

# Risk of Malignancy Index (RMI-2) in the Evaluation of Adenexal Masses

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## Abstract

The present prospective study, conducted in the department of Obstetrics and Gynaecology and department of Biochemistry, Government Medical College and Rajindra Hospital, Patiala. Fifty patients after taking a detailed history and examination underwent various investigations including CA-125 levels and ultrasonography. RMI-2 was calculated for each patient preoperatively and later compared with respective histopathological examination. The present study demonstrated that RMI-2 (at a cut-off value of 200) is a screening method with high sensitivity and specificity in predicting benign or malignant nature of adenexal masses. It is a simple, easy and useful method to apply in a tertiary care hospital. Our study reconfirms accuracy of RMI in diagnosing adenexal masses with high risk of malignancy. Small sample size, more number of pre-menopausal and more number of benign ovarian masses were some of the limitations of present study.

**Keywords-** RMI-2, Ovarian malignancy, CA-125, U-Score, Menopausal.

## Introduction

Over the years, many parameters have been evaluated to assess the risk factors like age, menopausal status, family history, size of tumor, hormonal assay and immunological study<sup>1</sup>

With the introduction of imaging modalities including transabdominal and vaginal ultrasonography,<sup>[2]</sup> doppler color scans and MRI, more characterization of the internal structure of the mass (i.e. wall complexity, mass contents) is possible. In addition to clinical examination the above modalities aid in diagnosis.

Transvaginal or transabdominal ultrasound examination is recommended as part of the initial workup

of a complex adenexal / ovarian mass. Ultrasound reports should be standardized to include size, unilateral / bilateral, location of the adenexal mass, its possible origin, thickness of septations, presence of excrescences, presence of internal solid components, vascular flow distribution pattern, and presence or absence of ascites. CA 125 antigen is the most extensively studied serum marker for distinguishing benign from malignant pelvic masses<sup>[3]</sup>.

Differentiation between benign and malignant adenexal masses is central to decision regarding surgical management. Transvaginal or transabdominal ultrasound examination is recommended as a part of the initial workup of a complex adenexal / ovarian mass. CA 125 antigen is the most extensively studied serum marker for distinguishing between benign and malignant pelvic masses<sup>3</sup>. Ultrasound findings, CA-125 levels with menopausal status is used in calculating the RMI-2 score to identify pelvic mass with high malignant potential.<sup>4</sup>

Present study was conducted with the aim to predict risk of malignancy (RMI-2) in adenexal masses

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preoperatively and compare it with histopathology.

## Material and Methods

The present prospective, observational, and clinical study was conducted in Department of Obstetrics and Gynaecology, Rajindra Hospital, Patiala. The study was conducted from January 2016 to December 2016 on a total of 50 patients with adenexal masses admitted in Department of Obstetrics and Gynaecology of Rajindra Hospital Patiala for exploratory laparotomy. Women of all age groups who were willing to participate in the study were included. Patients with adnexal masses with ectopic pregnancy were excluded from the study.

A detailed history regarding the nature, progression, and duration of the presenting symptoms. Specific signs and symptoms suggestive of an underlying malignancy such as pelvic / abdominal pain, urinary urgency / frequency, increased abdominal size / bloating, and difficulty in eating / feeling full were specifically sought, especially when these symptoms were persistent (present for <1 year and occurred >12 days per month). Any significant family history of neoplasia, such as breast, ovarian, endometrial, colorectal, and pancreatic carcinoma was noted. All routine and special investigations were done. Transvaginal and transabdominal ultrasonography wherever required was done for size, loculation, bilaterality, presence of solid components, ascites and intra-abdominal metastasis were noted. Serum CA-125 was done in Department of Biochemistry via ELISA. Expected normal CA-125 value was defined as <35 U/ml. RMI was calculated for each patient.

For our study RMI-2 Scoring system was used and calculated for each patient using formula:

$$\text{RMI-2} = (\text{U}) \times (\text{M}) \times (\text{CA-125})$$

Ultrasound scans were scored as one point for each of the following characteristics: multilocular cysts, evidence of solid areas, evidence of metastasis, presence

of ascites, bilateral lesions, using the scoring system. The total ultrasonography score of 0 or 1 gave U=1, and a score of 2 gave U=4. If < 1 feature then U=1 if > 1 feature then U=4. The score of premenopausal status M=1 and for postmenopausal status M=4.

Postmenopausal status was defined as no menstruation for more than one year or surgical menopause. The serum levels of CA-125 were taken in U/ml and levels of 35 or more were considered to be normal.

