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Original Research Article

# Diagnostic Value of the Risk of Malignancy Index (RMI) for Discrimination between Benign and Malignant Ovarian Masses

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## Abstract

Patients with pelvic mass, especially ovarian masses are commonly encountered in gynaecology clinic and this can be either benign or malignant. There is no single method which canaccurately predict ovarian malignancy. Prompt identification of ovarian malignancies and referralto a gynec-oncologist can enhance the patient survival rates. Aim of this descriptive analytical study is to evaluate the Diagnostic accuracy of the Risk of Malignancy Indices (RMI) in discriminating benign and malignant ovarian masses. Patients operated for ovarian masses between January 2017 and December 2017 were included in the study. Data regarding menopausal status, ultrasound findings, serum CA125 level and post op pathology findings were collected and analysed. A score was assigned for ultrasound findings as follows:the presence of multilocular cystic lesions, solid areas, bilateral lesions, ascites and intra-abdominal metastases, scored one point each. A total ultrasound score (U-score) was calculated for each patient. Postmenopausal status was defined as more than one year of amenorrhea, or an age of 50 years or more if the woman had undergone hysterectomy. All other women were considered to be premenopausal. RMI1, RMI 2, RMI 3, RMI 4 were calculated for all patients together with the sensitivity, specificity, positive and negative predictive values of the four methods. RMI 1 = U × M × serum CA125, where a total ultrasound score of 0 gave U = 0, a score of 1 gave U = 1 and a score of > 2 gave U = 3; premenopausal status gave M = 1, postmenopausal M = 3. The serum level of CA125 was multiplied directly into the formula. RMI 2 = U × M × serum CA125, where a total ultrasound score of 0 or 1 gave U = 1 and a score of > 2 gave U = 4; premenopausal status gave M = 1, postmenopausal M = 4; the serum CA125 concentration was substituted directly into the formula. RMI 3= *U* × *M* × CA-125, where a total ultrasound score of 0 or 1 made *U*=1, and a score of ≥2 made *U*=3; premenopausal status made *M*=1 and postmenopausal *M*=3. The serum level of CA-125 was applied directly to the calculation. RMI= *U* × *M* × *S* (size in centimetres) × CA-125, where a total ultrasound score of 0 or 1 made *U*=1, and a score of ≥2 made *U*=4. Premenopausal status made *M*=1 and postmenopausal status made *M*=4. A tumour size (single greatest diameter) of <7 cm made *S*=1, and ≥7 cm made *S*=2. The serum level of CA-125 was applied directly to the calculation. The four RMI indices were separately used for discriminating benign and malignant masses. Data was analysed using SPSS version 17 (SPSS Inc, Chicago, Illinois, USA). Findings were represented in ROC diagram and the cut-off points were determined. Sensitivity, Specificity, Diagnostic accuracy, Positive Predictive value (PPV), Negative predictive value (NPV), area under the curve, and p value were calculated taking the histopathology diagnosis as the gold standard. Results obtained concluded that the multi-parametric RMI score is a reliable method to predict malignancy in pre-operative evaluation of ovarian neoplasm and there is no significant difference in diagnostic accuracy between the 4 indices.

**Keywords:** pelvic mass, ovarian mass, ovarian malignancy, RMI, PPV, NPV.



## INTRODUCTION

Patients with pelvic mass, especially ovarian masses are commonly encountered in gynaecology clinic and this can be either benign or malignant. On physical examination size of the mass, its mobility, consistency, shape and associated pain are helpful features for diagnosis of the nature of the mass [1]. Discrimination between benign and malignant masses is pivotal to decisions regarding clinical management; a standardized method for preoperative identification of probable malignant masses would allow optimization of first-line treatment for women with ovarian cancer. Patients with malignant tumours should be referred to a gynec-oncologist, as the quality of cytoreductive surgery and surgical staging/lymph node dissection are important prognostic factors in ovarian cancer [2, 3].

Timely referral to a gynaecological oncologist has been proven to increase survival in patients with ovarian cancer [4].

**Aim**

To determine the diagnostic value of Risk of Malignancy indices in discriminating benign and malignant ovarian masses.

