

## The Role of Risk of Malignancy Index in the Preoperative Assessment of Patients with Adnexal Masses

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**Abstract:** Background: Ovarian cancer is a leading cause of death from gynaecologic malignancies. Efficiency of care for ovarian cancer patients can be improved by standardizing preoperative evaluation. The Risk of Malignancy Index (RMI) was developed for referral of relevant patients to gynaecologic oncologic centres. The main advantage of this method is that the RMI is a simple scoring system that can be applied directly into clinical practice without the introduction of expensive or complicated methods. The aim of is study is to determine the accuracy of the RMI to discriminate between benign lesions and malignant adnexal masses in gynaecologic practice. Methods: One hundred eighty cases - 120 premenopausal and 60 postmenopausal - presented by adnexal masses was included and assessed using RMI. All patients underwent exploration and histopathological results of the masses were correlated with RMI. Results: Comparing RMI to the results of histopathology, we found that there was statistical highly significant difference between types of adnexal masses concerning RMI in premenopausal and in postmenopausal women ( $p < 0.001$ ). Validating RMI as predictors in patients of adnexal masses using the standard cutoff point of the RCOG (250) at this study showed sensitivity of 70.5%, specificity of 93.5%, positive and negative predictive value was 91.2% and 76.8% respectively with an overall accuracy of 82.2%. Validating RMI using a cutoff point of 126.75 showed sensitivity and specificity to be 88.6% and 90.2% respectively, positive and negative predictive value was 89.7% and 89.2% respectively with an overall accuracy of 89.4%. Conclusion: Due to simplicity of its components RMI can be evaluated easily and it is mandatory to be applied in clinical practice by any gynecologist. [Hosam M.Hemeda, Khalid K.Ali and Khalid A. Onsil. **The Role of Risk of Malignancy Index in the Preoperative Assessment of Patients with Adnexal Masses.** *Life Sci J* 2014;11(1):241-246]. (ISSN:1097-8135). <http://www.lifesciencesite.com>. 36

**Keywords:** ovarian cancer, adnexal mass, RMI, risk of malignancy index

### 1.Introduction

Adnexal mass is defined as an enlarged structure in the uterine adnexa which can either be palpated on a bimanual pelvic examination or visualized using radiographic imaging. The definition used in the literature is quite variable, historically, because of the decrease in ovarian size after menopause, any palpable mass in a postmenopausal woman has been considered abnormal.<sup>(1)</sup>

Adnexal mass may be primary ovarian tumors (epithelial, sex cord-stromal, and germ cell), metastatic malignant tumors (breast and gastrointestinal tract), masses arising from the Fallopian tube (hydrosalpinx, pyosalpinx and primary Fallopian tube malignancies)<sup>(2)</sup>, masses arising from the uterus (leiomyoma), masses arising from the gastrointestinal tract (diverticulae of the colon, large colonic tumors, tumors of the appendix), masses arising from the urinary tract (pelvic kidneys, diverticulae of the ureter), masses arising from remnants of embryological development, endometriosis<sup>(3)</sup>, pelvic inflammatory disease<sup>(4)</sup> or it may be cysts arising from normal ovarian functions (follicular cysts and corpus luteum cysts).<sup>(5)</sup>

Ovarian cancer is a leading cause of death from gynaecologic malignancies. Approximately 70% of ovarian cancers are diagnosed at advanced stage and

only 30% of women with such cancers can expect to survive 5 years. While fewer than 20% of ovarian cancers are confined to the ovaries at diagnosis, the five-year survival of women with localized tumors exceeds 90%.<sup>(6)</sup>

Several studies have demonstrated that ovarian cancer patients operated by a gynaecologic oncologist are more likely to undergo accurate staging and optimal cytoreductive surgery compared to patients who are operated by general gynaecologists.<sup>(7)</sup>

The discriminative preoperative evaluation of adnexal masses is rather complicated. A variety of diagnostic procedures is used, leading to a wide variety of variables which can result in an inaccurate interpretation of the nature of the adnexal mass.<sup>(8)</sup>

