

# An original risk of ovarian malignancy index and its predictive value in evaluating the nature of ovarian tumour

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## Abstract

**Background:** We carried out this study to evaluate the predictive value of an original risk of ovarian malignancy index (ROMI) devised by us.

**Method:** Our ROMI was the simple sum of points from the three-stage gradation of serum cancer antigen 125 (CA-125), data from the patient's familial and personal history and the ultrasound characteristics of the tumour (i.e. tumour size  $\geq 6$  cm, multilocularity, tumour with  $\geq 1/4$  solid areas, dense and opalescent liquid, septum or papillary vegetation  $\geq 3$  mm), ascites, bilaterality, an unclear margin with respect to the surrounding tissue and thickness of the capsule  $\geq 3$  mm. Its originality lay in the three-stage CA-125 gradation, namely  $< 35$  U/ml (1 point), 35-129 U/ml (3 points) and  $\geq 130$  U/ml (5 points). The study group comprised 274 patients divided into a group with benign tumours (BOT) ( $n = 205$ ), and a group with malignant tumours (MOT) ( $n = 69$ ). Both groups were subdivided into three subgroups of ROMI  $\leq 11$  (low risk), ROMI 12-14 (unclear risk) and ROMI  $\geq 15$  (high risk).

**Results:** The cut-off ROMI of  $\leq 11$  showed high sensitivity, specificity and area under the curve (AUC) of 0.74, 0.93 and 0.83, respectively. The cut-off ROMI of  $\leq 14$  demonstrated extremely high specificity of 0.985, but lower sensitivity and AUC, of 0.57 and 0.78, respectively.

**Conclusion:** Our newly devised ROMI and its cut-off of  $\leq 11$  is very effective in excluding, as well as confirming, ovarian cancer.

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## Introduction

Ovarian cancer is the leading cause of death from gynaecological malignancies, with five-year survival rates of 6–22%. Various methods of evaluating ovarian cancer risk have been proposed. A risk of malignancy index (RMI), originally invented in 1990, now termed RMI 1,<sup>1</sup> is a simple scoring system of ultrasound scores (U), the menopausal score (M) and the absolute value of serum cancer antigen 125 (CA-125), i.e.  $RMI\ 1 = U \times M \times CA - 125$ . The ultrasound scan in RMI 1 is evaluated and the index increased by one point for each of the following characteristics if found: multilocular cyst, evidence of solid areas, metastases, ascites and bilateralism. After the ultrasound scan has been checked, if the index is 0, then  $U = 0$ . An index of 1 denotes  $U = 1$ , and an

index  $\geq 2$  denotes  $U = 3$ . If the test occurs premenopausally, then  $M = 1$ , and if postmenopausally, then  $M = 3$ .

The benign-malign determination of the adnexal masses, using a cut-off for RMI = 200, showed 85% sensitivity and 97% specificity. After six years, the RMI was modified to RMI 2,<sup>2</sup> and again in 1999, to RMI 3.<sup>3</sup>  $RMI\ 2 = U \times M \times CA-125$ , where a total ultrasound index 0/1 denotes  $U = 1$ , ultrasound index  $\geq 2$  denotes  $U = 4$ , premenopausal status denotes  $M = 1$  and postmenopausal  $M = 4$ .  $RMI\ 3 = U \times M \times CA-125$ , where a total ultrasound index 0/1 made  $U = 1$ , ultrasound index  $\geq 2$  denotes  $U = 3$ , premenopausal status denotes  $M = 1$  and postmenopausal status  $M = 3$ .

The fourth version, RMI 4, includes the tumour size (S).<sup>4</sup>  $RMI\ 4 = U \times M \times S \times CA-125$ , where a total ultrasound

index 0/1 denotes  $U = 1$ , ultrasound index  $\geq 2$  denotes  $U = 4$ , premenopausal status  $M = 1$  and postmenopausal status  $M = 4$ . A tumour diameter  $< 7$  cm denotes  $S = 1$ , and  $\geq 7$  cm denotes  $S = 2$ . The Risk of Ovarian Malignancy Algorithm (ROMA) is a combined test of human epididymis protein 4 (HE4) enteroinular axis enzyme immunoassay, ARCHITECT CA-125 II™ and menopausal status. In a recent Moore study,<sup>5</sup> ROMA was evaluated in 472 women, and identified 94% of ovarian cancer cases and 75% of benign disease cases.

