

# Evaluation of Risk of Malignancy Index 5—A New Indicator in Differentiating Benign and Malignant Ovarian Masses

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## ABSTRACT

**Objective:** To evaluate the effectiveness of the risk of malignancy index 5 (RMI5)—a new indicator in differentiating benign and malignant ovarian masses. To compare RMI5 with RMI1, RMI2, RMI3, RMI4, and the individual parameters (CA125, ultrasound score, and menopausal status).

**Materials and methods:** It is a 5-year retrospective record analysis of women admitted with ovarian masses. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), diagnostic accuracy of RMI1, RMI2, RMI3, RMI4, RMI5, and CA125, ultrasound score, and menopausal status were calculated.

**Results:** Risk of malignancy index 5 is a better indicator of malignancy compared to the other indices. This study confirms that the five RMI indices were more accurate than menopausal status, CA125 level, and ultrasound score separately. RMI2 and RMI5 had  $p = 0.047$  and  $0.034$ , respectively, and hence were more accurate as compared to other indices by univariate analysis. Risk of malignancy index 5 had sensitivity and specificity of 61.5% and 93.17%, respectively, at a cutoff of 25. CA125 has better sensitivity of 80% in detecting malignant ovarian tumors than other individual parameters.

**Conclusion:** Risk of malignancy index 5 better discriminates malignant from benign ovarian masses as compared to other malignancy indices.

**Keywords:** CA125, Menopausal status, Risk of malignancy index, Ultrasound score.

*Journal of South Asian Federation of Obstetrics and Gynaecology* (2019); 10.5005/jp-journals-10006-1706

## INTRODUCTION

Ovarian malignancies represent a great challenge as over two-thirds of the patients have advanced disease at diagnosis.<sup>1</sup> Ovarian cancer patients operated by gynec-oncologists are more likely to undergo accurate staging and optimal cytoreductive surgery as compared to patients who are operated by general gynecologists.<sup>2</sup> The preoperative diagnosis of whether a mass is benign or malignant cannot always be made out by CA125 and ultrasound features. Minimal invasive surgery or minilaparotomy can be planned if an ovarian neoplasm is known to be benign preoperatively. The risk of malignancy index (RMI) is a simple scoring method based on menopausal status ( $M$ ), ultrasound score ( $U$ ), and serum CA125 levels developed by Jacobs et al.<sup>3</sup> Risk of malignancy index has been modified by Tingulstad<sup>4,5</sup> to obtain RMI2 and RMI3. Yamamoto et al. developed RMI4 by including the size of tumor into the calculation.<sup>6</sup> We developed risk of malignancy index 5 (RMI5) to circumvent the drawbacks of the older malignancy indices. Risk of malignancy index 5 is calculated using the following formula:

$$RMI5 = U \times M \times S \times C,$$

where  $M$ , menopausal status;  $U$ , ultrasound score.

In premenopausal woman, tumor size ( $S$ , single greatest diameter) is of  $<7$  cm,  $S = 1$  and  $\geq 7$  cm,  $S = 2$ .

In postmenopausal women, tumor size is of  $<5$  cm,  $S = 1$  and  $\geq 5$  cm,  $S = 2$ .

CA125  $<35$  U/mL:  $C = 1$ .

35–100 U/mL:  $C = 2$ .

$>100$  U/mL:  $C = 3$ .

The RMI5 indicator developed is believed to be a more efficacious parameter to differentiate benign and malignant ovarian tumors. Thus, we wanted to test the efficacy of RMI5 as against RMI1, RMI2, RMI3, RMI4, and the individual parameters in differentiating benign or malignant ovarian tumors.

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**How to cite this article:** Shekar NC, Dasappa P, Rangaiah N, et al. Evaluation of Risk of Malignancy Index 5—A New Indicator in Differentiating Benign and Malignant Ovarian Masses. *J South Asian Feder Obst Gynae* 2019;11(4):258–262.

