (p=0.0488). Other differences were not statistically significant.

AUCs for ROMA, HE4, and CA125 were 0.851, 0.759, and 0.894, respectively, in type I, 0.979, 0.834 and 0.942 in type II, 0.754, 0.616, and 0.833 in not advanced (FIGO I and FIGO II) and 0.980, 0.940, and 0.950 in advanced ovarian cancer (FIGO III and FIGO IV). CA125 performed better than the other two parameters in not advanced and type I, whereas ROMA performed better in advanced and type II ovarian cancers. No significant differences were seen for advanced and type II ovarian cancer patients when the importance of AUC was compared. In not advanced and type I ovarian cancers, AUC proved more important than HE4 for ROMA (p=0.0191 in type I, p=0.0237 in not advanced ovarian cancer) and for CA125 (p=0.0271 in type I, p=0.0182 in not advanced ovarian cancer). The difference in AUCs for CA125 and ROMA was not statistically significant.

The greatest sensitivity in ovarian cancer was attributed to CA125 irrespectively of type and stage, ranging from 66.7% in premenopausal patients with not advanced cancer to 100% in premenopausal patients with advanced and type II cancer. ROMA with cutoff points calculated by us performed best in differentiating malignant from benign lesions in postmenopausal patients, with only one case below 90% (86.4%). The specificity of ROMA so calculated risk exceeded 90% in other subgroups and reached 100% in premenopausal patients with dermoid cysts and benign epithelial tumors. PPV was greatest for ROMA calculated with our cutoff points (Tables 3 and 4).

Using ROMA based on our cutoff points, we observed markedly fewer false positive cases in benign ovarian lesions, irrespectively of age. When the performance of ROMA based on different cutoff points for risk categorization was compared, false positive diagnoses were found in 11.5% vs. 4.6% for all, 8.4% vs. 3.2% for premenopausal, and 19.4% vs. 8.3% for postmenopausal patients (Table 5). The rate of false negative diagnoses was 12% vs. 14.5% for all, 23.8% and 23.8% for premenopausal and 8.1% vs. 11.3% for postmenopausal patients. The tendency toward lower sensitivity when using ROMA and cutoff points determined by authors vs. ROMA and cutoff points adopt from literature was seen irrespectively of stage and type of ovarian cancer.