There is still no consensus on a scoring system for ovarian malignancy. The International Ovarian Tumour Analysis (IOTA) published a consensus statement in 2000 on terms and definitions with respect to five simple ultrasound-based rules for predicting malignancy (M features), namely an irregular solid tumour (M1), ascites (M2), at least four papillary structures (M3), an irregular multilocular or solid tumour with a large diameter of at least 100 mm (M4), very high colour content on colour Doppler (M5), and five ultrasonic features for predicting a benign tumour (B features), namely a unilocular cyst (B1), a solid tumour with a diameter of  $\leq 7$  mm (B2), acoustic shadows (B3), a smooth multilocular tumour (B4) and no detectable blood flow on Doppler (B5). If one or more M features are present in the absence of a B feature, the mass is classified as malignant (rule 1). If one or more B features is present in absence of an M feature, it is classified as benign (rule 2). If both or none of the M and B features are present, the simple rules are inconclusive (rule 3). These rules can be applied to 75% of masses.<sup>6</sup> There is a worrying lack of agreement regarding the vascular imaging of tumours.

Twelve parameters are included in logistic regression model 1 (LR1):

- Family history.
- A personal history of ovarian cancer.
- Current hormonal therapy.
- Age, in years.
- Maximum diameter of the lesion.
- Pain during the examination.
- Ascites.
- Blood flow within a solid papillary projection.
- A purely solid tumour or maximal diameter of the solid component  $\leq 50$  mm.
- Irregular internal cyst walls.
- The presence of acoustic shadows.
- The colour score, i.e. 1, 2, 3 or 4.

Six variables are selected for the simpler version (LR2):

- Age.
- Ascites.
- Blood flow within a solid papillary projection.
- Maximal diameter of the solid component  $\leq 50$  mm.
- Irregular internal cyst walls.
- Acoustic shadows.

The mass is classified as malignant with an estimated probability of malignancy  $> 0.10$  according to LR1 or LR2.<sup>7</sup> Both LR1 and LR2 provide the clinician with a percentage risk of cancer, instead of a simple positive or negative diagnosis.<sup>8</sup>

We represent our original risk of ovarian malignancy index (ROMI) (Table 1) as a simple sum of points derived from:

- A three-stage gradation of serum CA-125.
- Data from the familial and personal history.
- The ultrasound characteristics of the tumour, i.e. tumour size  $\geq 6$  cm, multilocularity, a tumour with  $\geq 1/4$  solid areas, dense and opalescent liquid, and septum or papillary vegetation  $\geq 3$  mm.
- Ascites.
- Bilaterality.
- An unclear margin with respect to the surrounding tissue.
- Thickness of the capsule  $\geq 3$  mm.

**Table 1:** Our newly devised ROMI

Parameter	Point
<b>Family history</b>	
Negative	0
Breast cancer	1
Endometrial cancer	1
Colon cancer	1
Ovarian cancer	1
<b>Personal history</b>	
Negative	0
Breast cancer	1
Endometrial cancer	1
Colon cancer	1
Ovarian cancer	1
<b>Age</b>	
Childhood	1
Adolescence and generative age	0
Premenopausal or early menopausal	2
Senium	1
<b>Ultrasound</b>	
<b>Tumour size</b>	
$< 6$ cm	0
$\geq 6$ cm	1
<b>Tumour structure</b>	
Cystic	0
Solid	0
Cystic, with $< 1/4$ solid parts	1
Cystic, with $\geq 1/4$ solid parts	2
<b>Density of the intralocular liquid</b>	
Absence of liquid	0
Clear liquid	1
Opalescent	2