## MATERIALS AND METHODS

A retrospective, descriptive and analytic study was conducted in Department of Pathology, Father Muller Medical College and Hospital .Patients operated for ovarian masses between January 2017 and December 2017 were included in the study. Data regarding menopausal status, ultrasound findings, serum CA125 level and post op pathology findings were analysed. Data was collected from Histopathology report register, Clinical case records, and Hospital information system. Patients operated for ovarian mass, whose menopausal status, ultrasonogramfindings, serum CA125 levels and post op pathology findings were not available were excluded from the study.

A score was assigned for ultrasound findings as follows: the presence of multilocular cystic lesions, solid areas, bilateral lesions, ascites and intra-abdominal metastases, one point each. A total ultrasound score (U-score) was calculated for each patient. Postmenopausal status was defined as more than one year of amenorrhea, or an age of 50 years or more if the woman had undergone hysterectomy. All other women were considered to be premenopausal. RMI1, RMI 2, RMI 3, RMI 4 were calculated for all patients together with the sensitivity, specificity, positive and negative predictive values of the four methods.

- RMI 1 = U × M × serum CA125, where a total ultrasound score of 0 gave U = 0, a score of 1 gave U = 1 and a score of > 2 gave U = 3; premenopausal status gave M = 1, postmenopausal M = 3. The serum level of CA125 was multiplied directly into the formula [6].
- RMI 2 = U × M × serum CA125, where a total ultrasound score of 0 or 1 gave U = 1 and a score of > 2 gave U = 4; premenopausal status gave M = 1, postmenopausal M = 4; the serum CA125 concentration was substituted directly into the formula [7].
- RMI 3 = $U \times M \times$ CA-125, where a total ultrasound score of 0 or 1 made $U$=1, and a score of ≥2 made $U$=3; premenopausal status made $M$=1 and postmenopausal $M$=3. The serum level of CA-125 was applied directly to the calculation [8].
- RMI 4 = $U \times M \times S$ (size in centimetres) × CA-125, where a total ultrasound score of 0 or 1 made $U$=1, and a score of ≥2 made $U$=4. Premenopausal status made $M$=1 and postmenopausal status made $M$=4. A tumour size (single greatest diameter) of <7 cm made $S$=1, and ≥7 cm made $S$=2. The serum level of CA-125 was applied directly to the calculation [9].

The four RMI indices were separately used for discriminating benign and malignantmasses. Data wasanalysed using SPSS version 17 (SPSS Inc.,Chicago, Illinois, USA). Findings were represented in ROC diagram and the cut-off points were determined. Sensitivity, Specificity, Diagnostic accuracy, Positive Predictive value (PPV), Negative predictive value (NPV, area under the curve, and p value were calculated using the histopathology report as the gold standard of diagnosis-value less than 0.05 was considered significant. SPSS version 17 software was used for data analysis

## RESULTS

Out of the 80 patients included in the study, 63 were diagnosed with benigntumours and 17 were diagnosed with malignant ovarian neoplasm on histopathologicalexamination (Table-1).

The histopathological diagnosis of the 80 cases shown in Table-1.

**Table-1: The histopathological diagnosis of the 80 cases**

| Histological Diagnosis | Number of cases |
|---|---|
| **Benign cases** | **63** |
| Haemorrhagic cyst | 22 |
| Simple Serous cyst | 10 |
| Simple Mucinous cyst | 8 |
| Teratoma | 8 |
| Para tubal cyst | 11 |
| Corpus Luteal Cyst | 3 |
| Thecoma | 1 |
| **Malignant cases** | **17** |
| Serous cystadenocarcinoma | 9 |
| Mucinous cystadenocarcinoma | 5 |
| Dysgerminoma | 1 |
| Adult Granulosa cell tumour | 2 |

The distribution of benign and malignant cases individual parameters like age group, menopausal status, ultrasound score, CA-125 level and tumour size is described in Table-2.