**Source of support:** Nil

**Conflict of interest:** None

## MATERIALS AND METHODS

This is a retrospective study of 200 women admitted to gynec-ward at RajaRajeswari Medical College and Hospital between 2010 and 2015 with ovarian masses. The Ethical Committee approval was obtained from the Institutional Ethics Committee of RajaRajeswari Medical College and Hospital, Bengaluru. The data of the women were taken from the records, and preoperative serum CA125 levels, ultrasound findings, and menopausal status were noted. RMI1, RMI2, RMI3, RMI4, and RMI5 were calculated. Serum CA125 levels were measured using chemiluminescence assay (Roche Diagnostics, Tokyo, Japan) and ultrasound was performed transabdominally with 7 MHz transducer. Ultrasound features of malignancy like the presence of multilocular cystic lesion, solid areas, bilateral lesions, ascites, and intra-abdominal metastasis were given one score each. A total ultrasound score ( $U$ ) for each patient was calculated. Tumor size ( $S$ ) was measured.

### Ultrasound Score<sup>7</sup>

Unilocular simple cysts with regular fine wall or lesion suggesting dermoid cyst: 0.

Multilocular cyst with regular and smooth wall <3 mm or thick >3 mm or solid homogenous tumor with hyperechogenic and well-defined wall: 1.

Unilocular cyst or multilocular cyst with fine wall, with irregularity in the wall or septa 3 mm: 2.

Multilocular cyst with thick and irregular wall (irregularity <3 mm) and or irregular septa; or cyst with papillarity irregularity over 3 mm: 4.

Complex lesion with predominance of cystic or solid area, without irregularity in surface: 5.

Complex lesion with irregularity in surface (3 mm) or badly defined irregular wall or solid heterogeneous lesion: 10.

Multiplicity—unilateral or bilateral lesions: 0.

Associated lesions: ascites—1.

Wall expansive involvement—1.

Postmenopausal status was defined as more than a year of amenorrhoea or age greater than 50 years in women who had undergone hysterectomy. All others were considered premenopausal. RMI1, RMI2, RMI3, RMI4, and RMI5 were calculated for all patients using the formula mentioned below.

$RMI1^3 = U \times M \times CA125$ ; a total ultrasound score of 0 yielded  $U = 0$ , score of 1 yielded  $U = 1$ , and score of  $\geq 2$  yielded  $U = 3$ ; premenopausal status yielded  $M = 1$  and postmenopausal status,  $M = 3$ . Serum CA125 levels were applied directly to the calculation. A value of  $RMI1 \geq 200$  was considered significant.

$RMI2^4 = U \times M \times CA125$ ; a total ultrasound score of 0 or 1 yielded  $U = 1$  and a score of  $\geq 2$  yielded  $U = 4$ ; premenopausal status yielded  $M = 1$  and postmenopausal status yielded  $M = 4$ . The serum CA125 was applied directly to the calculation. A value of  $RMI2 \geq 200$  was considered significant.

$RMI3^5 = U \times M \times CA125$ ; a total ultrasound score of 0 or 1 yielded  $U = 1$  and a score of  $\geq 2$  yielded  $U = 3$ ; premenopausal status yielded  $M = 1$  and postmenopausal status yielded  $M = 3$ . The serum CA125 levels were applied directly to the calculation. A value of  $RMI3 \geq 200$  was considered significant.

$RMI4^6 = U \times M \times S \times CA125$ , where a total ultrasound score of 0 or 1 yielded  $U = 1$  and a score of  $\geq 2$  yielded  $U = 4$ . Premenopausal status yielded  $M = 1$  and postmenopausal status yielded  $M = 4$ . A tumor size or single greatest diameter less than 7 cm yielded  $S = 1$  and  $\geq 7$  cm yielded  $S = 2$ . The serum level of CA125 was applied directly to the calculation. A RMI value of  $\geq 450$  was considered as high risk of malignancy.

$RMI5 = U \times M \times S \times C$ , where a total ultrasound score of 0 or 1 made  $U = 1$  and a score of  $\geq 2$  made  $U = 4$ ; premenopausal status made  $M = 1$  and postmenopausal status,  $M = 4$ . A tumor size and single greatest diameter of <7 cm made  $S = 1$  and  $\geq 7$  cm made  $S = 2$  in premenopausal women.

Tumor size <5 cm yielded  $S = 1$  and  $\geq 5$  cm yielded  $S = 2$  in postmenopausal patient.

The serum CA125 < 35 U/mL yielded  $C = 1$ ,

35–100 U/mL yielded  $C = 2$ , and

>100 U/mL yielded  $C = 3$ .

