

Preoperative Analysis of Risk of Malignancy Indices in the Distinction of Malignant Ovarian Tumors

Abstract

Background: Ovarian cancers are three times more lethal than breast cancer, despite its lower prevalence rate. Thus, it is imperative to determine if an ovarian mass is benign or malignant to structure a pertinent management protocol. **Aim and Objective:** The study proposed to preoperatively compare the predictive values of the four risk of malignancy indices (RMIs) and categorized benign and malignant ovarian masses. **Methodology:** The study included 60 women undergoing surgery for ovarian masses. Parameters such as age, menopausal status, ultrasound findings, tumor size, and cancer antigen (CA)-125 levels were recorded. They were assessed through 4 RMI scores and compared with postsurgical histopathological examination (HPE) report. The sensitivity, specificity, positive predictive value (PPV), and negative predictive values (NPVs) were calculated. The level of significance was set at $P \leq 0.05$. **Results:** As per the HPE report, 54 (90%) patients were diagnosed with benign and 6 (10%) with malignant ovarian masses. The median levels of CA-125 were significant ($P = 0.014$). For the universally recommended RMI cutoff values, sensitivity was 66.7%, specificity ranged from 83.3% to 88.9%, PPV from 36.3% to 40.0%, and NPV from 95.7% to 96%. With the suggested cutoff values obtained by plotting the receiver operating characteristic from the study, sensitivity was 66.6%, specificity ranged from 87.03% to 100.0%, PPV was 100.0%, and NPV was 93.1%. The area under the curve ranged from 0.836 to 0.854. **Conclusion:** The results of the present study endorse the potency of the RMIs. This certifies that the RMIs are valuable diagnostic tools in discriminating ovarian masses, which could ensure appropriate management.

Keywords: Cancer antigen-125 antigen, ovarian neoplasms, ultrasonography

Introduction

Ovarian cancer ranks third after the cervical and uterine cancers, exhibiting not only an unfavorable prognosis but also a high mortality rate.^[1,2] Despite its lower prevalence, ovarian cancer is three times more lethal than breast cancer.^[3] According to the GLOBOCAN, 295,414 ovarian cancer cases (3.4% of all cancer cases in women) were identified, and 184,799 deaths were reported (4.4% of all cancer-related mortality in women) in the year 2018. Although the incidence rate is higher, the trend of mortality rate is reversing.^[2] However, the mortality rate of ovarian cancer was reported to have increased in India and decreased in Europe and North America.^[2]

To structure a clear course of management, it is of vital importance to determine if the ovarian mass is benign or malignant. In the case of benign or operable tumors,

cytoreductive surgery plays an essential role as it determines the survival rate of the patient.^[4] However till date, preoperative determination of malignant conditions remains a challenge for gynecologists. Radiological investigations, tumor markers, and pelvic assessments have been proposed to determine malignancy. These parameters, when considered separately, pose inadequate specificity or sensitivity.^[5] Various tools have been introduced to determine the malignancy of tumors, which include factors such as age, menopausal status, ultrasound findings, enzymes, and tumor makers.^[6]

The risk of malignancy index (RMI) was one such tool that was found to be statistically effective in identifying benign and malignant ovarian masses. The tool was originally developed by Jacobs *et al.*, which is now termed as RMI 1.^[7] They assessed the age, ultrasound score (U - based on multilocularity, solid areas, bilaterality, ascites, metastatic features), menopausal status (M), and serum cancer

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antigen (CA)-125 level to determine the type of the tumor. A modified version of RMI 1, known as RMI 2 was proposed by Tingulstad *et al.* as the RMI 1 results were not reproducible in their test population. They modified the scoring pattern of U and M.^[8] In 1999, they modified their own version of RMI 2, known as RMI 3, by revising the scores for U and M.^[9] The cutoff values recommended for RMI 1, RMI 2, and RMI 3 is 200, which is universally accepted. Another modified version of RMI 2 was introduced as RMI 4 by including the tumor size, where a cut-off value of 450 is universally accepted.^[10]

The application of all four RMIs was reported to be favorable in distinguishing benign and malignant ovarian masses in some studies.^[11-13] But some studies have reported better performance from RMI 2 and RMI 4 alone.^[14-16] Owing to the difference in the performance of the RMI variants, identifying a universally common index would be helpful to ease the preoperative evaluation of ovarian masses.

