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A prospective study of comparison of risk of malignancy indices (RMIs) in evaluation of ovarian neoplasm at a rural tertiary hospital in central India

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Abstract
Aim: To evaluate the ability of four types of the risk of malignance indices (RMI) based on serum levels of Ca-125, ultrasound score and menopausal status to discriminate between benign and malignant ovarian tumours.
Methods: it was a Prospective cross sectional Study conducted in the Department of Obstetrics and Gynecology. During this study 300 women were enrolled in the study over a period of 1 1/2 years (December 2015–July 2017). The RMI was evaluated for sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with reference to the actual presence of a malignant or benign pelvic tumour.
Results: In this study out of 300 patients with clinically suspected ovarian tumours were included. RMI 1,2,3,4 was calculated according to their formula. Sensitivity of RMI- 1, 2, 3 and 4 was calculated to be 63.43%, 77.61%, 63.43% and 76.49% respectively. Specificity of RMI- 1, 2, 3 and 4 was calculated to be 68.75%, 65.62%, 65.62% and 62.50% respectively. RMI- 2 and RMI-4 had maximum sensitivity while RMI-1 had maximum specificity. Overall RMI-2 appears to be the most accurate of all the four RMI.
Conclusions: Overall RMI 2 appears to be more accurate of all.it may be concluded that, the RMI is a simple scoring system with higher accuracy in differentiating benign from malignant ovarian masses, it can be easily introduced in clinical practice and can be the test of choice in the preoperative evaluation of the adnexal mass under primary settings. Based on our study, RMI 2 use with ultrasound findings can be a useful and applicable method for initial assessment of patients with pelvic masses.

Keywords: Ovarian tumor, ultrasound score, risk of malignancy index

Introduction
Ovarian cancer is the eighth most common cancer among women, and it includes about 4% of all women's cancers [1]. This disease has high morbidity and mortality rates among cancers of the reproductive system [2]. According to global estimates 225,000 new cases were detected each year, and 140,000 people annually die from the disease [1]. Lifetime risk of ovarian cancer in women is one in 71, and the chance of dying from the disease is 1 in 95 [3]. In the year 2005, an estimated 22,220 new cases of ovarian cancer were diagnosed in the US alone, with 16,210 deaths predicted (Jemal *et al.*, 2015) [2]. Malignant tumours are often clinically silent until well developed; may be solid, cystic, or mixed; and they may be functional or nonfunctional. At present, one clinical feature provides inadequate performance in discriminating benign and malignant ovarian masses. The Risk of Malignancy Index (RMI) is the most widely used model. The histopathological diagnosis was considered as the gold standard for defining the outcomes. Hence, the RMI was evaluated for sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) predictive values with reference to the actual presence of a benign or benign pelvic tumor. Considering the high burden of the disease and diagnostic difficulties in differentiating benign and malignant lesions, the present study was planned to assess the diagnostic value of RMI in discriminating benign from malignant ovarian diseases. The treatment efficiency in patients with ovarian tumor could be increased by standardization of preoperative evaluation. Jacobs [4] have introduced risk of malignancy index (RMI) and that was the first diagnostic model which has combined demographic, sonographic and biochemical parameters for investigating patients with adnexal masses. RMI was modified by Tingulstad for the first time in 1996 to RMI 2 [5] and for the second time in 1999 to RMI 3. These three versions of RMI were assessed in many prospective and retrospective clinical.

Studies. Yamomoto introduced RMI 4(6), but its validity is due to be confirmed in future studies. The RMI value of 200 has been proven to be the best for distinction of benign from malignant adnexal masses, with the high level of sensitivity and specificity.

The main advantage of four RMIs is that, it is a simple scoring system, that can be applied directly into the clinical practice without the introduction of expensive or complicated methods (such as Computed tomography scan, magnetic resonance imaging and whole-body positron emission tomography.) and can easily be applied in less specialized center along with selective referral of patients to the specialized oncology center. Appropriate and timely referral to a gynaecological oncologist has proven to increase survival in patients with ovarian cancer. This would lead to fewer operations for benign masses being performed by gynecological oncologists.