**Table-2: The distribution of benign and malignant cases individual parameters like age group, menopausal status, ultrasound score, CA-125 level and tumour size**

| Variables | Benign | Malignant | Test/value |
|---|---|---|---|
| **AGE(years)** | | | $x^2$/0.056 |
| <=20 | 6 | 2 | |
| 21-40 | 31 | 3 | |
| 41-50 | 14 | 3 | |
| >50 | 12 | 9 | |
| | | | |
| **Menopausal status** | | | $x^2$/0.057 |
| Premenopausal | 51 | 8 | |
| Postmenopausal | 12 | 9 | |
| | | | |
| **Ultrasound score** | | | $x^2$/0.06 |
| 0 | 37 | 5 | |
| 1 | 25 | 11 | |
| 2-5 | 1 | 1 | |
| | | | |
| **CA 125 level** | | | U test/<0.002 |
| Min | 4.63 | 12.51 | |
| Max | 96.6 | 1531.4 | |
| Mean | 22.38 | 195.57 | |
| **Size** | | | $x^2$/0.055 |
| <7cm | 22 | 2 | |
| >7cm | 41 | 15 | |

A significant linear trend for malignancy was found by increasing size of tumour and the occurrence of malignancy in post-menopausal patients. Also the risk of malignancy was increasing by age, but it did not reach the statistical significance (p=0.056).

The mean serum level of CA-125 was significantly higher in patients with malignant ovarian neoplasm as compared to the patients with benign neoplasm (195.57 U/mL vs. 22.38 U/ mL).

The sensitivity, specificity, and positive and negative predictive values and diagnostic accuracy of serum CA-125 level of 35 U/mL, the ultrasound score of 2, postmenopausal status and the size of more than or equal to 7 centimetre are shown in Table-3.

**Table-3: The sensitivity, specificity, and positive and negative predictive values and diagnostic accuracy of serum CA-125 level of 35 U/mL, the ultrasound score of 2, postmenopausal status and the size of more than or equal to 7 centimetre**

| Criteria | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | DA (%) |
|---|---|---|---|---|---|
| CA 125 | | | | | |
| 35 U/ML | 78.5% | 79% | 91.5 | 48.7 | 78.7 |
| Ultrasound score | | | | | |
| 2 | 48.5% | 67.8% | 71.1 | 45.6 | 63.6 |
| Menopausal Status | | | | | |
| Postmenopausal | 62% | 83.5% | 88.7 | 40.8 | 77.6 |
| Tumour Size | | | | | |
| >=7 | 63.5% | 87.2% | 90.5 | 51.5 | 80.7 |

Among these parameters CA-125 level was found to have better sensitivity than other parameters. Although other parameters had higher specificity than CA-125, this was at the cost of considerable loss of sensitivity which is of at most importance in diagnosing malignancy. The performance of RMI 1, RMI 2, RMI 3, and RMI 4 at different cut-off values is shown in Table-4.

**Table-4: The performance of RMI 1, RMI 2, RMI 3, and RMI 4 at different cut-off values**

| cut off | sensitivity | | | | specificity | | | | PPV (%) | | | | NPV (%) | | | | da | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| RMI 1,2,3 | RMI 4 | RMI 1 | RMI 2 | RMI 3 | RMI 4 | RMI 1 | RMI 2 | RMI 3 | RMI 4 | RMI 1 | RMI 2 | RMI 3 | RMI 4 | RMI 1 | RMI 2 | RMI 3 | RMI 4 | RMI 1 | RMI 2 | RMI 3 | RMI 4 |
| 50 | 350 | 87 | 91 | 91 | 86 | 61 | 68 | 71 | 83 | 35 | 43 | 45 | 52 | 93 | 92 | 95 | 94 | 65 | 72 | 76 | 80 |
| 100 | 400 | 76 | 84 | 79 | 83 | 82 | 79 | 81 | 82 | 50 | 52 | 51 | 57 | 91 | 92 | 93 | 93 | 81 | 80 | 83 | 84 |
| 150 | 450 | 75 | 76 | 75 | 83 | 84 | 82 | 84 | 85 | 52 | 53 | 54 | 59 | 92 | 93 | 92 | 94 | 82 | 83 | 83 | 86 |
| 200 | 500 | 76 | 77 | 75 | 86 | 88 | 85 | 86 | 87 | 62 | 54 | 56 | 63 | 91 | 92 | 94 | 96 | 87 | 84 | 84 | 88 |
| 250 | 550 | 66 | 74 | 71 | 70 | 94 | 86 | 93 | 90 | 77 | 58 | 74 | 65 | 90 | 94 | 93 | 93 | 88 | 83 | 86 | 85 |
| 300 | 600 | 48 | 71 | 53 | 59 | 95 | 92 | 96 | 92 | 74 | 65 | 83 | 65 | 86 | 91 | 87 | 91 | 85 | 85 | 87 | 86 |
| 350 | 650 | 46 | 57 | 52 | 61 | 97 | 97 | 98 | 93 | 84 | 79 | 92 | 71 | 85 | 87 | 85 | 91 | 86 | 87 | 88 | 86 |
| 400 | 700 | 32 | 48 | 30 | 50 | 97 | 98 | 99 | 98 | 76 | 75 | 83 | 85 | 84 | 87 | 86 | 87 | 83 | 86 | 85 | 87 |