For this reason, this study was aimed to assess the predictive values of all four RMIs to preoperatively differentiate the benign and malignant ovarian masses. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of all four RMI scores were calculated in accordance with the postoperative histopathological examination (HPE) reports. Furthermore, the scores of all four RMIs were compared to determine a decisive RMI for diagnosis.

Methodology

This hospital based cross-sectional study was conducted at a tertiary care center between January 2018 and June 2019. Approval from the institutional ethics committee and written informed consent from the patients participating in the study was acquired before conducting the study.

The sample size for our study was calculated based on the proportion formula as per previous literature.^[17] Considering the prevalence of ovarian cancer in India as 8.4%, with a confidence interval of 95% and the allowable error of 5%, the sample size calculated was 60. Women scheduled to undergo surgery for the ovarian masses were

included and those diagnosed with tubo-ovarian mass were excluded from the study.

A structured case history examination was carried out. Menopausal status, ultrasonogram findings and CA-125 and RMI scores were carried out preoperatively. HPE was conducted following the surgery, and this was compared with all 4 of the preoperative RMI scores.

The study parameters such as age, menopausal status, multilocularity, solid areas, bilaterality, ascites, metastases, and postoperative HPE report of the patients were measured qualitatively. The tumor size, CA-125 value, RMI 1, RMI 2, RMI 3, and RMI 4 scores of the patients were measured quantitatively/qualitatively.

The RMI 1, 2, and 3 scores were calculated using the formula $RMI = U \times M \times CA-125$. The score for RMI 4 was calculated using the formula $RMI = U \times M \times S \times CA-125$, where, U = ultrasound score (1 point was designated to features such as multilocularity, solid areas, bilaterality, ascites and metastases. When no ultrasound feature was noticed, a score of 0 was designated; the presence of a single feature was designated a U score of 1 and when ≥ 2 features were present, a U score of 3 was designated), M = Menopausal status of the patient, S = Tumor size and CA-125 value that was applied to the equation directly. The calculation of all 4 RMI scores is represented in Table 1.

The statistical analysis was performed using R v386 3.6.0 (R foundation, Vienna, Austria) Stata 14 (StataCorp LLC, Texas, USA) software's. The distribution of categorical variables such as age, menopausal status, and RMI were represented as numbers (%). Continuous variables such as age, menopausal status, and RMI were expressed as mean \pm standard deviation or median (interquartile range [IQR]) based on distribution. The comparison of different categorical parameters with the type of tumor was assessed using the Chi-square test. The mean/median difference of age, menopausal status, CA-125, and all four RMIs between the benign and malignant was compared using the Wilcoxon rank sum test. The receiver operating characteristic (ROC) was used to find out the ideal cutoff for RMIs. The sensitivity, specificity, PPV and the NPV

Table 1: Calculation formula for all 4 risk of malignancy indices variants

Features	RMI 1	RMI 2	RMI 3	RMI 4
Ultrasound (U)	Score of 0: U=0; Score of 1: U=1; Score of ≥ 2 : U=3	Score of 0/1: U=1; Score of ≥ 2 : U=4	Score of 0/1: U=1; Score of ≥ 2 : U=3	Score of 0/1: U=1; Score of ≥ 2 : U=4
Menopausal status (M)	Premenopausal: M=1 Postmenopausal: M=3	Premenopausal: M=1 Postmenopausal: M=4	Premenopausal: M=1 Postmenopausal: M=3	Premenopausal: M=1 Postmenopausal: M=4
CA-125 value	Direct application to the equation	Direct application to the equation	Direct application to the equation	Direct application to the equation
Tumor size (S)	-	-	-	<7 cm diameter, S=1 >7 cm diameter, S=2
Cut-off value	200	200	200	450

RMI: Risk of malignancy index, CA-125: Cancer antigen-125

along with the area under the curve (AUC) were calculated for all the four RMIs and comparatively analyzed. Significance was assessed at $P \leq 0.05$.

Results

As per the ultrasound findings, the presence of multi-locularity was observed in 54 (90%) patients, solid areas in 27 (45%), bilaterality in 6 (10%), and ascites in 19 (31.67%), but metastasis was not observed in any of them. However as per the postoperative HPE reports, 54 (90%) of the patients were diagnosed with benign and 6 (10%) with malignant ovarian masses. The histopathology reports of patients diagnosed with benign pathology were cases with the following presentations: simple cyst, seen in 14 (23.3%) patients, endometriosis in 9 (15%), dermoid cyst in 12 (20%), serous cystadenoma in 10 (16.7%), mucinous cystadenoma in 6 (10%), seromucinous cystadenoma in 2 (3.3%), and ovarian leiomyoma in 1 (1.7%) patient. Histopathology reports of patients diagnosed with malignant pathology were cases with diagnosis as the borderline serous tumor, serous cystadenocarcinoma, and malignant germ cell tumor; with 2 (3.3%) patients in each pathology.