The histopathological diagnosis was considered conclusive.

When a gynecological cancer was found, it was staged according to International Federation of Gynecology and Obstetrics (FIGO) classification.<sup>8</sup>

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated for RMI1, RMI2, RMI3, RMI4, and RMI5 and the individual parameters (CA125, ultrasound score, and menopausal status).

### RESULTS

The distribution of benign and malignant cases by age, menopausal status, ultrasound score, and tumor size are in Table 1. Amongst the 200 patients, 35 (17.5%) had malignant and 165 (82.5%) had benign tumors as determined by histopathological examination. The mean age of the patients with malignancy was  $36.92 \pm 14$  and  $34.06 \pm 12$  in those with benign ovarian tumors.

Distribution of diagnosis in premenopausal and postmenopausal women is shown in Table 2.

The performance of the individual parameters is shown in Table 3. CA125 has a good sensitivity of 80% than others among the individual parameters. The risk of malignancy was more with increased CA125 and in postmenopausal women with significant  $p$  value < 0.001.

The performance of RMI1–5 is presented in Table 4.

Direct comparison of the five indices shows that there is statistically significant difference in the performance of RMI2 and RMI5 with a McNemar's test value of 0.047 and 0.034, respectively, as shown in Table 5. Here, McNemar's test compared the indices with the histopathology which is the gold standard.

Seventeen (8.5%) patients had infertility and found to have ovarian cysts while evaluating.

Laparoscopy was done in 105 (52.5%), and laparotomy in 60 (30%) patients with benign masses.

Three cases with suspected dermoid cysts underwent laparoscopic salpingo-oophorectomy were later diagnosed as malignant. Laparotomy with salpingo-oophorectomy was done in six

**Table 1:** The distribution of benign and malignant cases by age, menopausal status, serum CA125, and ultrasound score

Variables	Benign (%)	Malignant (%)	Test/p value
Age (years)			$\chi^2 / < 0.001^*$
>30	81 (49.1)	6 (17.1)	
31–40	42 (25.5)	9 (25.7)	
41–50	21 (12.7)	7 (20.0)	
<50	21 (12.7)	13 (37.1)	
Menopausal status			$\chi^2 / < 0.001^*$
Premenopausal	131 (79.4)	17 (48.6)	
Postmenopausal	34 (20.6)	18 (51.4)	
Ultrasound score			$\chi^2 / < 0.001^*$
0	69 (41.8)	1 (2.9)	
1	43 (26.1)	0 (0.0)	
2–10	53 (32.1)	34 (97.1)	
CA125			$U$ test / < 0.001*
Mean	155.25	169.26	
Minimum	4	4	
Maximum	1,770	5,342	
Standard deviation	547.84	576.02	
Range	4–1,770	4–5,342	

\*Significant at 5% level of significance

**Table 2:** Distribution of diagnosis

	Postmenopausal (n = 52)		Premenopausal (n = 148)		Total	%
Benign diseases	34		131		165	
Corpus luteal cyst	2	3.85	1	0.68	3	1.5
Endometriotic cyst	6	11.54	34	22.97	40	20.0
Fibroma	0	0.00	2	1.35	2	1.0
Mature cystic teratoma	3	5.77	17	11.49	20	10.0
Mucinous cystadenoma	10	19.23	21	14.19	31	15.5
Paraovarian cyst	1	1.92	1	0.68	2	1.0
Seromucinous cystadenoma	1	1.92	2	1.35	3	1.5
Serous cystadenofibroma	3	5.77	4	2.70	7	3.5
Serous cystadenoma	6	11.54	45	30.41	51	25.5
Simple cyst	1	1.92	4	2.70	5	2.5
Xanthogranulomatous oophoritis	1	1.92	0	0.00	1	0.5
Malignant diseases	18		17		35	
Dermoid cyst with moderately differentiated squamous cell CA	0	0.00	1	0.68	1	0.5
Dermoid cyst with poorly differentiated squamous cell CA	1	1.92	0	0.00	1	0.5
Dysgerminoma	0	0.00	1	0.68	1	0.5
Granulosa cell tumor	1	1.92	4	2.70	5	2.5
Mature cystic teratoma with squamous cell CA in situ	1	1.92	0	0.00	1	0.5
Mucinous cystadeno Carcinoma	1	1.92	4	2.70	5	2.5
Papillary serous cystadeno Carcinoma	12	23.07	3	2.03	15	7.5
Papillary serous adeno Carcinoma	1	1.92	0	0.00	1	0.5
Spindle cell tumor	1	1.92	1	0.68	2	1.0
Steroid cell tumor	0	0.00	1	0.68	1	0.5
Yolk sac tumor	0	0.00	2	1.35	2	1.0
Grand total	52	100.0	148	100.0	200	100.0