RMI 1, RMI 2 and RMI 3 were seen to perform best at a cut-offlevel of 200 and RMI 4 at a cut off level of 500 and there was no statistically significant difference in performance of the four different methods (McNemar test, p=0.062).

Receiver operating characteristic (ROC) analysis of the RMI 1, RMI 2, RMI 3, and RMI 4 showed that the values of area under the curve were significantly high with a value of 0.824, 0.815, 0.824, 0.855, respectively ($p<0.001$). Area under the curve values of menopausal status, serum CA-125, ultrasound features, and tumour size are 0.705, 0.760, 0.703, and 0.750, respectively. We found that the risk of malignancy indices were more reliable in detecting malignancy compared to individual parameters.

The diagnostic performance of ultrasound score, CA-125, menopausal status, tumour size, RMI 1, RMI 2, RMI 3, and RMI 4 is shown in the receiver-operating characteristic curves (Figure-1).

## DISCUSSION

About 10% of women undergo exploratory surgery for evaluation of ovarian masses during their lifetime [18].

Early identification of ovarian malignancies and referral to a gynaec-oncologist can improve the patient'ssurvival rates [19]. Till date no single method is known to accurately predict ovarian malignancy. Pre-operative evaluation of adnexal masscommonly includes clinical examination and ultrasound examination. Due to limitations in pre op assessment, it is not surprising that gynaecologists may encounter an unexpected ovarian malignancy intra-operatively. Often the surgeon is confronted with need to perform an unplanned cytoreductive surgery. A scoring system that can predict ovarian malignancy can improve the chance of better preoperative preparation and when requiredreferring the patients to a specialized centre can be done. RMI index is one such multi-parametric scoring system.

RMI was initially developed by Jacobs *et al*., [6]. Subsequently the same research group had re-evaluated their diagnostic method in a new group of patients admitted for pelvic masses and confirmed that RMI performed better than individual criteria [20]. In this study we have evaluated the diagnostic accuracy of different RMI indices.

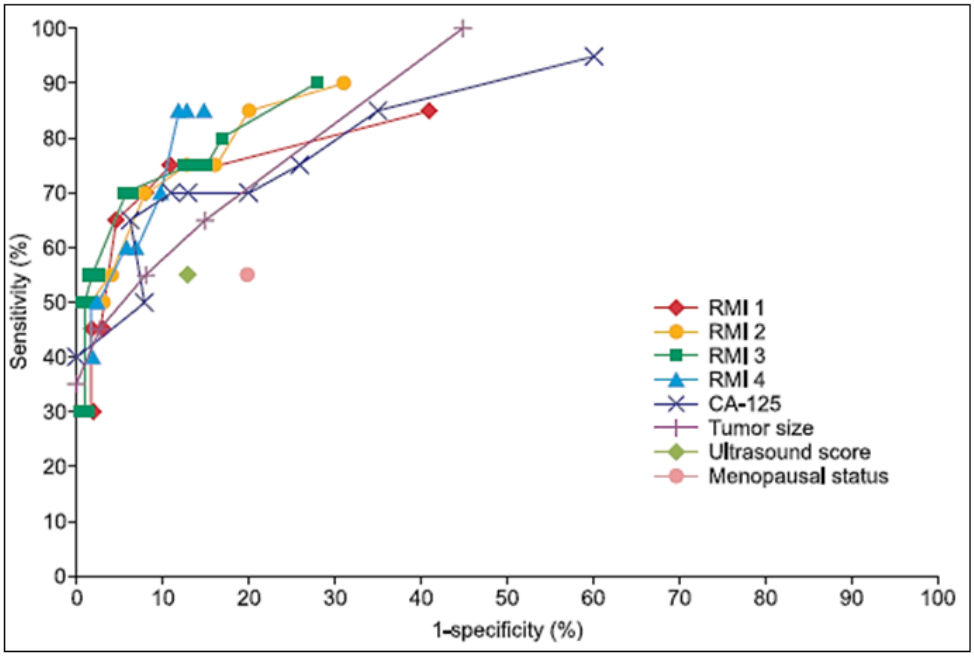


**Fig-1: ROC curves depicting diagnostic performance of ultrasound score, CA-125, menopausal status, tumour size, RMI 1, RMI 2, RMI 3, and RMI 4**