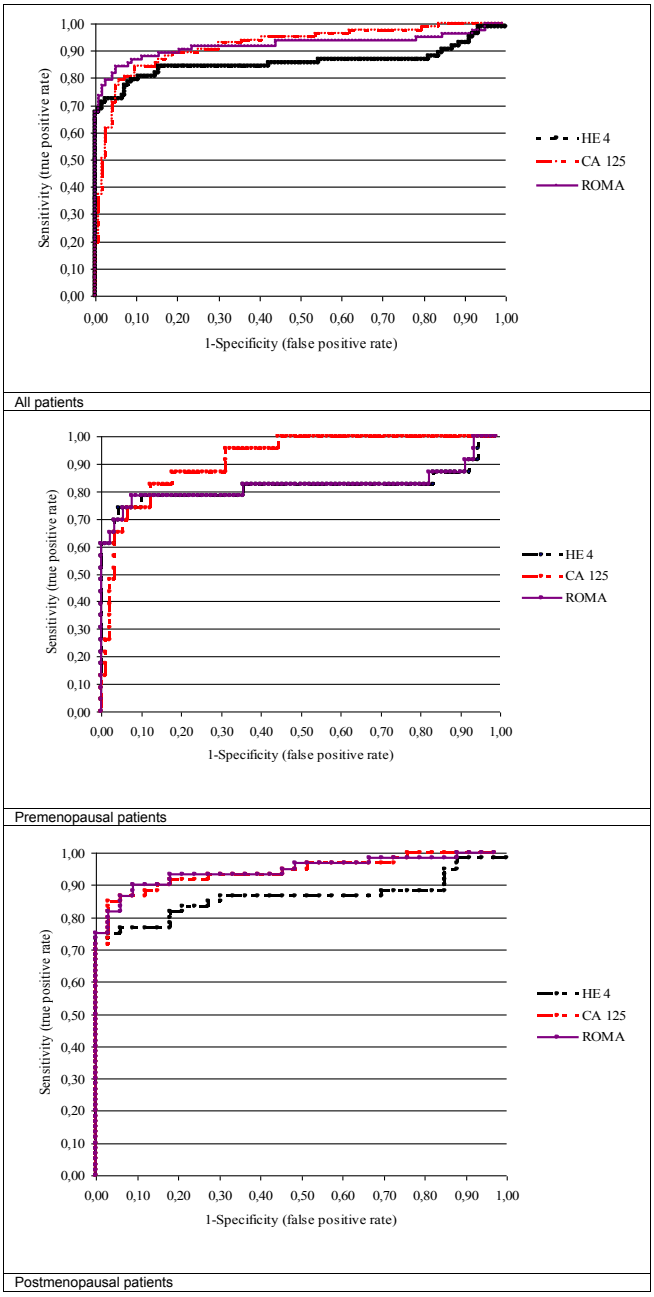

Figure 1: ROC curves for CA125, HE4, and ROMA in patients with benign ovarian lesions vs. epithelial ovarian cancer.

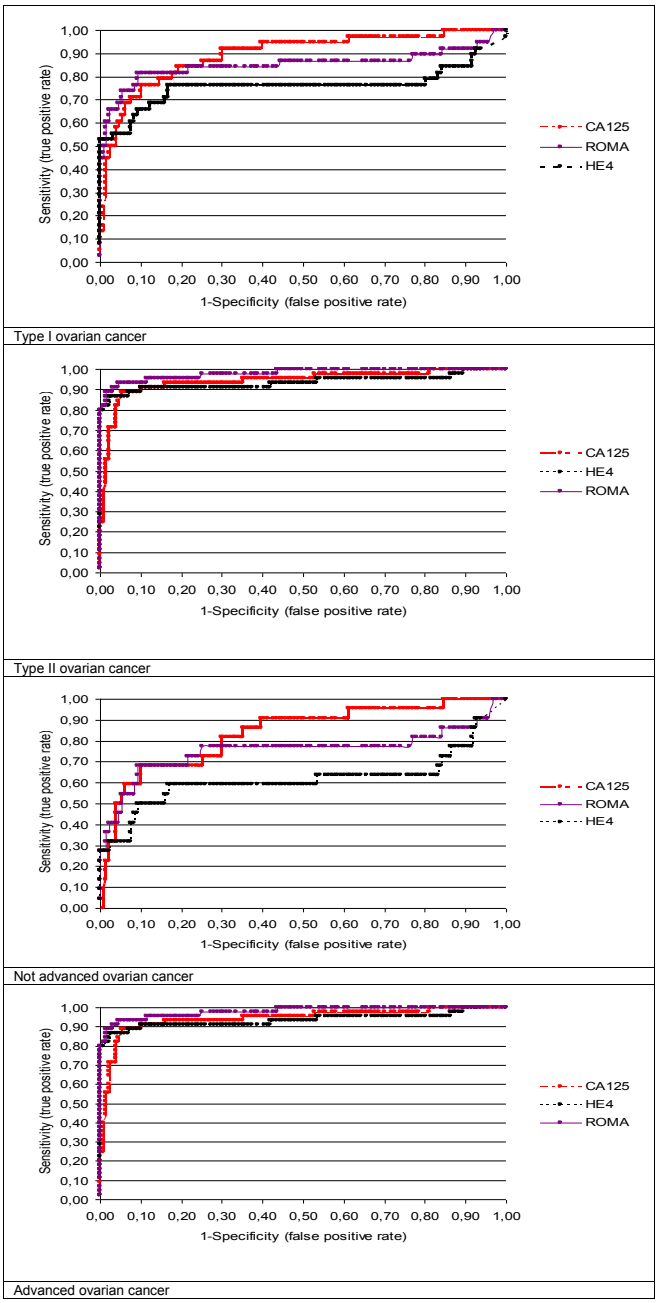

Figure 2: ROC curves for CA125, HE4, and ROMA depending on type and stage of ovarian cancer.

Discussion

Search is ongoing since many years for a novel, more sensitive, and more specific tumor marker or diagnostic algorithm to serve in the stratification of patients with a pelvic mass and for screening in ovarian cancer. It appears from the growing number of reports [10-22] that much hope has been attached recently to HE4 and the ROMA algorithm developed by Moore et al. [15]. By combining serum CA125 with HE4 levels and menopausal status of patients, ROMA proves advantageous as it reduces the number of false positive cases with elevated CA125. Moreover, 20% of ovarian cancer patients fail to reveal expression of CA125 but 50% of them will show elevated HE4 levels [32].