Assessment with ultrasound has been shown to be a sensitive but relatively nonspecific method leading to unnecessary surgical resection of many benign lesions. To improve the diagnostic accuracy of transvaginal sonography for differentiating benign from malignant ovarian lesions, a variety of morphology scoring scales have been proposed.<sup>(9)</sup> A morphology index based on morphologic characteristics of ovarian tumours was developed in 1993, specific categories included tumour volume, wall structure, and septal structure. A point scale (0-

4) was developed within each category with the total points per evaluation varying from 0-12.<sup>(10)</sup>

A modification of the classification of the previous morphology index was further introduced. Two descriptive components were evaluated: tumour volume and morphologic structure. A point scale (0-5) was developed within each category, with total points varying between 0 and 10 for each tumour. Septal structure, which was a standard variable in the original index, was not included as a major morphologic component, since it was shown to be less related to risk of malignancy than either wall structure or tumour volume. Rather, observations of diffuse echogenicity, tumour septa, and extratumoural free fluid were added as separate findings within the category of tumour structure.<sup>(11)</sup>

Several tumor markers have been employed in the assessment for adnexal masses; Human Chorionic Gonadotropin<sup>(12)</sup>, Alpha-fetoprotein<sup>(13)</sup>, Interleukin-6<sup>(14)</sup>, Plasminogen activator inhibitor-1 and -2<sup>(15)</sup>, Cancer-Associated Serum Antigen<sup>(16)</sup>, Inhibin<sup>(17)</sup>, Carbohydrate antigen 19-9<sup>(18)</sup>, Carcinoembryonic antigen<sup>(18)</sup>.

Serum Cancer-associated Antigen (CA) 125 is well established, being raised in over 80% of ovarian cancer cases and, if a cut-off level 30 u/ml is used; the test has a sensitivity of 81% and specificity of 75%.<sup>(19)</sup> The majority of non-mucinous epithelial ovarian cancer (80%) has elevated CA 125 and in early stage I and II disease, mucinous tumours had significantly lower CA 125 levels compared to non-mucinous early stage carcinomas. CA 125 is highest for serous & undifferentiated cancers. Non epithelial ovarian carcinomas are also accompanied by elevated CA 125 levels.<sup>(20)</sup>

Several benign diseases were found to be associated with frequent CA 125 positivity, some of which may cause differential diagnostic problems. Patients with effusions caused by benign diseases such as congestive heart failure, tuberculosis or liver cirrhosis can be highly positive, as can patients with benign gynecological diseases like uterine fibromyomata and benign ovarian tumours. Patients with endometriosis, or especially endometriotic cysts, may have highly elevated CA 125 levels, but patients with benign ovarian neoplasms may also be positive in, about 1-16 of the patients. It is also increased in pregnancy and pelvic inflammatory disease.<sup>(9)</sup>

Ultrasound often fails to differentiate between benign and malignant lesions, and serum CA125 levels, although raised in over 80% of ovarian cancers, is raised in only 50% of stage I cases. In addition, levels can be raised in many other malignancies and in benign conditions, including benign cysts and endometriosis.

Efficiency of care for ovarian cancer patients can be improved by standardizing preoperative evaluation. Jacobs et al<sup>(21)</sup> developed the Risk of Malignancy Index (RMI) for referral of relevant patients to gynaecologic oncologic centers. The main advantage of this method compared with other diagnostic procedures is that the RMI is a simple scoring system that can be applied directly into clinical practice without the introduction of expensive or complicated methods. Introduction of the RMI would improve the management of adnexal masses, with a higher percentage of ovarian cancer patients that are operated by a gynaecologic oncologist. At the same time, referral of patients with non-invasive (benign and borderline) lesions would be reduced.<sup>(8)</sup>

The original definition of RMI (RMI 1) was modified and adjusted in 1996 (RMI 2)<sup>(22)</sup> and again in 1999 (RMI 3)<sup>(23)</sup>. The three versions of the RMI have been validated retrospectively and prospectively in different clinical studies where a cut off value of 200 showed the best discrimination between benign and malignant adnexal masses, with high sensitivity and specificity levels (sensitivity 51–90%, specificity 51–97%).