In the past decade several retrospective studies have been published to emphasize the importance of risk of malignancy indices in discriminating benign and malignant ovarian masses [5, 10, 12]. A study similar to ours was conducted by Yamamoto et al in.2009 .All four RMI were determined, of which the RMI 4 had the highest(90.4%)diagnostic accuracy with a cut-off point at 450. They also reported the following characteristics: sensitivity=86.8%, specificity=91%, PPV=63.5%, and NPV=97.5% [9]. In 2011, ErhanAkturk et al compared all the four RMI indices and concluded that there was no statistically significant difference in the performance of these four different malignancy risk indices. Receiver operating characteristic (ROC) analysis of the RMI 1, RMI 2, RMI 3, and RMI 4 showed that the values of area under the curve were significantly high with a value of 0.825, 0.806, 0.825, 0.856, respectively ($p<0.001$) [10]. In 2015 MojganKarimi-Zarchi conducted a similar study and found that RMI 2 showed the best performance in predicting malignancy, compared with the other three indices [11].

Tingulstad *et al*., [7, 8] developed another RMI in 1996 (RMI 2) and modified it in 1999 (RMI 3). Later in 2009 Yamamoto *et al*., [9] developed RMI 4 which included the size criteria also. He found RMI 4 to be superior to the other three RMIs. They observed that at a cut-off level of 450, the sensitivity, specificity, positive predictive value, negative predictive value and accuracy were respectively 86.8%, 91.0%, 63.5%, 97.5%, and 90.4% [13]. In our study we found the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of RMI 4 at a cut off of 450 to be 83%, 85%, 59% and 94% respectively, which is comparable with the results of Yamamoto *et al.*, [13]. But we also found that in contrast to Yamamoto *et al.*, the diagnostic performances of other three indices were also reliable.

Few studies done in the past showsthat RMI 2 is better than the other indicesin discriminating benign and malignant disease [5, 7]. But the present study does not show a significant difference in diagnostic accuracy of RMI 2 compared to other indices. Some investigators have reported findings similar to our study [17, 21, 22]. In 2001 Manjunath *et al*., [12] compared RMI 1, RMI 2, and RMI 3 with each other and confirmed that there was no statistical difference in their diagnostic accuracy. Geomini *et al*., [16] in 2009 showed that RMI1 atcut-off of 200 had a sensitivity of 78% and a specificity 87% for malignant ovarian neoplasms which is similar to our results for RMI1 RMI2 and RMI3.

Any scoring system which is used to exclude malignancies, the false negative rate should ideally be zero or close to zero [14]. The present study had 3 false negative cases. One case was dysgerminoma, and 2cases were mucinous cyst adenocarcinoma. Gadducci *et al.*, [15] reported mucinous tumours expressed CA-125 less than non-mucinous types. Also ultrasound score is very subjective and itrelies on the expertise of the examiner. Thus the low ultrasound score and the less specificity of CA125 for mucinous ovarian tumours are likely to explain the false negative results in our study.

## CONCLUSION

This study shows that risk of malignancy index is very accurate in discriminating benign and malignant ovarian neoplasms and should therefore be the test of

choice in the preoperative evaluation of the adnexal mass. Any of the four malignancy risk indices (RMI 1, RMI 2, RMI 3, and RMI 4) described can be used for selection of cases for optimal therapy. Since the specificity of risk of malignancy index is high, there is a potential role for risk of malignancy index in the selection of cases for conservative management or minimal invasive surgery for benign tumours. Also it helps Gynaecologiststo identify patients with ovarian mass with high probability of malignancy and take decisions regarding type and technique of cyto-reductive surgery. Also unnecessary referrals to gynaecologic oncologists for benign ovarian lesions can be prevented.

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