Hence, this study was conducted to evaluate the performance of four types of risk of malignancy indices in order to identify cases of potential ovarian malignancy.

Methods

This prospective cross sectional study was conducted in the Department of Obstetrics and Gynecology at Mahatma Gandhi institute of medical sciences, sewagram, wardha, a tertiary rural care institute. Women who were clinically suspected to have ovarian lesions or on ultrasonography and who underwent laparotomy for the same were enrolled in the study over a period of 1 1/2 years (December 2015–July 2017). Patient related data was procured from our hospital database through the Hospital Information System (HIS) and personal interview and recorded in pre-designed questionnaire. Women fulfilling selection criteria were explained about the nature of the study and a written informed consent was obtained prior to the enrollment. Sample size (300) in the age group of 15 to 80 years was calculated using online sample size software Epi info.com with Hypothesized frequency-7.7%.After obtaining approval from the institutional ethics committee, Demographic details and detailed history was elicited. The selected women underwent all routine blood investigations followed by serum Ca-125, other serological markers, ultrasound and Computed tomography/ Magnetic resonance imaging.

Preoperative measurement of serum levels of Ca-125 was performed by using an Eletro- chemiluminescent immunoassay (ECLIA). Based on the data obtained, RMI 1, RMI 2, RMI 3, and RMI 4 were calculated for all patients together with the sensitivity, specificity, positive and negative predictive values of the four methods. Ultrasound score was calculated If the patients had bilateral ovarian tumour, the data of both were obtained. The findings were recorded on a predesigned and pretested proforma. The RMI was evaluated for sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with reference to the actual presence of a malignant or benign pelvic tumour. RMIs were then compared with respect to its sensitivity, specificity, positive predictive value and negative predictive value. The accuracy of RMI in differentiating benign and malignant lesions was determined. A ‘p’ value of less than or equal to 0.05 was considered as statistically significant.

Based on the cut off values of RMI, ovarian lesions were classified as benign or malignant. Patients were operated in the operation theatre of the same hospital after complete pre anaesthetic checkup. Post operatively, ovarian tissue samples were sent for histopathology. The histopathological diagnosis was considered as the gold standard for defining the outcomes. Efficacy of RMI Score was seen after comparing it with histopathology report.

Method of calculating RMI

	Scoring system			
Variables	**RMI 1***	**RMI 2***	**RMI 3***	**RMI 4***
Menopausal Status (M)				
Premenopause	1	1	1	1
Post menopause	3	4	3	4
Ultrasound score (U)	No feature U=0	No feature U=1	No feature U=1	No feature U=1
	1 feature=1	1 feature U=1	1 feature U=1	1 feature U=1
	≥2 features=3	≥2 features U=4	≥2 features U=3	≥2 features U=4
Multilocular				
Bitaterally				
Solid				
Ascites				
Intraabdominal metastasis				
Serum Ca 125 (Ca-125)	Absolute levels (U/ml)	Absolute levels (U/ml)	Absolute levels (U/ml)	Absolute levels (U/ml)

RMI: Risk of Malignancy Index

Patients were considered Postmenopausal, if they had at least 1 year of amenorrhea not related to other conditions or if they were at least 50 years old and had undergone a prior hysterectomy. All other women were considered Premenopausal.

Calculation for RMI 1(9), RMI 2 (8), RMI 3 (10)= M x U x CA-125.

Calculation for RMI 4(11) = M x U x CA-125 x S (When S = single greatest diameter of tumour size (cm). If size<7 cm, S=1, size >7cm.S=2.

