

## Preoperative evaluation of patients with ovarian masses using the risk of malignancy index 4 model

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**Keywords:** Ovarian masses, risk of malignancy index, ovarian cancer, CA-125

### Abstract

**Objective:** To evaluate the performance of the RMI 4 in discriminating benign from malignant ovarian masses.

**Study Design:** Cross-sectional study.

**Setting:** Assiut Women Health Hospital- Egypt.

**Materials and methods:** This was an observational cross-sectional study involving 91 patients at Women's Health Hospital, Assiut University, Egypt during the period between January, 2016 and January, 2017. Women with ovarian masses planned for surgical management were recruited from the outpatient gynecology clinic of the hospital. Risk of malignancy index (RMI 4) was calculated for all study participants. Biopsies obtained from the ovarian masses after surgical intervention were sent to the pathology lab for histopathological examination. The histopathologic diagnosis of the ovarian masses is considered the gold standard for diagnosis.

**Results:** The mean age of patients in the benign group was  $34.83 \pm 16.28$  years versus  $43.43 \pm 15.91$  in the malignant group. There were 12 postmenopausal patients (15.6%) in the benign group versus 4 postmenopausal patients

(28.6%) in the malignant group ( $p=0.0001$ ). An ultrasound score of 4 was recorded in 85.7% of patients in the malignant group versus only 6.5% in the benign group ( $p=0.0001$ ). Additionally, tumor size  $\geq 7$  cm was observed in 85.7% of patients in the malignant group versus 55.8% in the benign group ( $p=0.0001$ ). The mean value of CA-125 was significantly higher in malignant group than the benign group ( $142.09 \pm 41.50$  versus  $54.51 \pm 32.86$  ml, respectively) with  $p=0.01$ . RMI 4 had a sensitivity of 75%, specificity of 97.3%, PPV of 85.7%, NPV of 94.8% and an overall accuracy of 93.4%.

**Conclusions:** RMI 4 is a simple and reliable tool in the primary evaluation of patients with ovarian masses. It can further be used to discriminate benign from malignant ovarian masses with high sensitivity and accuracy.

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### Introduction

The ability to discriminate between benign and malignant ovarian masses is crucial for deciding between medical or surgical intervention in the management

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plan for patients who present with such masses. A consistent model for identification of malignant masses preoperatively would allow optimal first-line treatment for patients with malignant masses.<sup>1</sup>

Women with malignant ovarian masses should be managed by a gynecological oncologist, as the type and quality of surgical staging, lymph node dissection and cytoreductive surgery are of great prognostic importance in adnexal malignancy.<sup>2</sup> Additionally, prompt referral to an oncologist has been shown to improve survival in patients with ovarian malignancy.<sup>3</sup>

Clinical pelvic examination, tumor markers, and imaging modalities have all been proposed for use in the discrimination of ovarian masses, but no single parameter is sensitive or specific enough in this regard. As a result, other scoring models have been proposed for this purpose.<sup>4</sup>

Risk of malignancy index (RMI) is a combined model that was developed by Jacob, et al. in 1990. It is composed of three parameters; menopausal status, 2D ultrasonographic features of the adnexal mass, and CA-125 level.<sup>5</sup> A modified technique, called RMI 2, was developed in 1996 by Tingulstad et al.<sup>6</sup>, and yet another modification, called RMI 3, was added in 1999.<sup>7</sup> The final modification to the original RMI technique, RMI 4, which added the parameter "tumor size" (S) was developed by Yamamoto, et al. in 2009.<sup>8</sup>

Various studies have been done aiming to validate the four versions of the RMI.<sup>4</sup> Overall, a cutoff value of 200 for RMI 1-3 and 450 for RMI 4 showed the best

differentiation point between benign and malignant ovarian masses, with high levels of sensitivity and specificity (sensitivity 51%-90%, specificity 51%-97%).

A systematic review of diagnostic studies concluded that RMI I was the most effective for women with suspected ovarian malignancy.<sup>9</sup> The National Institute of Clinical Excellence (NICE) guidelines for ovarian cancer recommend that, for women with suspected ovarian malignancy, an RMI I score should be calculated and used to guide the woman's management.<sup>10</sup>

The four RMIs have many advantages. They are simple, cost-effective scoring systems that can be performed in low-resource settings without the need of advanced imaging modalities (such as computed tomography scanning or magnetic resonance imaging).<sup>11</sup> In addition, RMIs can be performed in less-specialized centers.

The purpose of this study was to evaluate the performance of the RMI 4 in discriminating between benign ovarian masses and malignant ovarian masses in women referred to our tertiary hospital.

## **Materials and Methods**

This was an observational, cross-sectional study conducted with 91 patients at Women's Health Hospital, Assiut University, Egypt, during the period between January, 2016 and January, 2017. Women with ovarian masses scheduled for surgical management were recruited from the outpatient gynecology clinic of the hospital. The study was approved by

Ethical Review Board of Assiut Faculty of Medicine.