The usefulness of ROMA in the preoperative stratification of patients with a pelvic mass has been generally advocated [15-17,33], even though some researchers have questioned its superiority over other markers and algorithms [12,20,22]. Some doubts remain shedding uncertainty on the findings and calling for further studies. Firstly, commercial tests for CA125 and HE4 are aplenty and their diagnostic performance should be tested in all combinations possible. Secondly, it remains to be decided whether cutoff points should be fixed arbitrarily or may vary depending on the population studied.

We have corroborated the usefulness of ROMA in the preoperative stratification of patients with an ovarian tumor or cyst. We have also compared the cutoff points of Moore et al. [15] with our cutoff points representing the 95th percentile in benign ovarian lesions. The sensitivity of CA125 was greater than of ROMA in premenopausal patients (85.7% vs. 76.2%) and identical in postmenopausal patients (91.7%). HE4 alone was least sensitive regardless of age or diagnosis (EOC vs. endometrioid cyst; EOC vs. dermoid cyst; EOC vs. benign epithelial tumor; EOC vs. other benign lesions). ROMA was exceptionally valuable due to its specificity and PPV using cutoff points from the literature or from the present study as it markedly outperformed CA125 and HE4 in all groups of patients (Table 3). The NPV of ROMA was greatest in postmenopausal patients compared with CA125 or HE4 and was greater or similar to CA125 in most cases for the differentiation of benign lesions from ovarian cancer. Thus, our findings are in agreement with the sensitivity (88.1%) and NPV (92.1%) reported for ROMA by Moore et al. [16]. However, we were able to achieve a greater specificity of this algorithm using cutoff points from the literature or calculated by us (88.5% vs. 96.8%). The same applies to PPV (83% vs. 92.2%). The sensitivity, specificity, PPV, and NPV found by us for ROMA are as good as or better than those reported by other researchers (Table 6). The present findings validate the combination of the HE4 Elecsys assay from Roche on the cobas e 601 analyzer with the Architect i2000 CA125 assay from Abbott which previously has not been studied (combinations reported in the literature: Abbott Architect i2000 CA125 and HE4 EIA from Fujirebio Diagnostics, Inc. [15-18,33,34]; CA125 and HE4 on Abbott Architect [18,19]; CA125 on cobas 4000, Roche, and HE4 EIA from Fujirebio Diagnostics, Inc. [14]; HE4 EIA from Fujirebio Diagnostics, Inc. and CA125 Immunite 2000 OM-MA from Siemens [21]; CA125 and HE4 EIA from Fujirebio Diagnostics, Inc. [20,22,35]; CA125 and HE 4 on the Triturus EIA analyzer from Grifols, USA [12]).

The discrepancies in opinions about ROMA seem to relate to differences in cutoff points adopted from the literature or manufacturer's instructions on one side [12,20,21,22] or determined by the authors for their study population on the other [13,14,18,19,22,33]. We have found that ROMA with our cutoff points retains its outstanding specificity and PPV with only a small and acceptable loss in specificity (from 88% to 85.5% in all and from 91.7% to 88.7% in postmenopausal patients) and NPV (from 92.1% to 91.2% in all and from 85.3% to 82.5% in postmenopausal patients). The specificity in premenopausal patients remained unchanged (76.2%) and NPV was almost identical (94.6% vs. 94.8%).

We have also studied the diagnostic performance of ROMA with the method of DeLong et al. [31] and with ROC curves. AUCs disclosed by us were similar to those in the literature. We confirmed the statistical superiority of ROMA over HE4 but not over CA125. Using ROC curves, Anton et al. [14] did not find any difference in the performance of ROMA, CA125, HE4, or RMI. Their AUCs for ROMA were: 0.824 for all, 0.791 for premenopausal and 0.840 for postmenopausal patients. Likewise, Montagnana et al. [12] reported no difference in the value