Table 1: Histopathological distribution of Adnexal masses (N=300)

Type of tumor			
		No.	**%**
Benign	Serous Cystadenoma	67	22.3
	Mucinous Cystadenoma	52	17.4
	Haemmorhagic Cyst	61	20.3
	Simple Serous Cyst	40	13.3
	Dermoid Cyst	7	2.3

	Follicular Cyst	21	7.0
	Endometriotic Cyst	17	5.7
	Corpus Luteum Cyst	3	1.0
	Total	268	89.3
Malignant	Serous Cystadenocarcinoma	13	4.3
	Mucinous Cyst Adenocarcinoma	09	3
	Papillary Cystadenocarcinoma	04	1.4
	Choriocarcinoma	02	0.7
	Yolk Sac Tumour	02	0.7
	Granulosa Cell Tumour	1	0.3
	Dysgerminoma	1	0.3
	Total	32	10.7
Grand Total		300	100

Table 1 represents total 300 cases of ovarian tumour, out of which 268 (89.3%) cases are benign and 32 (10.7%) cases are malignant.

Table 2: Relevance of RMI -1 in Comparison to Histopathology

RMI 1	**Type of Tumour**					
	Benign		**Malignant**		**Total**	
	No.	**%**	**No.**	**%**	**No**	**%**
<200	170	56.6	10	3.4	180	60.0
>200	98	32.7	22	7.3	120	40.0
Total	268	89.3	32	10.7	300	100
Relevance of RMI Score						
RMI 1	Sensitivity	Specificity	PPV	NPV	χ2-value	p-value
	63.43	68.75	94.44	18.33	12.34Df 1	0.00041

In the present study of the 32 malignant ovarian lesions on histopathology, 22 had RMI 1 score ≥ 200 while 10 women had RMI 1 score of < 200. The sensitivity of RMI 1 in predicting malignant lesions as compared to histopathology was 63.43% with 68.75% of specificity.

Table 3: Relevance of RMI -2 in Comparison to Histopathology

RMI 2	**Type of Tumour**					
	Benign		**Malignant**		**Total**	
	No.	**%**	**No.**	**%**	**No**	**%**
<200	208	69.3	11	3.7	219	73
>200	60	20	21	7.0	81	27
Total	268	89.3	32	10.7	300	100
Relevance of RMI Score						
RMI 2	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**χ2-value**	**p-value**
	77.61	65.62	94.97	25.92	27.11Df 1	0.0000012

In the present study of the 32 malignant ovarian lesions on histopathology, 21 had RMI 2 score ≥ 200 while 11 women had RMI 2 score of< 200. The sensitivity of RMI 2 in predicting malignant lesions as compared to histopathology was 77.61% with 65.62% of specificity.

Table 4: Relevance of RMI-3 in comparison to histopathology

RMI 3	**Type of Tumour**					
	Benign		**Malignant**		**Total**	
	No.	**%**	**No.**	**%**	**No**	**%**
<200	170	56.6	11	3.7	181	60.2
>200	98	32.7	21	7	119	39.8
Total	268	89.3	32	10.7	300	100
Relevance of RMI Score						
RMI 3	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**χ2-value**	**p- value**
	63.42	65.62	93.92	17.64	10.09Df 1	0.0041

In the present study of the 32 malignant ovarian lesions on histopathology, 21 had RMI 3 score ≥ 200 while 11 women had RMI 3 score of <200. The sensitivity of RMI 3 in predicting malignant lesions as compared to histopathology was 63.43% with 65.62% of specificity.

Table 5: Relevance of RMI-4 in Comparison to Histopathology

RMI 4	**Type of Tumour**					
	Benign		**Malignant**		**Total**	
	No.	**%**	**No.**	**%**	**No**	**%**
<450	205	68.3	12	4	217	72.3
>450	63	21	20	6.7	83	27.7
Total	268	89.3	32	11	300	100
Relevance of RMI 4 Score						
RMI 4	Sensitivity	Specificity	PPV	NPV	χ2-value	p-value
	76.49	62.5	94.47	24.09	76.19Df 1	0.00041

In the present study of the 32 malignant ovarian lesions on histopathology, 12 had RMI 4 score ≥ 450 while 20 women had RMI 4 score of < 450. The sensitivity of RMI 4 in predicting malignant lesions as compared to histopathology was 76.49% with 62.5% of specificity.