Exclusion criteria included patients with an existing tissue diagnosis (either malignant or benign), patients who were poor surgical candidates or cases that were inoperable. After obtaining written consent from the patients, a history was taken including menopausal status followed by a clinical examination including general, abdominal and vaginal. Post menopause was defined as one year or more of amenorrhea in women more than 50 years old. All other women were considered premenopausal.

Next, two dimensional ultrasound images with either the transabdominal or transvaginal approach was performed using a Sono-Ace X8 machine (Medison, Korea). Evaluation was done with the patient in a supine position by the same sonographer, who was an expert gynecologist (level II sonographer). Initially, we used a transabdominal approach, with the patient's bladder full; then another supplementary transvaginal examination was done with the patient's bladder empty. The following ultrasonographic features were assessed: bilaterality, presence of solid areas, multilocularity of the cyst, presence of ascites, and metastases.

A peripheral venous blood sample (5 ml) was drawn from each patient, prior to surgery for the estimation of serum CA-125 level, as determined by radioimmunoassay (MINIVEDAS CA-125 MACHINE).

From the data obtained, an RMI 4 was calculated for all women with ovarian

masses as follows:  $RMI\ 4 = U \times M \times S$  (size in centimeters)  $\times$  CA-125, where a total ultrasound score of 0 or 1 was assigned a value of  $U=1$ , and a score of  $\geq 2$  was assigned a value of  $U=4$ . The total ultrasound score was assigned using the following ultrasound features suggestive of malignancy: the presence of a multilocular cystic lesion, solid areas, bilateral lesions, ascites, and intra-abdominal metastases, scored as one point for each if present and 0 if absent). A score of  $M=1$  was assigned to premenopausal women while a score of  $M=4$  was assigned to postmenopausal women. Patients with tumors with a single greatest diameter  $< 7$ cm were given a tumor size score of  $S=1$  while those with tumors  $\geq 7$  cm were given a score of  $S=2$ . Serum CA-125 levels were applied directly to the calculation.<sup>8</sup>

After surgical intervention, all removed ovarian masses were sent to the pathology lab for histopathological examination. Histopathological diagnosis of the ovarian masses is considered as the gold standard for diagnosis. Frozen section biopsy was not used as it is unavailable in our hospital.

Data were entered and statistically analyzed using the Statistical Package for Social Sciences (SPSS), version 21. Quantitative data were described as mean and standard deviation. Student's T-test was used for comparison between groups. Qualitative data were described as numbers and percentages. Fisher's exact test was used for comparison between groups. P-value  $\leq 0.05$  was considered to be statistically significant. The sensitivity, specificity, diagnostic accuracy, positive and

negative predictive values (PPV, NPV) of the RMI 4 and its individual parameters were calculated.

The sensitivity was defined as the percentage of patients with malignant disease having a positive test result. The specificity was defined as the percentage of patients with benign disease having a negative test result. The PPV was defined as the percentage of patients with a positive test result having malignant disease and the NPV was defined as the percentage of patients with a negative test result having benign disease. The accuracy was defined as the percentage of all patients having malignant disease with a positive test result and benign disease with a negative test result.

To determine the best cut-off value to discriminate between benign and malignant adnexal masses, a receiver operating characteristics (ROC) curve was plotted. The best cut-off value was chosen according to the highest sensitivity with the lowest false-positive rate.

## Results

One hundred women with ovarian masses were enrolled in our study, from which 9 cases were excluded--4 were inoperable, 1 was unfit for surgery and 4 had borderline tumors in the final histopathological diagnosis. We excluded borderline tumors as they are not classified according to the specific cut-off points of RMI 4, so they could be misinterpreted in the study results. The remaining 91 patients were classified as follows: 77 patients (84.6%) had benign masses and 14 (15.4%) had malignant masses according to the final

histopathological examination. The pathologic findings from the 91 patients are summarized in Table 1.

**Table 1: The histopathological diagnosis of the included masses (n=91)**

Histopathology	n (%)
<b>Benign masses (n=77)</b>	
Serous cystadenoma	26
Dermoid cyst	13
Mucinous cystadenoma	11
Hemorrhagic functional cyst	10
Endometrioma	8
Luteal cyst	3
Serous cystadenofibroma	3
Fibroma	2
Sclerosing stromal tumor	1
<b>Malignant masses (n=14)</b>	
Serous cystadenocarcinoma	6
Granulosa cell tumor	4
Mucinous cystadenocarcinoma	2
Yolk sac tumor	1
Metastatic tumor	1

The mean age of patients included in the benign group was 34.83±16.28 years versus 43.43±15.91 in the malignant group. There was no statistical difference regarding age and parity in either group.

