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Diagnostic utility of Risk of Malignancy Index in differentiation of benign from malignant ovarian masses

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ABSTRACT

Background: Women with adnexal masses still pose a diagnostic dilemma and require efficient triaging. The Risk of Malignancy Index (RMI) is an algorithm used for differentiation of malignant from benign ovarian masses. **Aims and Objectives:** The present study aimed to evaluate the four indices RMI 1, RMI 2, RMI 3, and RMI 4 to discriminate a malignant ovarian tumor from a benign one. **Materials and Methods:** This cross-sectional study was carried out at a tertiary care hospital of Eastern Uttar Pradesh, India, in 312 patients with ovarian masses. RMI scores were calculated based on pre-operative cancer antigen-125 levels, ultrasonography, and menopausal status followed by post-operative histopathology, taken as gold standard. Using cutoff points of RMI indices, the sensitivity, specificity, positive predictive value, and negative predictive value of RMI were assessed. **Results:** Out of total 312 patients, 68 (21.8%) had malignant disease and 244 (78.2%) had benign pathology. All indices presented a significantly better performance in detecting malignancy than the use of a single parameter. Each of the RMIs had a different optimal threshold; however, using a threshold of 250, RMI 1, RMI 2, RMI 3, and RMI 4 had a sensitivity and specificity of 64.7%, 70.5%, 64.7%, and 65.2% and 93.4%, 83.6%, 90.2%, and 91.4%, respectively. **Conclusion:** The RMI is a simple, composite tool that at lower values can reliably predict benign nature of adnexal tumors. However, at values above the cutoff points, it is helpful for appropriate surgical planning and averts radical surgeries in women of reproductive age group.

Keywords: Ovarian tumor; Histopathology; Ultrasonography

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INTRODUCTION

Ovarian cancer is the seventh most common cancer worldwide in females.[1] Its presentation with non-specific symptoms and lack of screening strategies result in delay in diagnosis. Recognizing ovarian cancer at an early stage is very essential,[2] as the extent of disease at diagnosis is the primary determinant of survival.[3] Optimal debulking surgery performed in patients with ovarian cancer is another significant prognostic factor,[4] and accurate surgical staging of early-stage ovarian cancer patients has great significance, permitting accurate estimation of the true extent of disease and providing patients with appropriate information about prognosis and adjuvant treatment.[5]

Ultrasonography (USG) and the measurement of serum cancer antigen-125 (CA-125) levels are commonly performed preoperatively to predict the histopathological nature of adnexal masses.[6] CA-125 levels >30 kU/mL suggest a risk of malignancy,[7] although patient age and menopausal status are also important factors in the pre-operative evaluation of adnexal masses.[8]

Several studies have been conducted in order to develop a design to precisely differentiate malignant ovarian masses from the benign ones. The Risk of Malignancy Index (RMI 1) was introduced by Jacobs et al., which was based on three parameters, namely serum CA-125 levels, menopausal status, and USG findings.[7] Using the same parameters,

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Tingulstad et al.,[9,10] propounded RMI 2 and subsequently RMI 3. More recently, Yamamoto et al.,[11] suggested the use of RMI 4 for pre-operative evaluation of malignant adnexal masses by incorporating the size of adnexal mass on USG as a variable in the risk calculation.

The current study aimed to evaluate the diagnostic accuracy of four RMIs in discriminating between benign and malignant adnexal masses.

Aims and objectives

To evaluate the diagnostic accuracy of four RMIs in discriminating between benign and malignant adnexal masses.