A protocol was designed according to data from validation of RMI for triaging women into low risk when (RMI < 25), moderate risk (RMI 25–250) and high risk when (RMI > 250). A cut-off of 250 was chosen as the threshold for determining whether there was a high index of malignancy, hence justifying surgical operation by gynecological oncologist. Using a cutoff point of 250, a sensitivity of 70% and specificity of 90% can be achieved.<sup>(24)</sup> Thus the great majority of women with ovarian cancer will be dealt with by gynaecological oncologists in cancer centers, with only a small number of referrals of women with benign conditions.

The high specificity and sensitivity of the risk of malignancy indices makes them an ideal and simple way of triaging women for this purpose. Table (2) gives an example of a reasonable protocol for triaging women using the risk of malignancy index. The three risks of malignancy indices produce similar results.<sup>(25)</sup>

## 2. Patients and methods

One hundred eighty cases - 120 premenopausal and 60 postmenopausal - presented by adnexal masses were chosen from the outpatient clinic and Department of Obstetrics and Gynecology Clinic of Ain Shams University Hospital. Sample size was determined with an estimated sensitivity of 72% and specificity of 87%, confidence interval= 95% and power of the study was set at 90%. All patients were subjected to: evaluation of Serum CA-125 and transvaginal ultrasound examination, patients with

pelvic masses larger than 10 cm had in addition a transabdominal ultrasound, patients with simple pelvic masses less than 5cm in size were excluded as they are considered to be most probably functional cysts. Patients with evident signs of hepatic,

intrapertitoneal metastasis or lung metastasis were also excluded. Postmenopausal women defined as having more than one year of amenorrhea. All other women were considered premenopausal.

Table 1: Calculating the risk of malignancy index

RMI = U x M x CA125
U = 0 (for ultrasound score of 0); U = 1 (for ultrasound score of 1); U = 3 (for ultrasound score of 2–5) Ultrasound scans are scored one point for each of the following characteristics: multilocular cyst; evidence of solid areas; evidence of metastases; presence of ascites; bilateral lesions.
M = 1 for premenopausal women 3 for postmenopausal women
CA125 is serum CA125 measurement in u/ml

Table 2. An example of a protocol for triaging women using the risk of malignancy index (RMI); data from validation of RMI <sup>(21)</sup>

Risk	RMI	Women (%)	Risk of cancer (%)
Low	< 25	40	< 3
Moderate	25–250	30	20
High	> 250	30	75

### Risk of Malignancy Index (RMI):

The RMI is calculated using the formula  $RMI = M \times U \times \text{serum CA-125}$ .

(M) refers to the patient's menopausal status; (U) refers to the ultrasound score, and serum (CA-125) is the assayed level expressed in U/ml.

And for this study we refer to RMI <sup>3,(23)</sup> and its criteria is as follows:

Ultrasound Findings (U): scored one point for each of the following: Multi-locular cystic lesions, Evidence of Solid areas, Bilateral lesions, Evidence of Ascites, Evidence of metastases. U=0(ultrasound score of 0), U=1(ultrasound score of 1), U=3(ultrasound score of 2-5)

Menopausal Status (M): is scored as follows: Premenopausal status is graded M=1, Postmenopausal status is graded M=3

All the patients underwent abdominal exploration, masses were sent for histopathologic examination and then the results were correlated with RMI.

### 3.Results

The mean age of premenopausal women was  $34.3 \pm 8.8$  years for benign cases and  $38.1 \pm 9.6$  years for malignant cases, while it was  $54 \pm 7.4$  for benign cases and  $57 \pm 4.1$  for malignant cases in postmenopausal women. There was statistical highly significant difference between the two types of adnexal mass (benign and malignant) as regards the age in premenopausal women ( $p < 0.001$ ) but not in postmenopausal women ( $p > 0.05$ ).