Table 2 shows that there were statistically significant differences between the two groups with regard to all parameters of RMI 4. There were 12 postmenopausal patients (15.6%) in the benign group versus 4 such patients (28.6%) in the malignant group (p=0.0001). An ultrasound score of 4 was recorded in 85.7% of patients in the malignant group versus only 6.5% in the benign group (p=0.0001). Additionally, tumor size ≥ 7 cm was observed in

85.7% of patients in the malignant group versus 55.8% in the benign group (p=0.0001).

The mean value of CA-125 was significantly higher in the malignant group than the benign group (142.09±41.50 versus 54.51±32.86 ml, respectively) with p=0.01. Twelve (85.7%) patients in the malignant group had a score ≥ 450 versus 4 (5.2%) in the benign group (p=0.0001).

Overall, RMI 4 had a sensitivity of 75%,

specificity of 97.3%, PPV of 85.7%, NPV of 94.8 % and an overall accuracy of 93.4%. Tumor size and menopausal status had the lowest sensitivity among the RMI 4 parameters (21.8% and 25%, respectively) while the ultrasound score has the highest sensitivity (70.6%) (Table 3).

In ROC curve analysis, the best performance obtained for the RMI 4 was at the cut-off point 140 with area under the curve (AUC=0.917) (Figure 1).

**Table 2: Demographic and clinical data of the study participants (n=91)**

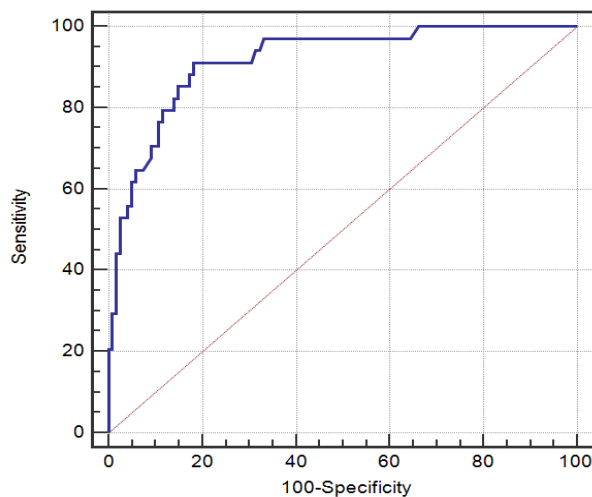
Variables	Benign masses (n=77)	Malignant masses (n=14)	P-value
<b>Age, mean±SD</b>	34.83±16.28	43.43±15.91	0.08
<b>Parity, mean±SD</b>	3.01±2.74	3.93±2.58	0.24
<b>Menopausal status, n (%)</b>			<b>0.0001*</b>
Premenopausal	65 (84.4)	10 (71.4)	
Postmenopausal	12 (15.6)	4 (28.6)	
<b>USG score, n (%)</b>			<b>0.0001*</b>
Score 1	72 (93.5)	2 (14.3)	
Score 4	5 (6.5)	12 (85.7)	
<b>USG features, n (%)</b>			
Bilaterality	3 (3.9)	7 (50)	<b>0.0001*</b>
Multilocularity	9 (11.7)	9 (64.3)	<b>0.0001*</b>
Solid areas	23 (29.9)	11 (78.6)	<b>0.016*</b>
Metastasis	1 (1.3)	3 (21.4)	<b>0.0001*</b>
Ascites	4 (5.2)	7 (50)	<b>0.0001*</b>
<b>Tumor size, n (%)</b>			<b>0.0001*</b>
< 7 cm	34 (44.2)	2 (14.3)	
≥ 7 cm	43 (55.8)	12 (85.7)	
<b>CA-125 level</b>			<b>0.01*</b>
Mean±SD	54.51±32.86	142.09±41.50	
< 35 U/mL, n (%)	61 (79.2)	2 (14.3)	
≥35 U/mL, n (%)	16 (20.8)	12 (85.7)	<b>0.0001*</b>
<b>RMI 4</b>			<b>0.0001*</b>
< 450	73 (94.8)	2 (14.3)	
≥ 450	4 (5.2)	12 (85.7)	

USG, ultrasonography; CA, cancer antigen; RMI, risk of malignancy index; SD, standard deviation

**Table 3: Performance of RMI 4 and its individual parameters for the detection of malignant ovarian masses**

Variables	Sensitivity %	Specificity %	PPV%	NPV %	LR+	LR-	Accuracy %
RMI 4	75	97.3	85.7	94.8	28.12	0.26	93.4
USG Score	70.6	97.3	85.7	93.5	26.12	0.30	92.3
Menopausal Status	25	86.7	28.6	84.4	1.87	0.86	75.8
Tumor Size	21.8	94.4	85.7	44.2	3.93	0.83	50.5
CA-125	42.8	96.8	85.7	93.5	13.5	0.59	80.2