**Table 1:** Our newly devised ROMI

Parameter	Point
<b>Tumour feature (locality)</b>	
Without a locular feature (solid)	0
Unilocularity	0
Bilocularity	1
Multilocularity	2
<b>Tumour feature (laterality)</b>	
Unilateral tumour	0
Bilateral tumour	1
Presence of septum	
No septum	0
Septum < 3 mm	1
Septum ≥ 3 mm	1
<b>Presence of papillary vegetation in the cyst</b>	
No vegetation	0
Vegetation thinner than 3 mm	0
Vegetation of 3–5 mm	1
Vegetation thicker than 5 mm	2
<b>Thickness of the capsule</b>	
< 3 mm	0
3–5 mm	1
> 5 mm	2
<b>Margin feature</b>	
Clear smooth margin	0
Clear rugged margin	1
Unclear margin with respect to surrounding tissue	2
<b>Presence of ascites</b>	
No ascites	0
Only in the pelvis	3
In the abdomen	5
Serum levels of CA-125	
< 35 U/ml	0
35–129 U/ml	3
≥ 130 U/ml	5

CA-125: serum cancer antigen 125

Its originality lies in the three-stage CA-125 gradation, i.e. < 35 U/ml (1 point), 35–129 U/ml (3 points) and ≥ 130 U/ml (5 points).

The differences between ROMI and other RMIs are as follows:

- ROMI is a simple sum of points, instead of a complicated mathematical formula, and provides a rapid result, with no need for a calculator or computer software.
- It includes additional semi-quantitative ultrasound features, i.e. multilocularity, solid areas in ≥ ¼ of the tumour, septum or papillary vegetation ≥ 3 mm, thickness of the capsule ≥ 3 mm. (Some are similar to those in LR1 and LR2, but with different cut-off values).

- Certain features, such as an unclear margin with respect to the surrounding tissue, dense or opalescent liquid, and ascites, are only included in ROMI.
- The three-stage gradation of CA-125, instead of an absolute value, is introduced for the first time with ROMI.
- Some data from the personal and familial history for cancer are only included in ROMI.
- All periods of the woman's life (gynaecological age) are only included in ROMI, and a risk equitation made between childhood and senium, as well as between the premenopausal age and early menopause. (LR1 and LR2 include the general age in years. Other RMIs only make a distinction between premenopausal and postmenopausal status).

The main advantage of ROMI over simple ultrasound rules, neural network logistic regression models, artificial neural networks (ANNs) and vector machine models is its simplicity. The ultrasonic variables, as well as data from the personal and familial history are straightforward to obtain, without the need for a calculator or computer software. The disadvantage of the simple rules is that they yield an inconclusive result in approximately 25% of tumours, whereas mathematical models, such as RMI, ROMA or LR1 and LR2, yield a useful result with respect to all masses.<sup>9</sup> ROMI is cheaper than ROMA because serum HE4 analysis and computer software is not needed.

## Specific objectives and hypothesis

This was a study of diagnostic accuracy with the following aims:

- Estimation of the diagnostic accuracy (predictive value) of ROMI, and comparison with CA-125.
- Determination of the optimal ROMI cut-off value, with concurrent maximal specificity and sensitivity.
- A comparison of its accuracy with that of the previously mentioned methods in predicting ovarian malignancy.

The hypothesis was that ROMI was suitably effective and comparable with other RMIs in predicting ovarian malignancy. This scoring system might even be a better tool for this purpose than CA-125.

## Method

### Study population

#### Inclusion and exclusion criteria

Participant recruitment was based on the ultrasound examination. The presence of an ovarian tumour was an inclusion criterion for eligibility. A histological diagnosis of the ovarian tumour was *la condition sine qua non* (a necessary condition without which something is not possible). For this reason, the patients for whom this diagnosis was unavailable, i.e. patients who did not undergo the operation, were excluded from the study.

### **The setting**

The setting was the Department for Urogynaecology and Pelvic Floor Disorders, University Clinic for Gynaecology and Obstetrics, Medical Faculty, University Saint Cyril and Methodius, Skopje, Republic of Macedonia. The study took place from 1 January 2012 to 1 January 2014. The study took place from 1 January 2012 to 1 January 2014.