		BENIGN OVARIAN LESION VS. OVARIAN CANCER			ENDOMETRIOID CYST VS. OVARIAN CANCER			DERMOID CYST VS. OVARIAN CANCER			BENIGN EPITHELIAL TUMOR VS. OVARIAN CANCER			OTHER BENIGN LESION VS. OVARIAN CANCER		
		All	PM	M	All	PM	M	All	PM	M	All	PM	M	All	PM	M
SENSITIVITY [%]	ROMA	88	76.2	91.9	88	78.3	-	88	78.3	-	88	78.3	91.9	88	78.3	-
	ROMA1	85.5	76.2	88.7	85.5	78.3	-	85.5	78.3	-	85.5	78.3	88.7	85.5	78.3	-
	HE4	79.5	71.4	81.7	79.5	73.9	-	79.5	73.9	-	79.5	73.9	81.7	79.5	73.9	-
	CA125	90.4	85.7	91.7	90.4	85.7	-	90.4	85.7	-	90.4	85.7	91.7	90.4	86.7	-
SPECIFICITY [%]	ROMA	88.5	91.6	80.6	83.3	85.7	-	95	94.1	-	85.3	100	72.7	91.2	89.5	-
	ROMA1	95.4	96.8	91.7	96.3	95.8	-	100	100	-	91.9	100	86.4	93.4	92.3	-
	HE4	87.8	89.5	83.3	92.6	90.9	-	95	94.1	-	81.1	100	90.9	89.5	87.2	-
	CA125	72.5	71.6	75	45.8	54.2	-	90	88.2	-	70.6	85.7	59.9	79.2	71.7	-
PPV [%]	ROMA	83	66.7	88.7	94.8	85.7	-	98.6	94.7	-	93.4	100	90.2	94.8	83.3	-
	ROMA1	92.2	84.2	87.5	98.6	94.7	-	100	100	-	95.9	100	94.6	95.9	85.7	-
	HE4	80.4	60	89.1	97.1	89.5	-	98.5	94.4	-	90.4	100	96.1	92.9	77.3	-
	CA125	67.6	40	85.9	85.2	61.9	-	97.4	90.9	-	88.2	90.9	85.9	88.2	64.5	-
NPV [%]	ROMA	92.1	94.6	85.3	66.6	78.3	-	65.5	76.2	-	74.4	66.6	76.2	81.5	82.9	-
	ROMA1	91.2	94.8	82.5	74.3	82.1	-	76.5	77.3	-	85	75	73.1	83.3	87.8	-
	HE4	87.1	93.4	73.2	59.5	78.6	-	52.7	72.7	-	63.8	71.4	64.5	71.7	85	-
	CA125	92.2	95.8	84.4	57.9	78.5	-	69.2	83.3	-	75	80	72.2	82.6	90.3	-

All – PM+M; PM – Premenopause; M – Postmenopause ; ROMA 1 – risk stratification based on cutoff points determined by authors

Table 3: Sensitivity, specificity, PPV, and NPV of CA125, HE4, and ROMA for ovarian cancer screening in patients with a pelvic mass.

OVARIAN CANCER		TYPE I			TYPE II			ADVANCED			NON ADVANCED		
		ALL	PM	M	ALL	PM	M	ALL	PM	M	ALL	PM	M
SENSITIVITY [%]	ROMA	78.9	60	85.7	95.6	90.9	97.1	96.7	91.7	98	63.6	55.6	69.2
	ROMA1	76.3	60	82.1	93.3	90.9	94.1	95.1	91.7	95.9	59.1	55.6	61.5
	HE4	65.8	50	71.4	91.1	90.9	91.2	90.2	91.7	89.8	52.4	44.4	53.8
	CA125	86.8	70	92.9	93.3	100	91.2	96.7	100	95.9	72.7	66.7	76.9
SPECIFICITY [%]	ROMA	88.5	91.6	80.6	88.5	81.8	80.6	88.5	91.6	80.6	88.5	91.6	80.6
	ROMA1	95.4	96.8	91.7	95.4	96.8	91.7	95.4	96.8	91.7	95.4	96.8	91.7
	HE4	87.8	89.5	83.3	87.8	89.5	83.3	87.8	89.5	83.3	87.8	89.5	83.3
	CA125	72.5	71.6	75	72.5	71.6	75	72.5	71.6	75	72.5	71.6	75
PPV [%]	ROMA	66.7	42.9	77.4	74.1	55.6	82.5	79.7	64.7	87.3	48.3	38.5	56.3
	ROMA1	82.9	66.7	88.5	87.5	76.9	91.4	90.7	78.6	94	68.4	62.5	72.7
	HE4	61	33.3	76.9	72	50	83.8	77.5	52.4	88	40.7	28.6	53.8
	CA125	52.2	20.6	74.3	53.8	28.9	77.5	37.9	30.8	83.9	30.8	18.2	52.6
NPV [%]	ROMA	93.5	95.6	87.9	98.3	98.9	96.7	98.3	98.9	96.7	93.5	95.6	87.9
	ROMA1	93.3	95.8	86.8	97.7	98.9	94.3	97.7	98.9	94.3	93.3	95.8	86.8
	HE4	89.9	50	78.9	96.6	91	90.9	95	98.8	85.7	52.4	94.4	83.3
	CA125	74.2	95.8	93.1	96.9	100	90	97.9	100	93.1	94.1	95.8	90