The cut-off levels for RMI-2 Score was taken as 200 for our study group. Patients having adenexal mass with RMI-2 <200 were labelled as benign and masses with RMI score >200 were labelled as malignant. Statistical analysis were done using SPSS trail system and chi-square “t”-test.

## Results

Out of a total of 50 cases with adenexal masses, 11 were malignant and 39 were benign on histopathology. Table no 1 shows that benign tumors were more common in the present study i.e. 39 (78.0%) in number. Benign serous cystadenoma twelve (24.0%) was the most common benign lesion followed by dermoid cyst eight (16.0%), inflammatory pathology five (10.0%), endometriotic cyst three (6.0%), hemorrhagic cyst, follicular cyst, and serous cyst present in two (4.0%) patients each. Mucinous cystadenoma, fibroma, corpus luteal cyst, benign serous cystadenofibroma and borderline mucinous tumor were present in one (2.0%) patient each. Malignant tumors were present in only eleven (22.0%) patients. Granulosa cell tumor was the most common malignant tumor which was present in four (8.0%) patients followed by dysgerminoma and serous cystadenocarcinoma that were seen in two (4.0%) patients each. Atypical proliferative mucinous tumor, carcinoma ovary and immature teratoma were found in one (2%) patient each Table 1).

**TABLE 1: DISTRIBUTION OF BENIGN AND MALIGNANT TUMORS AS PER HISTOPATHOLOGY**

Histopathological type	No. of patients	Percentage (%)
1. Benign tumors	39	78.0
Benign serous cystadenoma	12	24.0
Dermoid cyst	8	16.0
Inflammatory pathology	5	10.0
Endometriotic cyst	3	6.0
Haemorrhagic cyst	2	4.0
Follicular cyst	2	4.0
Serous cyst	2	4.0
Mucinous cystadenoma	1	2.0
Fibroma	1	2.0
Corpus luteal cyst	1	2.0
Benign serous cystadenofibroma	1	2.0
Borderline mucinous tumor	1	2.0
2. Malignant tumors	11	22.0
Granulosa cell tumor	4	8.0
Dysgerminoma	2	4.0
Serous cystadenocarcinoma tumor	2	4.0
Atypical proliferative mucinous tumor	1	2.0
Carcinoma ovary	1	2.0
Immature teratoma	1	2.0
Total	50	100

Four (8.0%) patients had pregnancy co-existent with benign adenexal masses out of which two (4%) were serous cystadenoma and one (2%) corpus luteal cyst and inflammatory pathology, each. Among 50 patients with adenexal masses, 39 (78%) were pre-menopausal and 11 (22.0%) patients were post-menopausal. Patients with

M-score 1 were 39 and with M-score 4 were 11. Out of the total benign tumors i.e. 39 (78.0%), M-score 1 was present in 34 (87.2%) patients whereas M-score 4 was seen in five (12.8%) patients. In malignant cases, M-score 1 was present in five (45.4%) patients while six (54.5%) patients had M-score 4. (Table 2)

**Table 2: DISTRIBUTION OF AGE, CA-125 Levels, U-score, M-score and RMI-2 in patients with adenexal masses**

PARAMETER	MALIGNANT (n=11)	MALIGNANT (100%)	BENIGN (n=39)	BENIGN (n=39)
Age (years)				
≤15	1	9.1	1	2.6
16-30	2	18.2	17	43.6
31-45	3	27.3	14	35.9
46-60	4	36.3	4	10.2
>60	1	9.1	3	7.7
Residential Area				
Rural	3	27.3	20	51.3
Urban	8	72.7	19	48.1
Serum CA-125 levels				
<35 U/ml	4	36.3	18	46.2
>35 U/ml	7	63.7	21	53.8
U-SCORE				
U-1	3	27.2	39	89.7
U-4	8	72.8	4	10.3
M-SCORE				
M-1	5	45.4	34	87.2
M-4	6	54.6	5	12.8
RMI				
<200	3	27.3	37	94.9
>200	8	72.7	2	5.1

Ultrasound features included in U-score suggestive of malignancy were absent in 34% patients and were present in 66% of the patients. All the patients with malignant disease had one or more feature suggestive of malignancy while 56.4% of the benign lesions had either one or more feature on ultrasound and 43.6% had none of the features suggestive of malignancy on ultrasound. The most common feature on ultrasound was presence of solid component in sixteen (32.0%) patients followed by bilateral adenexal masses thirteen (26.0%), multilocular masses eleven (22.0%), ascites six (12.0%) while intra-abdominal metastasis was not found in any of the patient. Out of the 50 patients, majority i.e. 38 (76.0%) of patients had U-SCORE 1 and 12 (24.0%) patients had U-SCORE 4. In the present study, 35 (89.7%) of the total benign tumors had U-score 1 and 4 (10.2%) had U-score 4. In malignant lesions, U-score 4 was present in eight (72.7%) patients and U-score 1 which was seen in three (27.2%) patients only (Table 3).