Histopathological examination of adnexal masses showed that 92 (51%) of cases were benign and 88 (49%) of cases were malignant. There was highly statistically significant association ( $p < 0.001$ ) between malignant adnexal mass and menopausal state; 50 (83.3%) of postmenopausal patients with adnexal mass were malignant versus 38 patients (31.7%) of premenopausal patients. There was also statistical highly significant association between malignant adnexal masses concerning CA 125 in premenopausal women and in postmenopausal women ( $p < 0.001$ ). Ultrasound score also showed statistical highly significant association with malignant adnexal masses in pre menopausal women and postmenopausal women ( $p < 0.001$ ), table (3).

RMI was calculated and compared to the results of histopathology, we found that there was statistical highly significant difference between types of adnexal masses concerning RMI in premenopausal and in postmenopausal women ( $p < 0.001$ ), table (4).

Validating RMI as predictors in patients of adnexal masses using the standard cutoff point of the RCOG (250) at this study showed sensitivity of 70.5%, specificity of 93.5%, positive and negative predictive value was 91.2% and 76.8% respectively with an overall accuracy of 82.2%. Validating RMI using a cutoff point of 126.75 derived from the ROC curve drawn by the data of the study showed sensitivity and specificity to be 88.6% and 90.2% respectively, positive and negative predictive value was 89.7% and 89.2% respectively with an overall accuracy of 89.4% figure (1).

Table 3. Ultrasound score showed statistical highly significant association with malignant adnexal masses in pre menopausal women and postmenopausal women

Table (3)	Premenopausal women		Postmenopausal women	
	Benign	Malignant	Benign	Malignant
Incidence no (%)	82 (68.3)	38 (31.7)	10 (16.7)	50 (83.3)
	Chi square ( $\chi^2$ ) = 42.732, $p < 0.0001$			
CA 125 mean $\pm$ SD	75.7 $\pm$ 85.8	385.1 $\pm$ 536.7	18.5 $\pm$ 14.7	881.6 $\pm$ 168.8
	$p < 0.0001$		$p < 0.0001$	
US score no (%)	1	80 (97.6)	24 (63.2)	10 (100)
	3	2 (2.4)	14 (36.8)	28 (56)
		$\chi^2 = 26.569, p < 0.0001$		$\chi^2 = 6.947, p = 0.001$

Table 4. RMI was calculated and compared to the results of histopathology

Table (4)	Premenopausal women		Postmenopausal women	
	Benign	Malignant	Benign	Malignant
RMI mean $\pm$ SD	76.1 $\pm$ 85.6	1023.1 $\pm$ 1759.8	18.5 $\pm$ 14.7	1077.8 $\pm$ 1632.2
P	< 0.0001		< 0.0001	

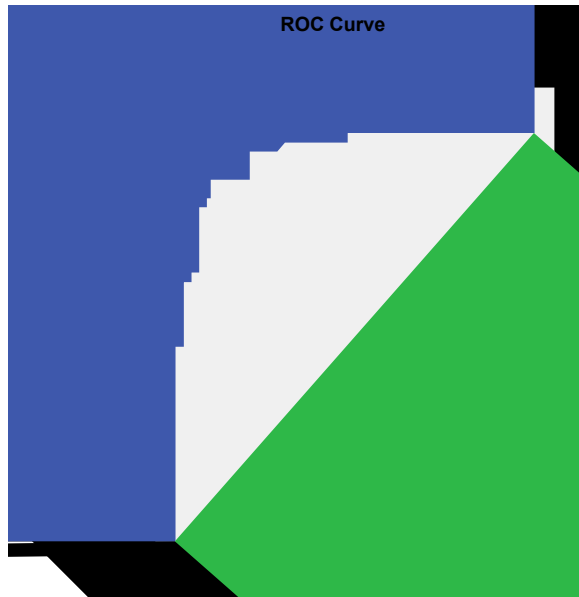


Figure (1): ROC curve of Sensitivity and Specificity of RMI; Area under curve = 0.92,  $p < 0.0001$  (95 % CI = 0.88 to 0.97).