MATERIALS AND METHODS

The current cross-sectional observational study was conducted in the Department of Obstetrics and Gynecology, BRD Medical College, Gorakhpur, Uttar Pradesh, India, from June 2019 to May 2021. All the women having ovarian mass on presentation who came to the hospital during the study period and also consented for the study were included (n=312) in the study. Subsequent post-operative histopathological examination, taken as gold standard, was performed to calculate the accuracy of RMI. Women with functional cyst ≤5 cm, abdominal mass other than ovarian mass, known history of ovarian or other established gynecological cancers, and ectopic pregnancy were excluded from the study. Informed written consent was obtained from all the patients. After detailed history and clinical examination, patients were subjected to various routine and special investigations. Four versions of RMI were compared, each incorporated serum CA-125 level, menopausal status, and ultrasound findings (Table 1). Serum CA-125 levels were measured using radioimmunoassay, and values >35 U/mL were considered to be abnormal.[12] Menopause being defined as one or more years of amenorrhea or women who had undergone hysterectomy, the menopausal status of all women were recorded. Transvaginal or transabdominal scans were done using a 7.5 MHz or 3.5 MHz transducer in Toshiba Nemio color Doppler ultrasound machine. The ultrasound score was computed based on the presence or absence of five features – multiloculated cyst, evidence of solid areas, bilateral lesions, presence of ascites, and evidence of metastasis (Figure 1). To calculate the RMI, the formula serum CA-125×M×U was used.[13] Serum CA-125 is the assayed level of the tumor marker expressed in kU/L, M refers to the menopausal status, and U is the ultrasound score. In case of RMI 4, an additional parameter of single greatest diameter of tumor size (cm) (S) was included and was calculated as RMI 4= CA-125×M×U×S, where S=1 if tumor size is <7 cm and 2 if tumor size is ≥7 cm.

Surgical specimens were sent for histopathological examination, and the results were documented. RMI was correlated with surgical findings and final histopathological report.

Statistical analysis

Statistical analysis was done using statistical software SPSS version 20. The Chi square test was used to compare the categorical variables and independent t test was used to compare discrete variables between groups. $P<0.05$ was considered statistically significant. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the four RMIs with reference to malignant or benign pelvic mass were calculated. Receiver operating curve (ROC) was plotted to calculate the predictive values of the four RMIs at their different cutoffs from 25 to 300. Accuracy was measured by the area under curve (AUC).

RESULTS

Three hundred and twelve women with adnexal masses were included in this observational study with a mean age of 47.9±13.03 years. Out of 312 patients, 244 (78.2%) cases had benign and 68 (21.8%) cases had malignant disease. The mean age was 40.74±12.32 years and 48.94±15.31 years in women with benign and malignant masses, respectively (Table 2).

Most of the women with two or more ultrasound abnormalities had malignant pathology. CA-125 levels in

Table 1: The four versions of RMI compared in the study

Variants	Menopausal score (M)	Ultrasound score (U)	Tumor size (S) cm
RMI 1=M × U×CA-125	1 if pre-menopausal	0 if no abnormality	1 if<7 cm
RMI 2=U × M×CA-125	3 if post-menopausal	1 if one abnormality	2 if≥7 cm
RMI 3=U × M×CA-125	1 if pre-menopausal	3 if≥2 abnormalities	
RMI 4=U × M×S×CA-125	4 if post-menopausal	1 if≤1 abnormality	
	1 if pre-menopausal	4 if≥2 abnormalities	
	3 if post-menopausal	1 if≤1 abnormality	
	1 if pre-menopausal	3 if≥2 abnormalities	
	4 if post-menopausal	1 if≤1 abnormality	
		4 if≥2 abnormalities	