### **Participant sampling**

The study population was a consecutive series of participants defined by the previously mentioned selection criteria. Every woman screened in the gynaecological ultrasound outpatient department of the clinic with an ovarian tumour on ultrasound examination in the period 1 January 2012 to 1 January 2014 was assessed for eligibility ( $n = 289$ ). Five patients refused to submit to the assessment and were excluded. An additional 10 patients were also excluded because of co-morbidities. Ultimately, 274 randomised patients were selected.

### **Data collection**

Data collection was planned before the index test, and a reference standard (prospective study) performed.

### **Precise details of the interventions for each group, and how and when they were administered**

The first study group consisted of patients in whom the histological tumour feature was benign (BOT) ( $n = 205$ ), and the second study group of patients in whom the histological feature was a malignant ovarian tumour (MOT) ( $n = 69$ ). The serum CA-125 was obtained, an ultrasound evaluation carried out according to our new ROMI, data on the patient's personal or familial history noted for every group. Interpreters of the index test and reference standard test were blind (masked) to each other's results. Ultrasound examination of the patients was performed by the first author of this article.

The study was approved by the local research ethics committee of the Association of Gynecologists and Obstetricians of Macedonia. Subjects were provided with an explanation of the study prior to it commencing, and written informed consent obtained therefrom.

### **Primary and secondary outcome measures**

#### **Demographic data**

Demographic data, such as personal age, gynaecological age, parity and familial history for ovarian tumour or any other cancer, were evaluated. The study subjects underwent an ultrasound examination of the genital organs with a 4-9 MHz vaginal probe (the GE Voluson® S8 system ultrasound model; GE Healthcare, Little Chalfont, UK) to determine several ultrasound characteristics of the ovarian

tumour as a complementary part of ROMI, such as tumour size, its features, margin thickness, the presence of septum or papillary vegetation in the cyst, the quality of cystic liquor and the presence of ascites. Serum CA-125 was estimated preoperatively using an enhanced chemiluminescence technique in each study subject, with use of the original CA-125™ II kit (Johnson & Johnson, New Brunswick, USA). Our newly proposed ROMI was also calculated in each patient.

### **Histopathological examination**

The patients were examined using light microscopy by a pathologist who was not informed of the study.

### **Statistical method**

In order to determine the optimal cut-off value of our new ROMI according to the estimated predictive values, we divided both study groups into three subgroups using three cut-off values:

- High risk (ROMI  $\geq 15$ ).
- Low risk (ROMI  $\leq 11$ ).
- Unclear risk (ROMI 12-14).

According to the results of our previous study,<sup>10</sup> we also divided the patients into three subgroups according to the two cut-off values for serum CA-125:

- Low risk (CA-125  $< 35$  U/ml).
- Unclear risk (CA-125 35-129 U/ml).
- High risk (CA-125  $\geq 130$  U/ml).

Finally, we overlapped these two modes of division intentionally to determine the real incidence rates and predictive values of these characteristics according to the three-level division of ROMI and serum CA-125.

The predictive values of ROMI and serum CA-125 were analysed according to standard formulae for sensitivity and specificity. The differences between the predictive values of the different cut-off values for ROMI and serum CA-125 were estimated using Mantel-Haenzel's chi-square test with a degree of freedom of 1.

## **Results**

Participants who satisfied the criteria for inclusion, but not those for exclusion, underwent the index test and/or the reference standard test. Patients included in the study underwent operative treatment for their ovarian tumour. The histological feature of the tumour was benign in 205 patients (BOT group) and malignant in 69 patients (MOT group).

There were no adverse events from performing the index or reference standard tests.

The results of the BOT group are presented in Table 2.

**Table 2:** A comparison of incidence rates using the original ROMI and CA-125, in the study group with benign ovarian tumours

Benign	ROMI $\geq 15$ (high risk)	ROMI $\leq 11$ (low risk)	ROMI 12–14 (unclear risk)
<i>n</i> = 205	3/205	191/205	11/205
%	1.46	93.17	4.88
<b>CA-125 (&lt; 35 U/ml)</b>			
160/205	0/205	156/205	4/205
79.05%	0.00	77.00	1.95
<b>CA-125 (35–129 U/ml)</b>			
34/205	0/205	30/205	4/205
17.42%	0.00	14.63	1.95
<b>CA-125 (<math>\geq 130</math> U/ml)</b>			
11/205	3/205	5/205	3/205
5.06%	1.46	2.44	1.46
<b>CA-125 (<math>\geq 35</math> U/ml)</b>			
45/205	3/205	35/205	7/205
21.95%	1.46	17.07	3.41
<b>CA-125 (&lt; 130 U/ml)</b>			
194/205	0/205	186/205	8/205
94.63%	0.00	90.73	3.90