#### 4. Discussion

Our results confirmed that there is a significant relationship between the menopausal state and prediction of malignancy, the benign cases were mostly premenopausal (68.3%) while in the postmenopausal state the malignant cases account for (83.3%). Previously the sensitivity and specificity rates of menopausal state in detecting malignancy were reported to be 87% and 59% respectively.<sup>(24)</sup> The difference in these rates found in this study (83.3% and 68.3%) is due to the lower mean age of the patients in this study makes it more towards the

premenopausal state, which in turn will increase the specificity.

The sensitivity of ultrasound score in detecting malignancy was 40.9%; and the specificity detecting benign cases was 97.8% with accuracy of 87%. These results are nearly similar to those reported by the previous studies.<sup>(21,22,24)</sup>

Our study showed the usefulness of the CA125 in prefferal evaluation of patients with adnexal masses. We were determined that the different serum level of CA 125 in benign and malignant adnexal mass is similar to other studies.<sup>(25)</sup> In the current study, for all specimens, premenopausal and postmenopausal women, the best sensitivity obtained (93.2%) with a relatively higher specificity (79.3%) was reached at Cutoff level 113.25 u/ml. The best performance of CA125 was at a cut-off level 88 U/ml, with a sensitivity of 88%, a specificity of 97%, a positive predictive value of 84%, and a negative predictive value of 99%.<sup>(26)</sup>

The ability of RMI to distinguish between benign and malignant adnexal masses reflects the complementarities of serum CA 125 level and ultrasound finding and menopausal state. Patients with malignant disease and low ultrasound score will have an elevated serum CA 125 while most patients with benign diseases with high CA 125 level will have ultrasound score of one only. In the current study comparing the individual predictors of malignancy and RMI, it showed the superiority of RMI at different Cutoff values, as regards the sensitivity and specificity over the individual predictor CA 125 at different Cutoff values, and also over the ultrasound and menopausal score in detecting ovarian malignancy.

Application of RMI in clinical practice would provide a rational basis for specialist referral of patients with malignant diseases before diagnostic surgery. The high specificity and sensitivity of the risk of malignancy index makes it an ideal and simple way of triaging women for this purpose.<sup>(25)</sup>

Previous studies showed that the best cut off point for RMI is 250.<sup>(8)</sup> A study on 302 women with adnexal mass indicated an RMI at a cut off point of 250 had a sensitivity of 88.2%, a specificity of 74.3%, a PPV of 71.3%, a NPV of 90% for diagnosing invasive lesions.<sup>(27)</sup> In another study on 182 women with pelvic masses indicated an RMI > 250 had a sensitivity of 88.5% for diagnosing invasive lesions.<sup>(28)</sup>

In a systematic review<sup>(29)</sup>, 116 diagnostic studies for adnexal malignancy were reviewed. The reported result showed that at the cut off point of 200, RMI has a sensitivity of 78% and specificity 87% for malignant mass diagnoses which is similar to our report.

With risk malignancy index, a Cutoff value of 126.75 used in this study shows the highest accuracy (89.4%) and the highest specificity (90.2%) with minimal decrease in the sensitivity (88.6%).

For the guidelines of RCOG<sup>(30)</sup> in the choice of cut off point, using a cut off point of 250, a sensitivity of 70% and specificity of 90% can be achieved. In our study with using the same cut off point 250, a sensitivity of 70.5% and specificity of 93.5% can also be achieved.

For our study triaging women using the risk of malignancy index is:

A-low RMI <25, risk of cancer 0%

B-moderate RMI 25-250, risk of cancer 38.2%

C-high RMI >250, risk of cancer 91.2%

Thus the great majority of women with ovarian cancer will be dealt with by gynaecological oncologists in cancer centres, with only a small number of referrals of women with benign conditions. However, as most of the cysts will be benign, gynaecologists in units at more local level will perform the majority of surgery.

## Conclusion

Due to simplicity of its components RMI can be evaluated easily and it is mandatory to be applied in clinical practice by any gynecologist.

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