All – PM+M; PM – Premenopause; M – Postmenopause ; ROMA 1 – risk stratification based on cutoff points determined by authors

Table 4: Sensitivity, specificity, PPV, and NPV of CA125, HE4, and ROMA for identification of type and stage of ovarian cancer.

of ROMA, CA125, and HE4, although in their opinion HE4 alone is a more accurate marker. In this study, AUCs for ROMA, HE4, and CA125 were 0.77, 0.77, 0.64, respectively, for premenopausal and 0.92, 0.94, and 0.84, respectively, for postmenopausal patients.

	Low risk		High risk	
All patients				
	ROMA <13.1% or <27.7%	ROMA <18.04% or <41.6%	ROMA ≥ 13.1% or ≥ 27.7%	ROMA ≥ 18.04% or ≥ 41.6%
Benign ovarian lesion	116/131 (88.5%)	125/131 (95.4%)	15/131 (11.5%)	6/131 (4.6%)
Ovarian cancer	10/83 (12%)	12/83 (14.5%)	73/83 (88%)	71/83 (85.5%)
• FIGO I and II	8/22 (36.4%)	9/22 (40.9%)	14/22 (63.6%)	13/22 (59.1%)
• FIGO III and IV	2/61 (3.3%)	3/61 (4.92%)	59/61 (96.7%)	58/61 (95.1%)
• Type I	8/38 (21.1%)	9/38 (23.7%)	30/38 (78.9%)	29/38 (76.3%)
• Type II	2/45 (4.4%)	3/45 (6.67%)	43/45 (95.6%)	42/45 (93.3%)
Premenopausal patients				
	ROMA <13.1%	ROMA <18.04%	ROMA ≥ 13.1%	ROMA ≥ 18.04%
Benign ovarian lesion	87/95 (91.6%)	92/95 (96.8%)	8/95 (8.4%)	3/95 (3.2%)
Ovarian cancer	5/21 (23.8%)	5/21 (23.8%)	16/21 (76.2%)	16/21 (76.2%)
• FIGO I and II	4/9 (44.4%)	4/9 (44.4%)	5/9 (55.6%)	5/9 (55.6%)
• FIGO III and IV	1/12 (8.3%)	1/12 (8.3%)	11/12 (91.7%)	11/12 (91.7%)
• Type I	4/10 (40%)	4/10 (40%)	6/10 (60%)	6/10 (60%)
• Type II	1/11 (9.1)	1/11 (9.1)	10/11 (90.9)	10/11 (90.9%)
Postmenopausal patients				
	ROMA <27.7%	ROMA <41.6%	ROMA ≥ 27.7%	ROMA ≥ 41.6%
Benign ovarian lesion	29/36 (80.6%)	33/36 (91.7%)	7/36 (19.4%)	3/36 (8.3%)
Ovarian cancer	5/62 (8.1%)	7/62 (11.3%)	57/62 (91.9%)	55/62 (88.7%)
• FIGO I and II	4/13 (30.8%)	5/13 (38.5%)	9/13 (69.2%)	8/13 (61.5%)
• FIGO III and IV	1/49 (2%)	2/49 (4.1%)	48/49 (98%)	47/49 (95.9%)
• Type I	4/28 (14.3%)	5/28 (17.9%)	24/28 (85.7%)	23/28 (82.1%)
• Type II	1/34 (2.9)	2/34 (97.1)	33/34 (97.1)	32/34 (94.1)

Table 5: Risk categorization using ROMA based on different cutoff points.