Table 6: Diagnostic Performance of RMI 1, RMI 2, RMI 3, RMI 4, CA-125 and USG Score

RMI	Sensitivity	Specificity	PPV	NPV	χ2- value	P value	Result
RMI1	63.43	68.75	94.44	18.33	12.34	0.000441	HS
RMI2	77.61	65.63	94.98	25.93	27.11	0.0000012	HS
RMI3	63.43	65.63	93.92	17.65	10.09	0.0014	HS
RMI4	76.49	62.50	94.47	24.10	76.191	0.00041	HS
Ca-125	76.11	90.62	98.55	31.18	64.928	0.000012	HS
USG	23.23	95.52	71.87	71.64	2.43	0.23	NS

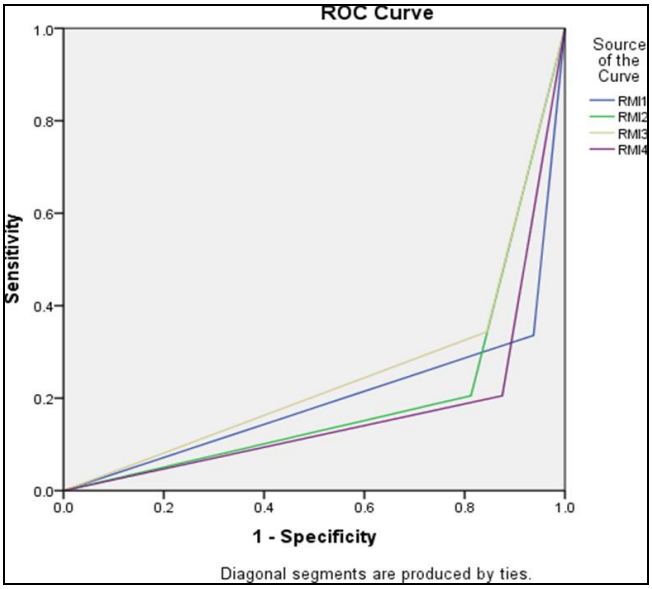
The cut off value used were 200 for the RMI 1, RMI 2, and RMI 3, and 450 for RMI 4.

*PPV = Positive predictive value, NPV = Negative predictive value, HS-Highly significant, NS-Not significant

In our study**,** a total of 300 patients were included in the study. RMI 1,2,3,4 was calculated according to their formula. Sensitivity of RMI- 1, 2, 3 and 4 was calculated to be 63.43%, 77.61%, 63.43% and 76.49% respectively. Specificity of RMI-1, 2, 3 and 4 was calculated to be 68.75%, 65.63%, 65.63% and 62.50% respectively

Table 7: Difference in the area under the curve (AUC) of the roc curve for the diagnosis of malignant ovarian tumours with the corresponding 95% confidence intervals (95%ci) and p-value

RMI	Area Under Curve	Difference	P Value	Asymptotic 95% Confidence Interval	
				Lower limit	Upper limit
RMI1	0.199	0.033	.000	0.134	0.265
RMI2	0.196	0.042	.000	0.113	0.279
RMI3	0.250	0.042	.000	0.167	0.332
RMI4	0.165	0.037	.000	0.093	0.238



ROC Curve for RMI1, RMI2, RMI3, RMI4

Table 8: The one-way analysis of variance (ANOVA) is used to determine whether there are any statistically significant differences between all the RMIs

Source	Type III Sum of Squares	D f	Mean Square	F	Sig.
Corrected Model	152407226.549a	7	21772460.936	138.259	.000
Intercept	196085247.765	1	196085247.765	1245.175	.000
RMI	40195927.420	3	13398642.473	85.084	.000
BM	113638196.952	1	113638196.952	721.622	.000
RMI * BM	26613184.932	3	8871061.644	56.333	.000
Error	185349243.621	1177	157475.993		
Total	419795265.413	1185			
Corrected Total	337756470.170	1184			

R Squared =0.451 (Adjusted R Squared =0.448) RMI-Risk of malignancy index, B-Benign, M-Malignant

The above table contained information of Multivariate ANOVA, here all RMI values differ significantly from one another with P value 0.000. Similarly, RMI shows significant difference with tumour type (P value 0.000) and it also reveals significant change by considering the interaction effect of RMI with tumour type. The total model explained almost 45% of variation.