CA-125: serum cancer antigen 125, ROMI: risk of ovarian malignancy index

Preoperative serum CA-125 levels were  $\leq 34$  U/ml (the standard, well-established cut-off value) in 79% (160/205) of the patients, slightly increased (35–129 U/ml) in 17.42% (34/205) patients, and  $\geq 130$  U/ml in only 5% (11/205) of the patients. On the other hand, the ROMI was  $\leq 11$  (the first proposed cut-off value) and  $\leq 14$  (the second proposed cut-off value) in 93% (191/205) and 98% (202/205) of patients, respectively, in the same study group.

When the same parameters were analysed in the MOT group (Table 3), serum CA-125 of  $< 35$  U/ml (low risk) was reported in only 26% (18/69) of the patients. It was slightly increased, i.e. a serum CA-125 of 35–129 U/ml (unclear risk) in 20% (14/69) of the patients, and a serum CA-125  $\geq 130$  U/ml (high risk) in 54% (37/69) of the patients. On the contrary, a ROMI of  $\leq 11$  (low risk) was reported in 26% (18/69) of the patients, ROMI of 12–14 (unclear risk) in 17% (12/69) of the patients and a ROMI of  $\geq 15$  (high risk) in 57% (39/69) of the patients.

The predictive values of both estimated diagnostic methods, i.e. ROMI and CA-125, are presented with their proposed cut-off values in Table 4. The first cut-off value, a ROMI of  $\leq 11$  showed very high specificity, negative predictive value (NPP) and area under the curve (AUC) of 0.93, 0.91 and 0.84, respectively; as well as high sensitivity and positive predictive value (PPV) of 0.73 and 0.79, respectively. The second proposed cut-off value of ROMI  $\leq 14$  showed very high specificity, PPV and NPV of 0.99, 0.92 and 0.87, respectively; a high AUC of 0.78, but low sensitivity of 0.57. Regarding the second parameter, serum CA-125, the first standard cut-off

**Table 3:** A comparison of incidence rates using the original ROMI and CA-125, in the study group with malignant ovarian tumours

Malignant	ROMI $\geq 15$ (high risk)	ROMI $\leq 11$ (low risk)	ROMI 12–14 (unclear risk)
<i>n</i> = 69	39/69	18/69	12/69
%	56.52	26.09	17.39
<b>CA-125 (&lt; 35 U/ml)</b>			
160/205	4/69	10/69	8/69
79.05%	5.80	14.49	11.59
<b>CA-125 (35–129 U/ml)</b>			
34/205	5/69	6/69	3/69
17.42%	7.25	8.70	4.35
<b>CA-125 (<math>\geq 130</math> U/ml)</b>			
11/205	30/69	2/69	5/69
5.06%	43.48	2.90	7.25
<b>CA-125 (<math>\geq 35</math> U/ml)</b>			
45/205	35/69	8/69	8/69
21.95%	50.72	11.59	11.59
<b>CA-125 (&lt; 130 U/ml)</b>			
194/205	9/69	16/69	7/69
94.63%	13.04	23.19	10.14

CA-125: serum cancer antigen 125, ROMI: risk of ovarian malignancy index

$< 35$  U/ml showed high sensitivity, specificity, NPV and AUC of 0.74, 0.78, 0.90 and 0.76, respectively, but a low PPV of 0.53. The second proposed cut-off value of serum CA-125 of  $\leq 129$  U/ml showed very high specificity and NPV of 0.95 and 0.88, respectively; high PPV and AUC of 0.77 and 0.74, respectively; but low sensitivity of 0.54.