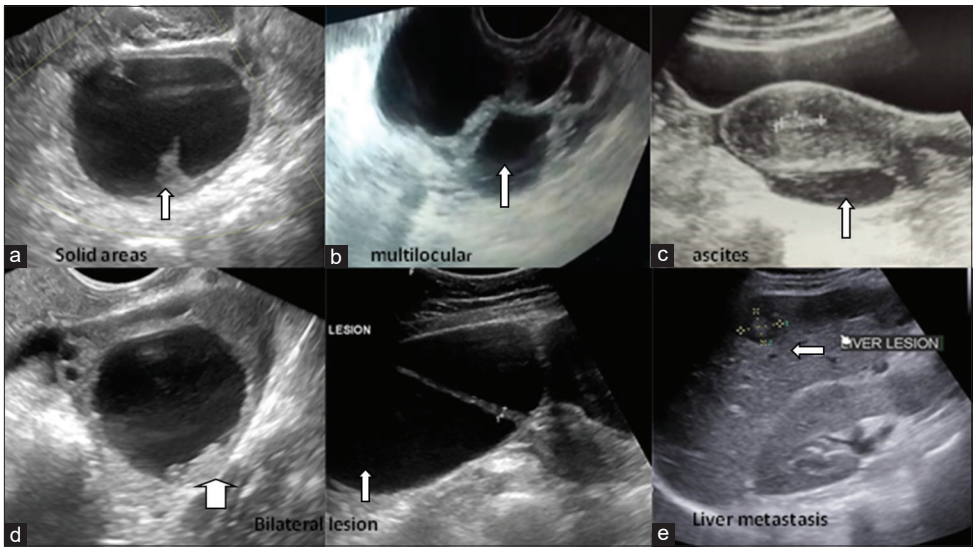

Figure 1: Illustrative ultrasound figures in RMI scoring system. Each of the ultrasound characters counts one point. (a) Evidence of solid areas. (b) Multiloculated cyst. (c) Presence of ascites. (d) Bilateral lesions. (e) Evidence of metastasis

Table 2: Distribution cases based on age, menopausal status serum 125, and USG score

Variables	Benign	Malignant	P-value
Age (years) 0.399			
<30	28	8	
31–40	48	8	
41–50	88	24	
≥50	80	28	
Menopausal status 0.9068			
Pre-menopausal	88	24	
Post-menopausal	156	44	
CA 125(U/mL) <0.001			
Mean	31.93±33.31	235.99±322.26	
Median	21–6	112.0	
Range	3.9–200.0	12.0–1100.0	
USG score			
RMI 1–0	92	8	0.0004
1	60	16	
3	92	44	
RMI 2–1	152	24	0.047
4	92	44	
RMI 3–1	152	24	0.047
3	92	44	
RMI 4–1	152	24	0.047
4	92	44	
Tumor size (cm) 0.98			
<7 cm	100	28	
>7 cm	144	40	

the patients with benign disease were 31.9±33.31 U/mL and 21.6 U/mL for mean and median, respectively; the corresponding values in the subjects with malignant disease were 235.9±322.26 U/mL and 112.0 U/mL, respectively. This association was statistically significant (P<0.001) (Table 2).

Abdominal pain was the most common symptom (52.9%) followed by lump in abdomen (41.2%) in the malignant group. On the contrary, the benign group predominantly presented with non-specific abdominal symptoms (42.6%) (Table 3).

The most commonly encountered benign ovarian lesions were serous cystadenoma (36.06%) , followed by mucinous cystadenoma (18.03%), and mature teratoma (9.83%) (Figure 2). The most common malignant histologic diagnoses were serous cystadenocarcinoma and mucinous cystadenocarcinoma together accounting for 58.81% of malignant ovarian tumors (Table 4 and Figure 3).

Using a threshold of 200, RMI 1 had a sensitivity of 64.7% and a specificity of 91.8%, RMI 2 had a sensitivity of 76.5% and a specificity of 80.3%, RMI 3 had a sensitivity of 64.7% and a specificity of 86.9%, and RMI 4 had a sensitivity of 65.4% and a specificity of 87.1% (Table 5).

ROC curves were plotted to show the relation between the sensitivity and specificity of all the four RMIs in distinguishing between benign and malignant masses (Figure 4). RMI 1 was associated with the highest AUC (0.84, 95% CI: 0.708–0.973) among all the four RMIs.