USG, ultrasonography; CA, cancer antigen; RMI, risk of malignancy index; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio



**Figure 1: The ROC for the RMI 4 showed best cut off at 140**

**Discussion**

Accurate preoperative differentiation between benign and malignant ovarian masses results in more women being correctly referred for gynecologic oncology care and more women with benign masses undergoing conservative management.<sup>12</sup>

The aim of the current study, over a period of 1 year, was to evaluate the role of RMI 4 in discriminating benign from malignant ovarian masses. Ninety-

one consecutively admitted patients were included during the study period. Of these, 14 had malignant masses according to the final histopathological examination. The prevalence of ovarian malignancy in our study was 15.4%. This prevalence was lower than the 28.8% prevalence reported in a similar, 2014 study carried out in our tertiary hospital by Abbas et al.<sup>13</sup>

In our study, RMI 4 had a sensitivity of 75%, specificity of 97.3%, PPV of 85.7%, NPV of 94.8 % and an overall accuracy of 93.4%. The sensitivity of RMI 4 in our study was similar to previous studies that evaluated RMI 4 performance in discriminating ovarian masses. Mohammed et al., in a 2014 retrospective study of 172 patients, reported sensitivity, specificity, PPV, NPV and accuracy for RMI 4 at 76.9%, 93.8%, 71.4%, 95.3%, and 91% respectively.<sup>14</sup> With regard to the individual parameters of RMI 4, our results coincide with those of this study in that all parameters showed statistically significant differences between patients with benign and malignant ovarian masses.<sup>14</sup>

In the original 2009 study by Yamamoto et al.<sup>8</sup> that first described RMI 4, the

prevalence of malignancy was 15.8% like our study. A RMI 4 at a cut-off score of 450 reported higher sensitivity (86.4%) and NPV (97.5%), but lower specificity (91%) and overall accuracy (90.4%) than our results. This difference could be due to the small sample size and higher number of cases with benign masses in our study. The same was observed in a 2011 study by Aktürket al.<sup>4</sup> in which the sensitivity of RMI 4 was higher (84%) and accuracy was lower (86%) using the same cut-off score of 450.

In a 2016 study by Campos et al., following 158 cases with a higher prevalence of malignant ovarian masses (32.2%), the sensitivity of RMI 4 was 75% with 86% specificity.<sup>15</sup> These results are very similar to our study.

The parameters of RMI 4 in our study were menopausal status, ultrasound score, tumor size and serum CA-125 level. Only 28.6% of women with ovarian cancer were postmenopausal. This leads to the low sensitivity of menopausal status in the diagnosis of malignancy (25%) and overall accuracy (75.8%). This was similar to the findings of Mohammed et al., where 30.8% of women with ovarian cancer were postmenopausal.<sup>14</sup> Since both our research and that of others relied on results from primarily premenopausal subjects, we cannot determine if menopausal status may play a significant role in the diagnosis of ovarian cancer.

Conversely, 85.7% of women with ovarian malignancy had ultrasound scores greater than 1, while only 6.5% of benign cases had ultrasound scores greater than 1. In fact, the sensitivity of

the ultrasound score (70%) is similar to the sensitivity of the RMI 4 technique overall (75%). Furthermore, the ultrasound score had 93% accuracy in diagnosing malignancy. The most important sonographic feature for diagnosis of malignancy was presence of solid areas that were evident in 78.6% of cases, followed by multilocularity of the cystic masses in 64.3% of cases. ascites and bilaterality are not constant features for ovarian malignancy so they were evident in only 50% of cases.

We found that most malignant cases (85.7%) had tumor size greater than 7 cm. But at the same time, nearly half of the benign cases (55.8%) also had tumor size greater than 7 cm. Therefore, tumor size greater than 7 cm. could not be used reliably to identify malignant ovarian masses. Most previous studies confirm this finding, as in the 2011 study by Petronella et al., which found that tumor size was useless for diagnosis of malignant ovarian masses because 60% of benign cases had the tumor size greater than 7 cm.<sup>16</sup>

Although serum CA-125 level was high in 85.7% of malignant cases, 20.8% of benign cases also had CA-125 levels above the allowable cut-off level 35 U/mL. Furthermore, high CA-125 levels are known to be indicative of other gynecological conditions such as endometriosis and pelvic infections.<sup>17,18</sup> As a result, serum CA-125 levels show low sensitivity (42.8%) and accuracy (80.2%) in our study.

The main limitations of the current study were the small sample size included in the study and the low number of cases diagnosed with ovarian cancer.



## Conclusions

In conclusion, RMI 4 is a simple and reliable tool in the primary evaluation of patients with ovarian masses and the discrimination of benign from malignant ovarian masses with high sensitivity and accuracy. Further larger studies are recommended to validate RMI 4 as a tool for ovarian malignancy screening.

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