The differences between the predictive values of the two proposed cut-off values for ROMI are detailed in Table 5. Higher sensitivity was reported as a measure of probability that the test result would be positive in the presence of disease, as well as higher AUC for the ROMI cut-off value of  $\leq 11$  ( $p < 0.05$  and  $p < 0.001$ , respectively); and higher specificity and PPV for the ROMI cut-off value of  $\leq 14$  ( $p < 0.001$  and  $p < 0.01$ , respectively).

The differences between the predictive cut-off value of  $\leq 11$  (ROMI) and both cut-off values for CA-125 are outlined in Table 6. Higher specificity, PPV and AUC was reported for the cut-off  $\leq 11$  (ROMI) versus the cut-off  $< 35$  U/ml (CA-125) ( $p < 0.001$ ,  $p < 0.01$  and  $p < 0.001$ , respectively). Additionally, the cut-off  $\leq 11$  (ROMI) showed higher sensitivity than the higher cut-off  $\leq 129$  U/ml (CA-125) ( $p < 0.05$ ). Regarding the differences between both cut-off values for CA-125, higher specificity and AUC were reported for the cut-off value of  $< 35$  U/ml (CA-125) ( $p < 0.001$  and  $p < 0.01$ , respectively), but higher sensitivity for the cut-off value  $\leq 129$  U/ml (CA-125) ( $p < 0.05$ ).

**Table 4:** The predictive values of ROMI and CA-125 and their proposed cut-off values

Predictive values	ROMI with cut-off of $\leq 11$	ROMI with cut-off of $\leq 14$	CA-125 cut-off of 34 U/ml	CA-125 cut-off of 129 U/ml
Sensitivity	0.74, 95% CI: 0.73–0.76	0.56, 95% CI: 0.55–0.59	0.74, 95% CI: 0.62–0.76	0.54, 95% CI: 0.38–0.56
Specificity	0.93, 95% CI: 0.94–0.92	0.98, 95% CI: 0.10–0.98	0.78, 95% CI: 0.79–0.78	0.95, 95% CI: 0.96–0.94
PPV	0.78, 95% CI: 0.80–0.78	0.93, 95% CI: 0.93–0.92	0.53, 95% CI: 0.54–0.52	0.77, 95% CI: 0.96–0.97
NPV	0.91, 95% CI: 0.92–1.0	0.87, 95% CI: 0.88–0.87	0.90, 95% CI: 0.90–0.81	0.88, 95% CI: 0.89–0.87
AUC	0.84, 95% CI: 0.89–0.80	0.77, 95% CI: 0.83–0.73	0.76, 95% CI: 0.82–0.71	0.74, 95% CI: 0.83–0.66

AUC: area under the curve. CA-125: serum cancer antigen 125, CI: confidence interval, NPV: negative predictive value, PPV: positive predictive value, ROMI: risk of ovarian malignancy index

**Table 5:** Differences between the predictive values of the two proposed cut-off values for ROMI

Predictive values	ROMI with a cut-off value of $\leq 11$	ROMI with a cut-off value of $\leq 14$	Chi-square test <sup>a</sup>
			Total
Sensitivity	0.74	0.56	3.91**
Specificity	0.93	0.98	14.92***
Positive predictive value	0.78	0.93	10.67****
Negative predictive value	0.91	0.87	1.68
Area under the curve	0.84	0.77	11.23***

ROMI: risk of ovarian malignancy index

<sup>a</sup>: Mantel-Haenzel's chi-square test with a degree of freedom of 1

\*\* $: p < 0.050$

\*\*\* $: p < 0.001$

\*\*\*\* $: p < 0.010$

**Table 6:** The differences between the predictive cut-off value of  $\leq 11$  for ROMI and both the proposed cut-off values for CA-125

Predictive values	ROMI with cut-off of $\leq 11$	CA-125 cut-off of 34 U/ml	CA-125 cut-off of 129 U/ml	Chi-square test (1) <sup>a</sup>	Chi-square test (2) <sup>a</sup>	Chi-square test (3) <sup>a</sup>
	Column 1	Column 2	Column 3	Columns (1-2)	Columns (1-3)	Columns (2-3)
Sensitivity	0.74	0.74	0.54	0.00	5.30	5.30
Specificity	0.93	0.78	0.95	17.82**	0.68	25.34**
Positive predictive value	0.78	0.53	0.77	9.65***	0.00	8.77***
Negative predictive value	0.91	0.90	0.88	0.11	2.76	1.51
Area under the curve	0.84	0.76	0.74	11.46**	0.16	5.21***