Discussion

Ovarian tumour has emerged as one of the most common gynaecological malignancies affecting women. Symptoms of the ovarian tumour are very vague, that is why, it is also known as ‘silent killer’. A pelvic mass is one of the most frequent indications for referral of the patient to specialist gynecologists.

The preoperative diagnosis of whether a mass is malignant cannot always be made with current diagnostic modalities. Surgery can be optimally planned if an ovarian neoplasm is known to be benign or malignant in advance. An improved method for preoperative discrimination of a pelvic mass would result in more women receiving first-line therapy from trained and experienced personnel.

Ovarian cancer is the fifth most common cause of death from malignancy in women. The 5 year survival rate for localized ovarian cancer is 92% and for advanced ovarian cancer is 30%, however only 19% ovarian cancer case are localized when diagnosed, finding an effective screening strategy that would shift diagnosis to early most treatment stage would improve out come and decreases mortally from ovarian cancer(7).Jacobs *et al* in his study(11) assessed age, ultrasound score, menopausal status, a clinical impression score and serum Ca- 125 level to see how they could best distinguish between patients with benign (n=101) and malignant (n=42) pelvic masses. Each criterion used alone provided statistically significant discrimination. Using an RMI cut-off level of 200, the sensitivity was 85% and the specificity was 97%. Patients with an RMI score of greater than 200 had, on average, 42 times the background risk of cancer and those with a lower value 0.15 times the background risk. These findings were comparable with the present study where the sensitivity of RMI in predicting malignant lesions as compared to histopathology was 93.33% with 87.76% of specificity [8].Similar results were reported in recent study where sensitivity of RMI was 83.33%, specificity 94.12%, positive predictive value was 89.29% and negative predictive value was 90.57% using RMI cut off value of 200.The RMI has been evaluated in 16 studies (137), (138), (139).

Finally, RMI III and RMI IV also have been developed. RMI III and RMI IV both apply different ultrasound scores compared with RMI I and RMI II. RMI III is evaluated in one study and showed at validation sensitivity and specificity of 74% and 91%, respectively. RMI IV has not been validated in other studies [6]. All indices presented a significantly better performance in diagnosing malignancy than did each predictor taken separately. These indices were tested by Morgante *et al*., on another population with evident malignant criteria in the ultrasonography, such as hepatic or distant metastasis, and they found that the RMI 2 performed better for detecting ovarian malignancy.

In this study, RMI 2 showed the best performance in predicting malignancy, compared with the other three indices. At the cutoff point 90 (above which the probability of malignancy of masses was high) RMI 2 had the most area under the curve (0.0865), showing the greatest concordance with pathologic results. Specificity of RMI- 1, 2, 3 and 4 was calculated to be 68.75%, 65.62%, 65.62% and 62.5% respectively. Thus, we can conclude that, Risk of malignancy index is a good diagnostic tool to differentiate between benign and malignant pelvic masses. RMI-2 and RMI-4 had maximum sensitivity while RMI-1 had maximum specificity. Overall RMI-2 appears to be the most accurate of all the four RMI. The above findings correlate with the study done by Karimi Zarchif *et al*., and Morgante *et al*. Overall, the RMI is a simple method that can be used by general gynecologists to aid in selecting a patient for referral to cancer centers for primary surgery and further management.

Conclusions

In this study, RMI 2 showed the best performance in predicting malignancy, compared with the other three indices. At the cutoff point 90 (above which the probability of malignancy of masses was high) RMI 2 had the most area under the curve (0.0865), showing the greatest concordance with pathologic results. Gynecologists may identify women with high probability of malignancy using the reasonably high sensitivity of RMI 2 and may separate patients with benign lesions who do not need immediate surgical intervention because of its high specificity.

Conflict of Interest

Not available

Financial Support

Not available

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