The consensus prevails that an ideal marker or algorithm in ovarian cancer should be maximally effective in the early stage of the tumor. Recently, two types of OC have been identified on the basis of the expressed proteins, genetic profile, activity of metabolic routes, and clinical course. Type I consists of serous and endometroid (G1 and G2), mucinous, clear-cell, and Brenner tumors, which reveal the PTEN, KRAS, BRAS, and PAX8 gene mutations, slow growth, limited response to chemotherapy, and relatively good prognosis. Type II cancers encompass serous and endometrioid (G3) and undifferentiated forms notable for their fast growth, p53 mutation, genetic instability, and poor prognosis. Basing on this classification and using ROC curves and AUCs, we found ROMA and CA125 to be equally accurate for stratification in type I and not advanced ovarian cancers. The diagnostic power of HE4 alone was inferior to CA125 and ROMA. In type II and advanced cancers, ROMA performed best as evidenced by the largest AUC, but there was no statistically significant difference between CA125, HE4, and ROMA. The sensitivity and PPV of ROMA were lower in type I and not advanced cancers compared with type II and advanced cancers in all age groups. In type I cancers, the sensitivity of ROMA was smaller than of CA125 but greater than of HE4 in the pre- and postmenopausal subgroups and in the whole group of patients studied by us. In type II and advanced cancers, ROMA ranked equal to CA125 in sensitivity but outperformed the marker in specificity, PPV, and NPV. Contrary to our findings, Moore et al. [17] found a greater specificity (85.3%), NPV (97.9%), and AUC (0.909), but a very small PPV (27.1%) in not advanced ovarian cancers. The sensitivity of ROMA in FIGO I and II cancers was 75% for the whole group of pre- and postmenopausal patients [16]. The separate sensitivities of

Author	ROMA cutoff point [%]	SENSITIVITY [%]			SPECIFICITY [%]			PPV [%]			NPV [%]		
		All	PM	M	All	PM	M	All	PM	M	All	PM	M
Moore et al. [15]	M-27.7 PM-13.1	88.7	76.5	92.3	74.7	74.8	74.7	60.1	33.8	74.0	93.9	95	92.6
Molina et al. [19]	M-27.7 PM-13.1	90.1	74.1	95.2	87.7	88.9	83.1	74	44.4	88.9	95.8	96.6	92.5
Moore et al. [17]	M-27.7 PM-13.1	88.1	81.3	90.2	74.9	74.2	76	38.1	17.8	56.1	97.3	98.3	95.8
Anton et al. [14]	M-39.7 PM-13.9	75.9	77.8	63.9	81.8	79.3	97.3	-	-	-	-	-	-
Partheen et al. [33]	M -26 PM-17.	-	75	75	-	81	87.1	-	60.7	62.8	-	90.7	90.7
Van Gorp et al. [22]	M- 12.5 PM-14.4	84.7	66.7	91.0	76.8	87.8	58.8	71	60.5	74.3	88.2	90.4	83.3
Novotny et al. [13]	M-37.7%	-	-	85.7	-	-	95	-	-	62.06	-	-	98.65
ROMA this study	M-27.7 PM-13.1	88	76.2	91.9	88.5	91.6	80.6	83	66.7	88.7	92.1	94.6	85.3
ROMA this study	M-41.1 PM-18.04	85.5	76.2	88.7	95.4	96.8	91.7	92.2	84.2	87.5	91.2	94.8	82.5

All – PM+M; PM – Premenopause; M – Postmenopause

Table 6: Sensitivity, specificity, PPV, and NPV of ROMA for the stratification of patients with a pelvic mass reported in the literature and found by us.

CA125 and HE4 were not reported by these authors. Lenhard et al. [18] demonstrated an outstanding sensitivity of ROMA (86.4%), markedly better than that of CA125 or HE4, in FIGO stage I cancers, but not in FIGO II (same sensitivity 93.3%).

Conclusions

In conclusion, ROMA is currently a very useful diagnostic tool for the preoperative stratification of patients with a pelvic mass, revealing a very good sensitivity and specificity. Further studies are needed, however, in a large group of patients and with assays from various manufacturers to determine the optimal cutoff points for the algorithm. ROMA performs better than CA125 and HE4 in type II and advanced cancers. In type I and not advanced cancers, the very high specificity and PPV of ROMA, in spite of its somewhat smaller sensitivity and NPV, continue to speak in favor of the diagnostic potential of this algorithm.

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