CA125: serum cancer antigen 125, ROMI: risk of ovarian malignancy index

<sup>a</sup>: Mantel-Haenzel's chi-square test with a degree of freedom of 1

\*\* $: p < 0.050$

\*\*\* $: p < 0.010$

\*\*\*\* $: p < 0.010$

## Discussion

The reported very high specificity in this study, as probability that the test result would be negative in the absence of malignancy and a high AUC for the cut-off value of  $\leq 11$  (ROMI), could be interpreted as ROMI's high effectiveness in excluding or confirming malignancy. The higher reported sensitivity, as a measure of probability that the test result would be positive in the presence of malignancy for the cut-off value of  $\leq 11$  (ROMI) versus that of  $\leq 14$  (ROMI) could also denote its better accuracy in the detection of malignancy than serum CA-125.

A ROMI  $> 11$  was attributed to 51/69 patients with ovarian malignancy in our series, and a ROMI  $> 14$  for only 39/69 patients. So, an additional 12 patients with ovarian cancer would be overlooked using a cut-off value of  $\leq 14$  (ROMI).

If CA-125 alone was used, and its well-established cut-off value of  $< 35$  U/ml was taken into consideration (Table 2), overtreatment would occur for 45/205 patients with benign tumour. However, if the higher cut-off value of  $\leq 129$  U/ml (CA-125) was used, only 11/205 patients would be overtreated. By comparison, by using a cut-off value of  $\leq 11$  (ROMI), only 14/205 patients would be overtreated.

If CA-125 alone was used, and the well-established cut-off value of  $< 35$  U/ml (Table 3) taken into consideration, or a cut-off value of  $\leq 11$  (ROMI) alone was used, undertreatment would occur in only 18/69 patients with ovarian malignancy, but by using a higher cut-off value of  $\leq 129$  U/ml (CA-125), 32/69 patients would be undertreated.

The higher specificity and AUC for the cut-off value of  $\leq 11$  (ROMI) ( $p < 0.001$ ) versus that of  $< 35$  U/ml (CA-125) ( $p < 0.01$  and  $p < 0.001$ , respectively), as well as higher sensitivity of

the cut-off value of  $\leq 11$  (ROMI) versus the higher cut-off value of  $\leq 129$  U/ml (CA-125) ( $p < 0.05$ ) indicates the higher effectiveness of ROMI in predicting ovarian malignancy. The high sensitivity of the cut-off value of  $< 35$  U/ml (CA-125) and the cut-off value of  $\leq 11$  (ROMI) indicate that they are both highly effective in excluding malignancy. On the hand, the higher specificity of the cut-off value  $\leq 11$  (ROMI) versus that of  $< 35$  U/ml (CA-125) ( $p < 0.001$ ) indicates ROMI's higher effectiveness in confirming malignancy.

Differences were not found with respect to the AUC receiver operating characteristic curve using  $< 35$  U/ml (CA-125), HE4 and ROMA by Lenhard et al.<sup>11</sup> in a series that featured 60 ovarian cancer and 116 benign ovarian tumours. A higher AUC for the cut-off value of  $\leq 11$  (ROMI) versus that of  $< 35$  U/ml (CA-125) ( $p < 0.001$ ) was reported in our study.

In determining sensitivity, as a measure of the probability that the test result would be positive in the presence of malignancy, was reported by Anton et al.<sup>12</sup> in their series on 128 patients, the following was reported: CA-125  $< 35$  U/ml (70%), HE4 (80%), ROMA (74%) and RMI (63%). We found the same sensitivity (74%) for the cut-off value of  $\leq 11$  (ROMI) and that of  $< 35$  U/ml (CA-125).

In determining specificity, as a measure of probability that the test result would be negative in the absence of malignancy, the following was reported by Karlsen et al.<sup>13</sup> in their series on 809 benign tumours and 252 ovarian cancers: 62% (CA-125), 63% (HE4), 77% (ROMA) and 82% (RMI). They concluded that ROMA performed equally well as the ultrasound-dependent RMI. We found 93% higher specificity for the cut-off value of  $\leq 11$  (ROMI).