**Table 3-DISTRIBUTION OF ULTRASOUND FINDINGS ACCORDING TO U-SCORE CRITERIA**

ULTRASOUND FINDING	NO. OF PATIENTS	PERCENTAGE
Bilateral	7	14
Solid	7	14
Multilocular	7	14
Solid+Ascites	5	10
Bilateral+Solid	2	4

**Cont... Table 3-DISTRIBUTION OF ULTRASOUND FINDINGS ACCORDING TO U-SCORE CRITERIA**

Bilateral+Multilocular	2	4
Bilateral+Ascites	1	2
Solid+Multilocular	1	2
Bilateral+Solid_Multilocular	1	2
Intra Abdominal metastasis	0	0
Total findings	33	66
No positive ultrasound findings	17	34
Total	50	100

Normal range of CA-125 is 0-35 U/ml. In the present study, 28 (56.0%) patients had CA-125 levels >35 U/ml and 22 (44.0%) had CA-125 levels < 35 U / ml. The mean value of CA-125 levels in the present study was  $68.05 \pm 140.88$  U/ml. Among patients with malignant lesions, four (36.4%) had serum CA-125 levels  $\leq 35$  U/ml followed by three (27.3%) patients who had CA-125 levels between 36-100 U/ml. Patients having benign lesion on histopathology had 18 (46.2%) patients with serum CA-125 levels <35 U/ml followed by 17 (43.6%) patients having serum CA-125 levels between 36–100 U/ml. Only four (10.3%) patients had CA-125 levels between 101-175 U/ml. None of the patients with benign lesions had CA-125 levels >176 U/ml.(Table 4)

**Table 4 :DISTRIBUTION OF PATIENTS ACCORDING TO SERUM CA-125 LEVELS**

CA-125 (U/ml)	No.of patients	Percentage(%)
<35	22	44
35-100	20	40
101-175	6	12
>175	2	4
Total	50	100
Mean		68.05+/-140.88

Among patients with malignant disease on histopathology, maximum number i.e five (45.5%) of malignant tumors were found in patients with RMI -2 >300 followed by three (27.3%) patients who had RMI-2 between 201-300. Only two (18.2%) patients had RMI between 101-200 and one (9.1%) patients had RMI-2  $\leq 100$ . Maximum number of benign lesions i.e. 30 (76.9%) had RMI-2 <100 followed by seven (17.9%) patients with RMI between 101–200. Only one (2.6%) patients had RMI-2 between 201-300 and >300, each. p-value is highly significant 0.000 (< 0.05). Majority of

benign adenexal lesion i.e. 37 (94.9%) had RMI -2<200 whereas only 2 (5.1%) had RMI-2 >200. RMI-2 >200 was present in majority 8 (72.7%) of the malignant lesions and only 3 (27.3%) malignant lesions had RMI-2 <200.

The sensitivity, specificity, PPV and NPV was calculated for CA-125, M-score, U-score and RMI. As shown in table no 3, in the present study, **CA-125 levels** when taken as <35 U/ml as normal had sensitivity of 63.6 %, specificity of 46.2%, negative predictive value of 81.8% and positive predictive value of 25%

in predicting benign or malignant nature of adenexal masses. p-value of CA-125 in the present study at 35 U/ml is 0.230 which is non-significant. When cut-off value of CA-125 levels was taken as 142.5 U/ml specificity was increased to 94.5% and specificity was decreased to 27.3%. PPV at this cut-off level was 75% and NPV was 82.6%.p-value at 142.5 U/ml was 0.029 which was significant. Significance was increased at 142.5 U/ml then 35 U/ml. Ultrasound score had sensitivity of 72.7%, specificity of 89.7%, PPV of 66.7% and NPV of 92.1% in defining benign or malignant character of adenexal masses. p-value of U-score in the present study is 0.000

which is highly significant. M-score had sensitivity of 54.5%, specificity of 87.2%, PPV of 54.5%, and NPV of 87.2% in predicting benign or malignant nature of adenexal masses. p-value of **M-score** in the present study is 0.008 which is significant. RMI was calculated for all the patients, when 200 was taken as cut-off value for RMI then it had sensitivity of 72.7%, specificity of 94.9%, PPV of 80.0% and NPV of 92.5% in predicting benign or malignant nature of adenexal masses. p-value of RMI in the present study at 200 cut-off value is 0.003 which is significant. (Table 5)

