Research Article

Comparison of four malignancy risk indices in the preoperative evaluation of patients with adnexal masses

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Abstract

Background: Adnexal masses are the fourth most common gynaecological causes for hospitalization with differential diagnosis varying from benign masses to malignant tumors. As amount of tumor left after the primary cytoreductive surgery is one of the most important prognostic factors in ovarian cancers, preoperative determination of whether a mass is benign or malignant is very important for timely referral to a gynaecologic oncologist. **Objectives:** The aim of this study was to evaluate the ability of four malignancy risk indices (RMI 1, RMI 2, RMI 3 and RMI 4), incorporating menopausal status, serum CA125 levels, and ultrasound findings, to discriminate a benign from a malignant pelvic mass. **Materials and Methods:** This is a descriptive correlative study of 100 women admitted to Department of Obstetrics and Gynaecology, Father Muller Medical College, Mangalore, Karnataka, India from September 2012 to August 2013 for surgical exploration of pelvic masses. The sensitivity, specificity, and positive predictive value of serum CA 125 levels, ultrasound findings, and menopausal status were taken separately and combined into the RMI 1, RMI 2, RMI 3 and RMI 4 to diagnose ovarian cancer. The histopathological diagnosis was considered as the gold standard for defining the outcomes. Data was analysed using the Statistical Package for the Social Sciences, and Pearson's Chi square test was used to compare the individual RMI scores between the benign and malignant cases. **Results:** In this study we found that there is no statistically significant difference in the performance of the four different RMIs in discriminating malignancy. Individual variables that were analysed showed significant differences in ultrasound score of ≥2 and mean serum CA-125 level ($p < 0.001$and $p = 0.001$, respectively) between the benign and malignant cases. **Conclusions:** We concluded that the risk of malignancy index is able to identify malignant and benign pelvic masses efficiently to optimize therapy and any of the four malignancy risk indices described can be used for selection of cases for optimal therapy. These methods are simple techniques that can be used even in less-specialized gynaecology clinics to facilitate the selection of cases for referral to an oncological unit.

Keywords: Risk of malignancy index, Adnexal mass, Serum CA-125, Menopausal status, Preoperative evaluation, Ovarian cancer.

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INTRODUCTION

Adnexal masses, however benign in 90% of cases, are the fourth most common gynaecological causes for hospitalization. The differential diagnosis of an adnexal mass varies from functional cysts to benign and malignant tumors[1].Up to 24% of ovarian tumors in premenopausal women is malignant and up to 60% are malignant in postmenopausal women[2]. Surgery can be optimally planned if it is known in advance whether an ovarian neoplasm is benign or malignant as the amount of tumor left after the primary cytoreductive surgery is one of the most important prognostic factors in ovarian

cancers[3]. A method for better preoperative discrimination of pelvic mass would result in more women receiving first-line therapy from appropriately trained and experienced personnel. For such referrals to be efficient, specific and sensitive improved methods for diagnosing ovarian cancer are needed. Initially clinical, demographic, biochemical, and ultrasonographic features were used to distinguish benign from malignant adnexal masses, but none of these indicators alone was very sensitive or specific for detecting malignancy. It has been suggested that decisions on how to manage women with an adnexal mass be taken on the basis of the Risk of Malignancy Index (RMI).The risk of malignancy index (RMI) is a simple scoring system based on menopausal status, ultrasound, and serum concentrations of CA-125. This has given much better results than any single parameter[4,8]. It can be applied in less specialized centres. The risk of malignancy index is the product of the ultrasound scores (U), the menopausal score (M), and the absolute value of serum CA-125 levels: RMI = U x M x CA-125.It was originally developed by Jacobs *et al* in1990 which is termed as RMI 1^4. Tingulstad *et al* developed their version of the RMI in 1996 and it is known as RMI $2^{(5)}$. In 1999, Tingulstad *et al* modified the RMI, which is termed RMI 3^6. Yamamoto *et al* created their own model of a malignancy risk index. They added the parameter of the tumor size (S) to the RMI and have termed it the RMI 4^9. The purpose of this study was to evaluate the ability of the four malignancy risk indices to discriminate a benign from a malignant pelvic mass and to evaluate the performances of the four malignancy risk indices.

OBJECTIVE OF THE STUDY

To evaluate the ability of four malignancy risk indices (RMI 1, RMI 2, RMI 3 and RMI 4) to discriminate a benign from a malignant pelvic mass.