DISCUSSION

Ovarian carcinoma is one of the most common malignancies in women.[14] The proportion of malignancy in pelvic masses of pre-menopausal women is approximately 24% and it increases to more than 60% in post-menopausal women.[15] Unfortunately, most of these masses are asymptomatic or having non-specific symptoms, leading to a delay in diagnosis. Often theses patients seek admission at advance stages of carcinoma when metastasis has already occurred causing difficulty in curative surgery and

Table 3: Clinical symptoms in benign and malignant lesions

Symptoms	Malignant ovarian tumors *n*=68		Benign ovarian tumors *n*=244		*P*-value
	No.	%	No.	%	
Asymptomatic	4	5.9	32	13.1	0.1281
Non-specific symptoms	12	17.6	104	42.6	0.0004
GI symptoms	24	35.3	104	42.6	0.4591
Pain in abdomen	36	52.9	36	14.7	<0.0001
Lump in abdomen	28	41.2	84	34.4	0.1675
Menstrual irregularity	20	29.4	44	18.0	0.0203

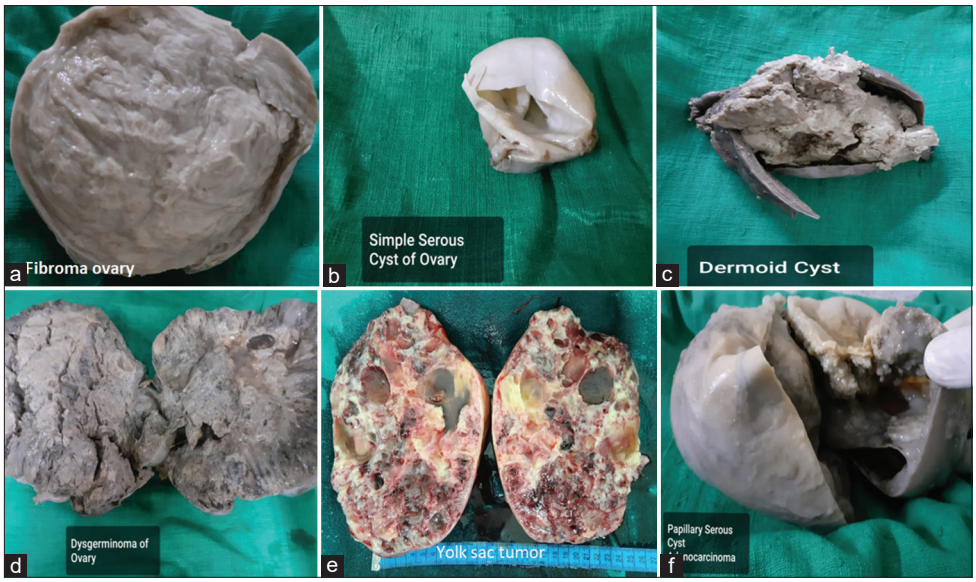

Figure 2: Gross of benign and malignant ovarian tumors. (a) Cut section of fibroma ovary. (b) Gross specimen of simple serous cyst of ovary. (c) Cut section of dermoid cyst. (d) Cut section of dysgerminoma of ovary. (e) Cut section of yolk sac tumor. (f) Gross specimen of papillary serous cyst adenocarcinoma

subsequently decreased survival of the patient. Two-thirds of ovarian cancers are diagnosed only after metastasis or at stages 3 and 4.[16] The importance of estimating the risk of malignancy preoperatively has been well emphasized in the literature. With the development of RMI, a straightforward predictive algorithm, the current study was done to ascertain if the four versions of RMI, i.e., RMI 1, RMI 2, RMI 3, and RMI 4, that incorporate serum CA-125 levels, ultrasound findings, menopausal state, and tumor size (RMI 4) can discriminate between benign and malignant masses and their best cutoff levels to do so.

The occurrence of ovarian cancer is rare before the age of 40 years. It increases steadily thereafter and reaches a peak at the age of 50–60 years.[17] In this study, the mean age was 40.74±12.32 years for women with benign disease and 48.94±15.31 years for those with malignant tumors. In a research by Manjunath et al.,[18] done on 152 patients with pelvic masses, the mean age for benign masses was 45, and for malignant ones, it was 49. In the present study, a statistically significant relationship of malignant tumors with age, USG score, and CA-125 was observed similar to the finding of Park et al.[19] However, no significant association was found with menopausal status and tumor size which is contrary to the study performed by Ong et al.[20]