CA, carcinoma

**Table 3:** The performance of serum CA125, ultrasound score, and postmenopausal status with histopathological diagnosis as the gold standard

Criteria	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	DA (%)	p value
CA125						
35 U/mL	80.0	76.97	42.42	94.78	77.5	<0.001*
Ultrasound score						
≥2	42.86	56.36	17.24	82.30	54	0.456
Menopausal status						
Postmenopausal	51.43	79.39	34.62	88.51	74.5	<0.001*

\*Significant at 5% level of significance, Chi-square test

**Table 4:** Sensitivity and specificity of RMI1, RMI2, RMI3, RMI4, and RMI5

Criteria	Sensitivity	Specificity	Positive predictive value	Negative predictive value
RMI1	68.57	92.12	64.86	93.25
RMI2	77.14	84.24	50.94	94.56
RMI3	71.43	90.30	60.98	93.71
RMI4	71.43	89.09	58.14	93.63
RMI5	61.54	93.17	68.57	90.91

**Table 5:** McNemar's test

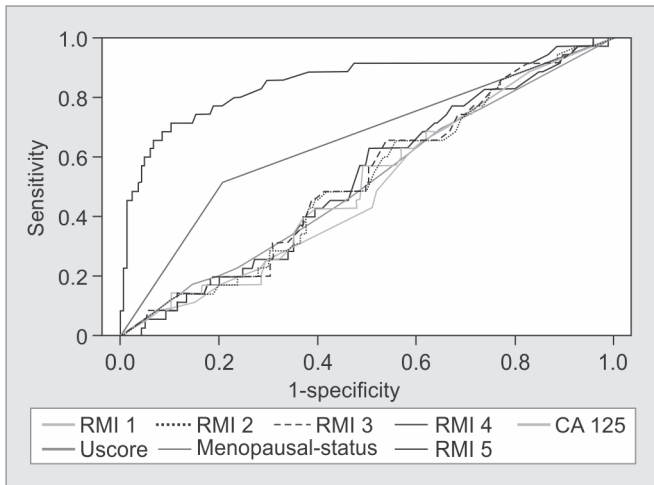
Criteria	p value
RMI1	0.897
RMI2	0.047*
RMI3	0.526
RMI4	0.382
RMI5	0.034*

\*There is significant difference in the performance of the methods, McNemar's test = 0.034

cases of suspected benign serous cystadenomas turned malignant. Staging laparotomy was done in 26 patients.

Mature cystic teratomas or ovarian cysts dealt laparoscopically were removed by using bag without spillage.

Laparoscopy was abandoned in two patients and converted to laparotomy as findings were more in favor of malignancy. Endometrial hyperplasia was found in 4 (2%) patients.



**Fig. 1:** Receiver operator characteristic curve showing the performance of RMI1, RMI2, RMI3, RMI4, RMI5, CA125, ultrasound score, and menopausal status. RMI, risk of malignancy index

**Table 6:** Values of area under curve

Variables	Area	Significance	95% confidence interval	
			Lower boundary	Upper boundary
RMI1	0.899	<0.001	0.837	0.961
RMI2	0.934	<0.001	0.849	0.960
RMI3	0.913	<0.001	0.864	0.961
RMI4	0.903	<0.001	0.844	0.956
RMI5	0.950	<0.001	0.832	0.945
U score	0.971	<0.001	0.926	1.000
CA125	0.552	0.330	0.443	0.662
Menopausal status	0.464	0.500	0.361	0.566

Significant at 5% level of significance

**Receiver Operating Characteristic**

Figure 1 shows analysis of the RMI1, RMI2, RMI3, RMI4, and RMI5. The values of area under the curve were highly significant with the values of 0.899, 0.934, 0.913, 0.903, and 0.950, respectively ( $p < 0.001$ ). Area under the curve values of menopausal status, serum CA125, and ultrasound score are 0.464, 0.552, and 0.971, respectively. The risk of malignancy indices was more reliable in detecting malignancy in terms of area under the curves. Risk of malignancy index 5 is closer to the left-hand border and then the top border of the receiver operating characteristic (ROC) space, so the test is accurate with a high specificity of 93.17% at a cutoff of 25. Values of area under curve are shown in Table 6.