MATERIALS AND METHODS

The clinical data of 100 women with pelvic masses appointed for laparotomy or laparoscopy between September 1, 2012, and August 31st, 2013, to our hospital were obtained. Inclusion criteria**:** Women in the age group of 15 to 80 years presenting with at least one persistent adnexal mass that was selected for surgical intervention were eligible for the study.

Exclusion Criteria: Pregnant women with adnexal masses

Data Collection: Preoperative menopausal status, ultrasound findings and serum CA-125 levels were noted. Postmenopausal status was defined as more than 1 year of amenorrhea or age older than 50 years in women who had undergone hysterectomy. All other women were considered premenopausal. The ultrasound was performed transabdominally by a 7.5-MHz transducer (Philips HD11 machine). A score was assigned for 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. A total ultrasound score (U) was thus calculated for each patient.Tumour size was measured by ultrasonography for each patient. Peripheral venous blood samples were drawn preoperatively from each patient and serum CA 125 levels were measured by electrochemiluminescence immunoassay using a commercial kit by Roche diagnostics. Based on the data obtained, the RMI 1, RMI 2, RMI 3 and RMI 4 were calculated for all patients together with the sensitivity, specificity, positive and negative predictive value.

1. RMI 1^4 = U x M x CA125; a total ultrasound score of 0 yielded U = 0, a score of 1 yielded U = 1, and a score of ≥2 yielded U = 3. Premenopausal status yielded M = 1 and postmenopausal status yielded M = 3. The serum level of CA125 was applied directly to the calculation.
2. RMI 2^5 = U x M x CA125; a total ultrasound score of 0 or 1 yielded U = 1, and a score of≥2 yielded U = 4. Premenopausal status yielded M = 1 and postmenopausal status yielded M = 4. The serum level of CA125 was applied directly to the calculation.
3. RMI 3^6= U x M x CA125; a total ultrasound score of 0 or 1 yielded U = 1, and a score of≥2 yielded U = 3. Premenopausal status yielded M = 1 and postmenopausal status yielded M = 3. The serum CA125 level was applied directly to the calculation.
4. RMI 4^9= U x M x S x CA125, where a total ultrasound score of 0 or 1 yielded U = 1, and a score of ≥2 yielded U = 4. Premenopausal status yielded M = 1 and postmenopausal status yielded M = 4. A tumor size (single greatest diameter) of <7 cm yielded S = 1, and ≥7 cm yielded S = 2. The serum level of CA125 was applied directly to the calculation.

The histopathological diagnosis was considered the gold standard for defining the outcomes. When a gynaecological cancer was found, it was staged according to the International Federation of Gynecology and Obstetrics classification. The data were analysed using the Statistical Package for the Social Sciences version 13, and Pearson's Chi square test was used to compare the individual RMI between the benign and malignant cases. A p value < 0.05 was considered to be statistically significant.

RESULTS

Of the 100 adnexal masses included in the study, 94 (94%) were benign, 6 (6%) were malignant. The histopathological classification is detailed in Table 1 and FIGO stages of the malignant cases are shown in Table 2.

Table 1: Distribution of diagnosis in 100 patients presenting with a pelvic mass

Diagnosis	Premenopausal	Postmenopausal	Total
Total Malignant Cases	5	1	**6**
Serous cystadenocarcinoma	4	1	5
Mucinous adenocarcinoma	1		1
Total Benign Cases	76	18	**94**
Simple cyst	10	6	
Endometriotic cyst	11		
Functional cysts	11		
Paraovarian cyst	4		
Benign mullerian cyst	1		
Dermoid cyst	9	1	
Mucinous cystadenoma	8	6	
Serous cystadenoma	16	4	
Benign Brenner tumor		1	
Serous cystadenofibroma	2		
Fibrothecoma	1		
Hydrosalpinx/pyosalpinx	2		
Leiomyoma	1		

Table 2: Ovarian cancer staging

Ovarian Cancer	n = 6 (%)
Stage I	4 (66.7)
Stage II	
Stage III	2 (33.3)
Stage IV	

The distribution of benign and malignant cases by age, menopausal status, tumor size and ultrasound score is described in Table 3. The mean age of the patients with malignant disease was 44.83 years, and in those with benign pathology, it was 37.68 years. In univariate analysis, statistically significant differences were seen in mean CA-125 levels and ultrasound score of ≥2 ($p = 0.001$ and $p < 0.001$, respectively) between the benign and malignant cases. Although the risk of malignancy was increasing with age and tumor size, it did not reach the statistical significance ($p<0.05$). There was no significant difference in the distribution of benign and malignant cases with respect to the menopausal status.