In our study, 68 (21.8%) of adnexal masses were malignant with majority 44 (64.1%) seen in post-menopausal age group. These findings were in accordance with Meray et al.,[21] and Hada et al.,[13] who showed predominance in post-menopausal patients. In the present study, the most common benign and malignant masses were serous cystadenoma and serous cystadenocarcinoma, respectively. This was comparable to studies performed by Manjunath et al.,[18] and Van den Akker et al.[22] However, Hada et al., observed mature teratoma as the most common benign tumor followed by functional ovarian cysts and serous cystadenocarcinoma as the most frequent malignant tumor followed by granulosa cell tumor[13] in their study.

In the present study, majority of the patients with benign ovarian disease presented with non-specific symptoms (42.6%) and gastrointestinal symptoms (42.6%) whereas abdominal pain 52.9% was the most predominant presenting symptom among malignant cases. In a study

conducted by Goff et al.,[23] in 2000 on 1725 ovarian cancer patients, the symptoms most commonly seen are those related to abdominal bloating and gastrointestinal disturbances. Specific gynecological symptoms were reported by only 25% of the surveyed women.

The high false-positive rate of ultrasound limits its use as a screening modality of ovarian cancer.[10] In addition to ovarian carcinoma, CA-125 levels are also found to be raised in benign ovarian cysts, endometriosis, pelvic infection as well as cancers of endometrium, fallopian tube, breast, and colon. Since the RMI gives results in numerical data, it lessens the bias arising due to examiner's subjectivity, thus making it more reliable than any of the individual parameters, i.e., ultrasound, CA-125 level, menopausal status, or tumor size[11] and also in distinguishing malignant and benign masses.[12] In the current study, menopausal state, tumor size, and USG parameters individually did not appear to predict malignancy though the serum CA-125 levels were found to be a relevant predictor of malignancy (P <0.001).

Table 4: Distribution of patients on the basis of histological diagnosis

S. No.	Ovarian masses	No. of patients (n=312)	%
A.	Benign	244	
1.	Non-neoplastic	60	
i)	Endometrioma	28	11.47
ii)	Follicular cyst	20	8.19
iii)	Bilateral tubercular salpingo-oophoritis	12	4.91
2.	Neoplastic tumors	184	
i)	Serous cystadenoma	88	36.06
ii)	Mucinous cystadenoma	44	18.03
iii)	Fibroma	16	6.55
iv)	Thecoma	8	3.27
v)	Adenofibroma	4	1.63
vi)	Mature teratoma	24	9.83
B	Malignant	68	
1.	Epithelial cell tumors	52	
i)	Serous cyst adenocarcinoma	24	35.29
ii)	Mucinous adenocarcinoma	16	23.52
iii)	Endometrioid adenocarcinoma	8	11.76
iv)	Clear cell adenocarcinoma	4	5.8
2.	Sex cord-stromal tumors	16	
i)	Immature teratoma	6	8.82
ii)	Endodermal sinus tumor	2	2.94
iii)	Dysgerminoma	5	7.35
iv)	Granulosa cell tumor	3	4.41

The present study showed that all the four risk of malignancy indices were highly specific at an optimal cutoff of 200. The specificity of RMI 1, RMI 2, RMI 3, and RMI 4 was 91.8%, 80.3%, 86.9%, and 87.1%, respectively, which is similar to that seen in other studies.[18,24] A high specificity is important because it reduces the number of surgical procedures performed for benign cases, thus optimizing the resources for patients with malignant pelvic masses. At the cutoff of 200, the pre-operative RMI yielded a sensitivity of 64.7%, 76.5%, 64.7%, and 65.4% for RMI 1, RMI 2, RMI 3, and RMI 4, respectively. Akturk et al.,[25] observed a comparatively high sensitivity of RMIs 1, 2, 3, and 4 which were 75%, 75%, 75%, and 85%, respectively, at a cutoff value of 200. Similar findings were also observed by Tingulstad et al.,[9] PPV and NPV of RMIs 1, 2, 3, and 4 were 68.8%, 52.0%, 57.9%, and 60.0% and 90.3%, 92.5%, 89.8, and 87.8%, respectively. The results were comparable