It was reported by Chan et al.<sup>14</sup> in their series on 414 women with adnexal masses, of whom 65/414 had epithelial ovarian cancer (EOC), that a lower sensitivity of 57% was found using HE4 compared to 91% using CA-125, but there was improved specificity of 97% vs. 67%, respectively. Almost the same specificity (93%) was demonstrated using our cut-off value of  $\leq 11$  (ROMI) as the 97% achieved using HE4 in the study by Chan et al.,<sup>14</sup> but we reported much higher sensitivity of 74% vs. 57%. Li et al.<sup>15</sup> analysed data from 11 studies, and reported the following comparisons with regard to the different tests used for EOC prediction: sensitivity of 0.86 (ROMA) and 0.80 (HE4), and specificity of 0.94 (HE4), 0.84 (ROMA) and 0.78 (CA-125). Our newly devised ROMI and its cut-off value of  $\leq 11$  showed high sensitivity of 0.74, and especially high specificity of 0.93.

We compared the AUC for ROMI with that for ultrasound alone using IOTA LR or simple rules, ROMA and CA-125  $< 35$  U/ml, based on data from all of the literature. On internal validation during IOTA phase 1, both LR1 and LR2

performed very well, together with AUC in predicting malignancy (0.94 and 0.92, respectively).<sup>7</sup> A value of 0.95 AUC (93%) was reported for LR1, and 0.92 AUC (90%) for LR2 during IOTA phase 2 (2005–2007). The performance of LR1/LR2 was equivalent to subjective assessment by experienced gynecologists or radiologists (0.96 AUC).<sup>16</sup> In our study, the AUC for the cut-off value of  $\leq 11$  (ROMI) was 0.84, but the corresponding figure for  $< 35$  U/ml (CA-125) was only 0.76.

The sensitivity and specificity using the simple rules were 92% and 96%, respectively; similar to the performance of subjective assessment by an experienced operator (91% and 96%, respectively).<sup>17</sup> Van Gorp et al.<sup>18</sup> reported the largest AUC for RMI (0.86), compared to that for ROMA (0.82), HE4 (0.78) and CA-125 (0.80). In their study, the detection of malignancy did not increase using HE4 and ROMA when compared with CA-125 alone. Testa et al.<sup>19</sup> used a meta-analysis approach to centre-specific data during IOTA phase 3, and reported that the AUC pertaining to LR1, LR2, subjective assessment and RMI, was 0.93, 0.92, 0.91 and 0.88, respectively. There was sensitivity of 67% and specificity of 91% using the RMI.

RMI, or the two IOTA LR1 and LR2, are not good enough to discriminate between benign and malignant tumours when an inconclusive result is yielded using the simple rules. The rules seem to work less well for abscesses, fibromas and stage I serous tumours. These conditions are also difficult to classify using an subjective assessment of ultrasonic findings, which requires expertise. External validation of the results using the simple rules is required. The simple rules are used as a triage test, and subjective assessment can be used by an experienced examiner when the rules do not apply. Overall sensitivity of 91% and specificity of 93% were obtained in the study by Timmerman et al.<sup>17</sup> The accuracy obtained using an expert sonographer has not been matched using a biomarker test or algorithm, multimodal scoring system, such as RMI, neural networks logistic regression model, ANN or vector machine model.<sup>8</sup>

## Conclusion

In our study, the cut-off value of  $\leq 11$  ROMI was more effective than  $< 35$  U/ml (CA-125) in excluding ovarian cancer and had a higher specificity ( $p < 0.001$ ). It was also more effective in confirming ovarian malignancy, with a higher PPV ( $p < 0.01$ ). The inclusion of additional ultrasound features pertaining to the tumour and the new, proposed three-stage grouping of CA-125 into the ROMI calculation could improve predictive values and diminish the chances of false positive and false negative results. It is probable that this new, simple tool could be more effective, as well as cheaper, than HE4 and RMI, or even ROMA, in identifying ovarian tumour.

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