Table 3: The distribution of benign and malignant cases by age, menopausal status, serum CA-125, tumor size and ultrasound score

Variables	Benign	Malignant	Test	P Value
Age (years)				
< 20	5 (5.3%)	0 (0%)	χ^2	0.172
21 – 30	29 (30.9%)	0 (0%)		
31 – 40	23 (24.5%)	2 (33.3%)		
41 – 50	24 (25.5%)	3 (50.0%)		
>50	13 (13.8%)	1 (16.7%)		
Menopausal Status				
Premenopausal	76 (80.9%)	5 (83.3%)	χ^2	0.881
Postmenopausal	18 (19.1%)	1 (16.7%)		
Ultrasound Score				
0-1	85 (90.4%)	1 (16.7%)	χ^2	<0.001
≥2	9 (9.6%)	5 (83.3%)		
Tumor Size (cm)				
<7	38 (40.4%)	1 (16.7%)	χ^2	0.247
≥7	56 (59.6%)	5 (83.3%)		
CA 125 (U/ml)				
Mean	32.0497	230.5883	χ^2	0.001
Median	14.3700	160.9000		
Minimum	1.24	26.06		
Maximum	445.00	737.30		
Standard deviation	56.49935	260.09483		

The mean serum level of CA-125 was significantly higher among women with malignancy when compared to women with benign tumors (230.5883 U/mL vs. 32.0497U/ mL). The sensitivity, specificity, positive and negative predictive values of serum CA-125 level of 35 U/mL, the ultrasound score of ≥ 2, postmenopausal status and tumor size of ≥7 cmin predicting malignancy are reported in Table 4. When individual parameters were compared in Table 4, ultrasound score was associated with the highest specificity of 90.4%.

Table 4: The sensitivity, specificity, and positive (PPV) and negative (NPV) predictive values and diagnostic accuracy (DA) of serum CA-125, ultrasound score, postmenopausal status and tumor size

Criteria	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CA 125 ≥35 U/ml	83.3	78.7	20	98.7
ULTRASOUND SCORE ≥2	83.3	90.4	35.7	98.9
MENOPAUSAL STATUS Postmenopausal	16.7	80.9	5.3	93.8
TUMOR SIZE ≥7cm	83.3	40.4	8.2	97.4

The performance of RMI 1, RMI 2, RMI 3 at a cut off of 200 and RMI 4 at a cut off of 450 is shown in table 5. A direct comparison showed no statistical difference between the four indices to discriminate between benign

and malignant cases. When compared with the two most useful individual parameters, CA 125 and ultrasound score, RMI scored better regarding the specificity but with a lower sensitivity.

Table 5: Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) for Predicting Malignancy of the Four Risks of Malignancy Indices (RMI 1, RMI 2, RMI 3 and RMI 4)

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
RMI 1	50%	97.9%	60%	96.8%
RMI 2	66.7%	92.6%	36.4%	97.8%
RMI 3	50%	96.8%	50%	96.8%
RMI 4	66.7%	97.9%	66.7%	97.9%

Receiver operating characteristic curve (ROC) analysis of 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 0.973, 0.959, 0.961, 0.965, respectively ($p<0.001$) (Figure 1). The details of false positive and false negative cases based on the cut-off level criteria of RMI 1, 2, 3 and RMI 4 according to their histology are shown in Table 6.

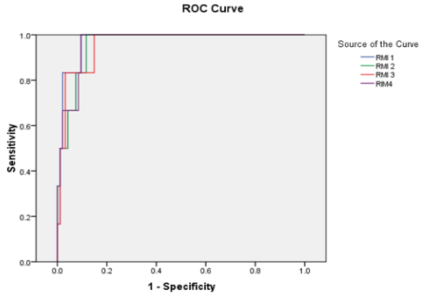

Figure 1: Receiver operator characteristic curve showing the performance of RMI 1, RMI 2, RMI 3 and RMI 4

Table 6: False-positive and false-negative cases of four malignancy risk indices RMI 1, RMI 2, RMI 3, and RMI 4

	RMI 1	RMI 2	RMI 3	RMI 4
False positive cases				
Simple cyst	1	2	1	0
Endometriosis	0	1	1	0
Mucinous cystadenoma	1	3	1	2
Serous cystadenoma		1		1
False negative cases				
Mucinous adenocarcinoma (stage I)	1	1	1	1
Serous cystadenocarcinoma (Stage I)	1	1	1	1