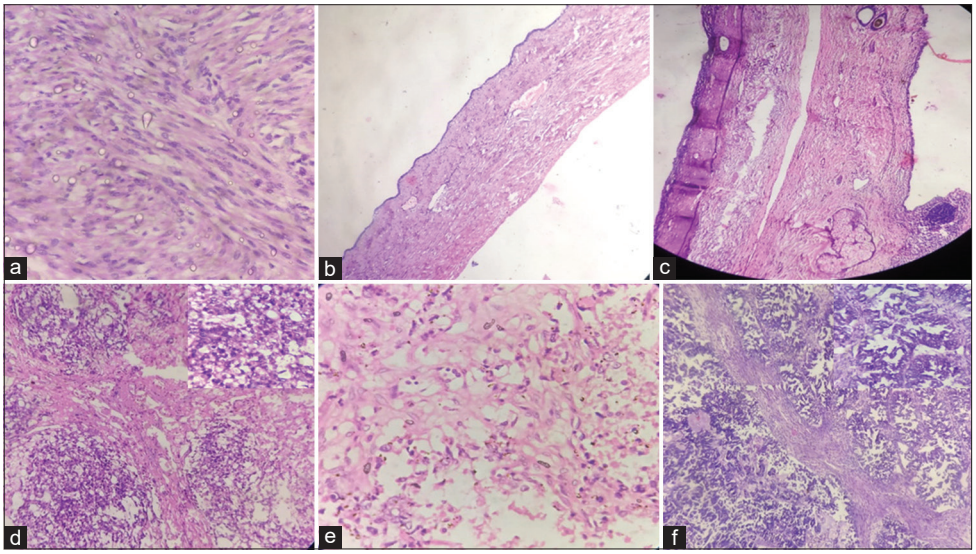

Figure 3: Microscopic pictures of ovarian tumors. (a) Histopathology of fibroma ovary (H and E ×400). (b) Histopathology of simple serous cyst of ovary (H and E ×100). (c) Histopathology of dermoid cyst (H and E ×100). (d) Histopathology of dysgerminoma ovary with inset showing sheets of polygonal cells with clear and eosinophilic cytoplasm (H and E ×400). (e) Histopathology of yolk sac tumor (H and E ×400). (f) Histopathology of papillary serous cyst adenocarcinoma with inset showing tubulopapillary structure with neoplastic cells showing high-grade nuclear features with significant pleomorphism (H and E ×400)

Table 5: Sensitivity, specificity, positive predictive value, and negative predictive value for predicting malignancy at different cutoff levels of RMI 1, RMI 2, and RMI 3

RMI cutoff	Sensitivity (%)				Specificity (%)				PPV (%)				NPV (%)			
	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
25	82.4	94.1	94.1	94.1	50.8	26.2	31.1	33.3	31.8	26.2	27.6	29.7	91.2	94.1	95.0	87.0
75	76.5	88.2	82.4	84.7	70.5	49.2	60.6	62.8	41.9	32.6	36.8	38.9	91.5	93.8	92.5	84.5
150	70.6	76.5	76.5	78.8	86.9	70.5	83.6	85.8	60.0	41.9	56.5	58.6	91.4	91.5	92.7	84.7
200	64.7	76.5	64.7	65.4	91.8	80.3	86.9	87.1	68.8	52.0	57.9	60.0	90.3	92.5	89.8	87.8
250	64.7	70.5	64.7	65.2	93.4	83.6	90.2	91.4	73.3	54.5	64.7	66.8	90.5	91.1	90.2	91.2
300	64.7	64.7	64.7	65.2	95.1	86.9	91.8	92.7	78.6	57.9	68.8	69.9	90.6	89.8	90.3	90.2