**DISCUSSION**

The mean value of CA125 levels in benign cases was 155.25 (4–1,770), and in malignant cases, it was 169.25 (4–5,342) with  $p < 0.001$ .

When individual parameters were compared, CA125 had better sensitivity than the ultrasound score, size, and menopausal status. The postmenopausal status had better specificity than CA125 but less sensitivity.

According to Ulusoy et al., the median value of preoperatively determined CA125 serum levels of the patients with benign cases

was 31.42 (3–1,153), and in those with malignant cases, it was 152.75 (1–5,000). There was a significant difference between the two groups ( $p < 0.001$ ).<sup>9</sup>

The determination of adnexal masses with use of RMI1 (for cutoff of 200; sensitivity and specificity were 85.4% and 96.9%, respectively) was better as compared to ultrasound and serum CA125 individually.<sup>3</sup>

RMI2 was better than RMI1 with McNemar’s test ( $p = 0.001$ ).<sup>4</sup> RMI3 had a sensitivity and specificity of 71% and 92%, respectively, at a cutoff level of 200.<sup>5</sup>

Yamamoto et al. confirmed high performance values of the RMI2 and RMI3 at a cutoff level of 200. The sensitivity and specificity of RMI2 were 90% and 80%, while that for RMI3 were 82.6% and 86.4%, respectively.<sup>6</sup>

In the present study, RMI2 had a sensitivity and specificity of 77.14% and 84.22%, respectively.

Yamamoto et al. in 2003 developed RMI4 to overcome the low PPV of other indices. He derived a sensitivity of 86.8%, a specificity of 91%, a PPV of 63.5%, and a NPV of 97.5% at a cutoff of 450.<sup>6</sup>

This is comparable with the performance of RMI4 in our study.

RMI4 uses tumor size but uses the cutoff of 7 cm both in pre- and postmenopausal women. The adnexal masses of >8 cm and >5 cm in pre- and postmenopausal women, respectively, should be considered for intervention.<sup>10</sup> Also, the older indices use CA125 directly.

CA125 levels are elevated in a variety of conditions like endometriosis, uterine fibroids, pancreatitis, pelvic inflammatory disease, and cirrhosis. Also malignancies of endometrium, lung, breast, pancreas, and gastrointestinal tract can have a raised CA125.<sup>11</sup>

The specificity and sensitivity of CA125 are 78% and 75%, respectively, at a cutoff of 35 U/mL.<sup>8</sup> More the CA125 more is the specificity.

In malignant ovarian tumors, CA125 is elevated to a greater extent. Hence, to incorporate the two aspects and improve the efficacy, RMI5 was developed.

Risk of malignancy index 5 has a specificity of 93.17%, better than any of the four indices. Univariate analysis of the five indices shows RMI5 to be a good index to indicate malignancy ( $p = 0.034$ ). RMI2 has also proved to have  $p$  value = 0.047 (McNemar’s test).

This helps us to involve oncosurgeons or refer to better center where these surgeries can be performed more efficiently. This helps in deciding the surgery to be performed preoperatively than deciding intraoperatively. Also, benign tumors can be efficiently and cosmetically dealt laparoscopically. Furthermore, this can be done by general gynecologists and eliminates the involvement in gynec-oncologists while screening. This helps in earlier diagnosis and appropriate referrals.

**CONCLUSION**

Risk of malignancy index 5 has a specificity of 93.17% and a NPV of 90.91 at a cutoff of 25. Also, the ROC curve indicates that the RMI5 is better index with an area under curve of 0.950 with significant  $p$  values. Hence, RMI5 is simple score that can be used to differentiate benign and malignant ovarian masses. Amongst the individual parameters, CA125 is better parameter to detect malignancy.

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