**Table 5 : Comparison of sensitivity ,specificity , PPV, NPV and p-value of CA-125 levels, U-score, M-score and RMI -2**

PARAMETER	SENSITIVITY(%)	SPECIFICITY(%)	PPV(%)	NPV(%)	p-value
CA-125 levels	63.6	46.2	25.1	81.8	0.230 Non-significant (>0.05)
U-score	72.7	89.7	66.7	92.1	0.000 Highly Significant
M-score	54.5	87.2	54.4	87.2	0.008 significant (<0.05)
RMI	72.7	94.9	80	92.5	0.003 significant (<0.05)

### Discussion

About 10% of women undergo exploratory laprotomy for evaluation of ovarian masses during their lifetime. Prompt identification of ovarian malignancies and referral to a gynaeco-oncologist can enhance the patient survival rates but a single method which can accurately predict ovarian malignancy is still unavailable. In the pre-operative assessment of adenexal masses, the major diagnostic tools are still clinical impression and ultrasound examination. However, due to limitation of clinical impression and sonographic findings to predict ovarian malignancy, it is not surprising that Gynaecologists may detect an unexpected ovarian malignancy intra-operatively.<sup>[7]</sup>

Serum CA-125 was earlier used as an independent marker for preoperative evaluation. The main limitation of CA-125 is that it may be high in benign disease such as ovarian cysts, endometriosis and pelvic infection. The combination of serum CA-125 with menopausal status, other tumor markers and ultrasound parameters increases the discriminating power of the method for the two types of ovarian pathology.<sup>1</sup>

In the present study sensitivity of CA-125 was 63.6%, sensitivity was more than specificity, so this test is screening rather than confirmatory test. The PPV was 25%, PPV was less than NPV 81.8%, so CA-125 levels are not diagnostic to correctly identify the disease.

Serum Ca-125 levels as per present study is a screening tool similar to the previous studies conducted by Abdulrahman GO et al (2014), Aziz AB et al (2015) and Javdekar R et al (2015). The specificity of CA-125 levels was 46.2% in the present study which was different from the previous studies conducted by Abdulrahman GO et al (2014), Aziz AB et al (2015) and Javdekar R et al (2015) with specificity of 67%, 67.6% and 85.3% respectively. This smaller study population size and large number of benign lesions on histopathology in our study.

In the present study, sensitivity of RMI-2 was 72.7% which was similar to the sensitivity of RMI in the previous studies conducted by Tingusled et al (1996), Bouzari Z et al (2011), Insin P et al (2013), Yavuzcam A et al (2013), Abdulrahman GO et al (2014), Yamamoto Y et al [60] (2014) and Javdekar R et al (2015) of 71%, 76%, 71%, 75%, 74%, 81.1% and 70.5% respectively. Sensitivity of RMI was different from Clarke SE et al (2009) study i.e. 91.0%, this may be due to different cut-off values of RMI i.e. 200 in our study and 355 in Clarke SE et al [53] (2009) and from Jacobs et al (1990) as Jacobs used RMI-1 and our study used RMI-2.

The specificity of RMI was 94.9% in the present study which was similar to the previous studies conducted by Jacobs et al (1990) (96.9%), Tingusled et al (1996) (96.0%), Clarke SE et al (2009) (96.0%), Bouzari Z et al (81.0%), Yavuzcam A et al 2013 (85.1%), Yamamoto Y et al (2014) (89.6%) and

Javdekar R et al (2015) (87.8%). The results in the present study were different from Insin P et al (2013) (71%) and Abdulrahman GO et al (2014) (79%). This may be due to large study size in both these studies (547 patients in Insin P et al (2013) and 247 in Abdulrahman GO et al (2014) study) compared to our study and different geographical distribution (Thailand in Insin P et al [23] (2013) and South Wales in Abdulrahman GO et al (2014) study).

### Conclusion

Key message- RMI-2 is a simple, easy, cost effective method to differentiate between benign and malignant adnexal mass with high sensitivity with consequent decision for appropriate surgical approach. However, smaller study size, larger number of premenopausal

women, most of benign ovarian tumors were some of the limitations in present study.

**Ethical Clearance-** Taken from institute ethics committee, GMC Patiala

**Source of Funding-** Self

**Conflict of Interest-** Nil

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