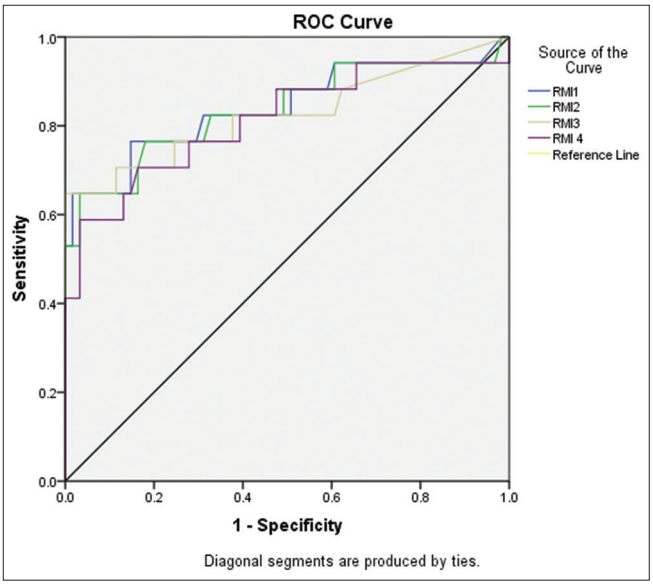

Figure 4: Receiver operator characteristic ROC curve showing the relationship between specificity and sensitivity for RMI 1, RMI 2, RMI 3, and RMI 4

to the study performed by Akturk et al.,[25] who showed a sensitivity, specificity, PPV, and NPV of 85%, 87%, 60%, and 95%, respectively, and also with the results of Yamamoto et al.[11]

Some studies have shown that RMI 2 was more reliable in pre-operative evaluation of women with pelvic masses.[9,26,27] However, in this study, the performance of malignancy indices varied depending on the threshold used.

According to the NICE's recommendation,[29] pelvic masses with a RMI 1 score of <25 is considered as low risk, 25–250 as intermediate risk, and >250 as high risk. Patient in low risk category with RMI score of<25 can be managed by gynecologist at her hospital, patients with RMI score between 25 – 250 should be discussed with gynecology oncologist and can be managed locally if found appropriate. Patients having RMI score of >250 would require further investigations and immediate referral to a cancer institute. The NICE recommends a cutoff of 250 because it was thought that this would ensure access to specialist centers without overburdening them with benign disease. Based on this, RMI 1 at a threshold of 250 had a higher specificity (93.4%) in our study, although the sensitivity had been affected relative to specificity, i.e., 64.7%.

Receiver operating characteristic curve (ROC) analysis of RMI 1, RMI 2, RMI 3, and RMI 4 revealed that the values of area under the curve were significantly high with a value of 0.841, 0.835, 0.825, and 0.812, respectively (P<0.05). This showed that the risk of malignancy indices was more reliable in detecting malignancy in terms of area under the

curves. This was comparable to other studies.[12,28] To the best of our knowledge, this was the first study undertaken in Eastern Uttar Pradesh (Gorakhpur region) to validate the use of risk of malignancy indices in the pre-operative assessment of women with pelvic masses.

Limitations of the study

Further comprehensive studies on larger population incorporating more indices such as CA-125/HE4 combination, ROMA, OVA-1 test, and IOTA logistic regression are recommended to improve diagnostic precision of RMI.

CONCLUSION

RMI is a simple, non-invasive, and reliable tool which should be adopted in clinical practice for the assessment of pelvic masses. Routine use of RMI at institution with proper facilities in cases of ovarian tumor could provide early and reliable prediction of ovarian malignancy with consequent appropriate surgical approach. There is a potential role of this index in the selection of cases for conservative management or minimally invasive surgery for benign cases such as ultrasound-guided aspiration or laparoscopic excision of other cysts. Moreover, prediction of malignancy with accuracy at center with lack of adequate facilities may provide a basis for timely referral to gynecological oncology center, thereby improving the survival and prognosis of the women. In the current study, a cutoff of 250 was found to be better than 200. Furthermore, RMI 1 showed the best performance in predicting malignancy, as it showed higher specificity than RMI 2, RMI 3, and RMI 4 at all cutoffs without any major loss of sensitivity.

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