DISCUSSION

This study has revealed the usefulness of RMI to correctly discriminate benign from malignant pelvic masses. The RMI was originally developed by Jacobs *et al*[4] and subsequently the same group reproduced the results in a new group of patients, establishing the superiority of RMI over the individual parameters[7]. In our study serum CA 125 at a cut off level of 35 U/ml and ultrasound score of ≥ 2 were highly significant to discriminate between benign and malignant masses. The major limitation of CA125 is that it may be high in benign diseases, such as endometriosis, ovarian cysts, and pelvic inflammatory disease. We found a significantly higher level of serum CA125 among women with endometriosis when compared to women with other benign tumors (70.26 U/ml versus 26.98 U/ml), similar to study by Yamamoto *et al*[9]. In our patient group we found that all the four malignancy risk indices (RMI 1, RMI 2, RMI 3, and RMI 4) were highly significant to discriminate between benign and malignant masses. There was no statistically significant difference in the performance of the four indices in discriminating malignancy similar to other studies[11,12]. But RMI 2 was found to be more reliable in discriminating between benign and malignant disease by other investigators[5,8]. Tingulstad *et al*. in their study concluded that at a cut off level of 200, RMI 2 was significantly better at predicting malignancy than RMI 1[5]. Morgante*et al.* also found a similar observation that for all cut off values between 80 and 250, RMI 2 performed better than RMI 1 (p= 0.0001)[8]. Tingulstad *et al.* modified the RMI and called it RMI 3, and they observed that at a cut off level of 200 the sensitivity and specificity were 71 and 92%, respectively[6.] In our study on application of this modified RMI (RMI 3), we found a sensitivity and specificity of 50% and 96.8%, respectively. In 2001 Manjunath *et al*[10] compared RMI 1, RMI 2, and RMI 3 with each other and also confirmed that there was no statistical difference between these three indices. In 2009 Yamamoto *et al* developed their own RMI by using tumor size and called it RMI 4. Their study showed that at a cut off level of 450, the accuracy of the RMI 4 was better than RMI 1 (p=0.0013), RMI 2 (p=0.0009) and RMI 3 (p=0.0013) with a cut off level of 200. They observed that at a cut off level of 450 the sensitivity, specificity, positive predictive value and negative predictive value were respectively, 86.8%, 91.0%, 63.5% and 97.5%[(9)]. In our study we found a lower sensitivity of 66.7%, whereas the specificity, positive predictive value and negative predictive value was97.9%, 66.7%, 97.9%, respectively, which is comparable with the results of Yamamoto *et al*. But we also found that the other three indices' diagnostic performances were reliable, being different than Yamomoto *et al*'s results. It has been shown that using a cut-off value of 200 (regardless of scoring system) for an RMI score achieves sensitivities ranging from 70% to 87%, and specificities from 89% to 97%[(4-7)]. The specificities of RMI 1, RMI 2, RMI 3 and RMI 4 were 97.9%, 92.6%, 96.8% and 97.9% respectively. This finding is critical for the decision regarding referral of

patients with ovarian tumors to specialized centres. A lower specificity would lead to an undue number of referrals of benign cases, which is unacceptable for the referring hospital and unmanageable for the special centres. On the other hand, this will aid in selection of cases for a conservative nonsurgical approach, for example, ultrasound guided aspiration of clear cysts or those which can be managed by a a general gynaecologist. It is observed that the sensitivity of the RMI was much lower in recent studies[5,6,8] being the least in our study, when compared with the earlier studies from Jacobs *et al* and his group[4,7]. The reason may be that we had a higher percentage of ovarian cancer patients in the premenopausal age group than reported in the previous studies (83.3% vs 19 and 20%)[(4,7)]. Also, the relatively higher rate of early stage (stage I) ovarian tumor found in this study may be another contributing factor. In contrast to other studies[4,5] where the RMI was found to be more accurate in predicting malignancy than each one of its components measured individually, the present study showed that serum CA 125 and an ultrasound score of ≥ 2 performed as well as the various risk of malignancy indices in differentiating between benign and malignant pelvic masses.

CONCLUSION

The present study has demonstrated the RMI to be a valuable, reliable, and applicable method in the primary evaluation of patients with pelvic masses. Because of the simplicity of the method it can be used in daily clinical practice in nonspecialized gynecologic departments. 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 this index in the selection of cases for conservative management or minimal invasive surgery of benign cases, like ultrasound guided aspiration or laparoscopic excision of other cysts. A significant problem is the relatively low sensitivity in identifying patients with stage I invasive disease. As thorough surgical staging of these cases is an important part of the treatment strategy, further research is needed to evaluate methods able to identify these patients better than in the present and similar studies.

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