The distribution of patients with respect to the main findings of this study is represented in Table 2. The mean age of patients in the study was 38.85 ± 13.15 years. The mean age group of patients diagnosed with benign tumor was 38.8 ± 12.7 and for malignant tumor was 39.5 ± 18.0 years. However, comparison of the mean age between the benign and malignant group of patients was insignificant ($P = 0.77$). About 48 (80%) patients were in the pre-menopausal stage and 12 (20%) in the postmenopausal stage, and the association of menopausal status and type of the ovarian mass was insignificant ($P = 0.58$). The association of CA-125 levels and type of the ovarian mass was significant ($P = 0.014$). The median (IQR, at 1st and 3rd quartile) of CA-125 of patients diagnosed with benign tumor was 17.6 (10.4–26.1) U/ml and with malignant tumor was 79.1 (30.5–247). This association was noted to be significant ($P = 0.004$). The association of tumor size and the type of ovarian mass was insignificant ($P = 1.0$).

The association of RMIs at the universally recommended cutoff values that distinguish between benign and malignant ovarian masses with the type of the tumors revealed that 48 patients with an RMI 1 score of <200 , 45 with an RMI 2 score of <200 , 48 patients with an RMI 3 score of <200 and 47 patients with an RMI 4 score of <450 had benign tumor, while 2 patients had malignant tumors at the respective RMI cutoff values in each of the indices. The sensitivity, specificity, PPV, and NPV were compared and are represented in Table 3.

The median (IQR) for both benign and malignant tumors was statistically significant, with a P value of 0.005 for RMI 1 and RMI 3. RMI 2 and RMI 4 showed a P value of 0.006 and 0.007, respectively [Table 4].

Table 2: Distribution of patients in the study

Variables	Number of patients (%)		P
	Benign (n=54)	Malignant (n=6)	
Age (years)			
<20	1 (1.85)	1 (16.67)	0.28
20-39	32 (59.25)	2 (33.33)	
40-59	16 (29.62)	2 (33.33)	
≥ 60	5 (9.25)	1 (16.67)	
Menopausal status			
Premenopausal	44 (81.5)	4 (66.7)	0.58
Postmenopausal	10 (18.5)	2 (33.3)	
Ultrasound score - RMI 1			
0	5 (9.25)	0	0.42
1	18 (33.33)	1 (16.67)	
2-5	31 (57.40)	5 (83.33)	
Ultrasound score - RMI 2, RMI 3, RMI 4			
0	0	0	0.38
1	23 (42.59)	1 (16.67)	
2-5	31 (57.40)	5 (83.33)	
CA-125 (U/ml)			
≥ 35	8 (14.81)	4 (66.7)	0.014*
≤ 35	46 (85.18)	2 (33.33)	
Tumor size (cm)			
< 7	8 (14.81)	1 (16.67)	1.0
≥ 7	46 (85.18)	5 (83.33)	

*Significant. RMI: Risk of malignancy index, CA-125: Cancer antigen-125

ROC curve was plotted for all the RMI scores obtained from the study [Figure 1], from which the suggested cut-off for RMI 1 was 380.314, RMI 2 was 549.2904, RMI 3 was 380.8428, and RMI 4 was 1172.208.

The association of RMIs at the suggested cutoff values with the type of the tumor exhibited by the patients revealed 54 patients with an RMI 1 score of <380.14 , 54 with an RMI 2 score of <549.2904 , 54 patients with an RMI 3 score of <380.8428 and 54 patients with an RMI 4 score of <1172.208 had a benign tumor, while 4 patients had malignant tumor at the respective RMI cutoff values. The sensitivity, specificity, PPV, NPV, and AUC for the suggested cutoff values were compared and are represented in Table 5.

Discussion

An Approximately 10% of women globally undergo exploratory surgery to evaluate ovarian masses during their lifetime. Accurate identification of the ovarian malignancy and its referral to a gynaeco-oncologist enhances the patient's survival rate. But a single yet thorough screening method that can detect ovarian malignancy accurately is not available.^[18,19] In this study, the utility of four RMI scores in predicting ovarian malignancies in rural regions with economic constraints was scrutinized.

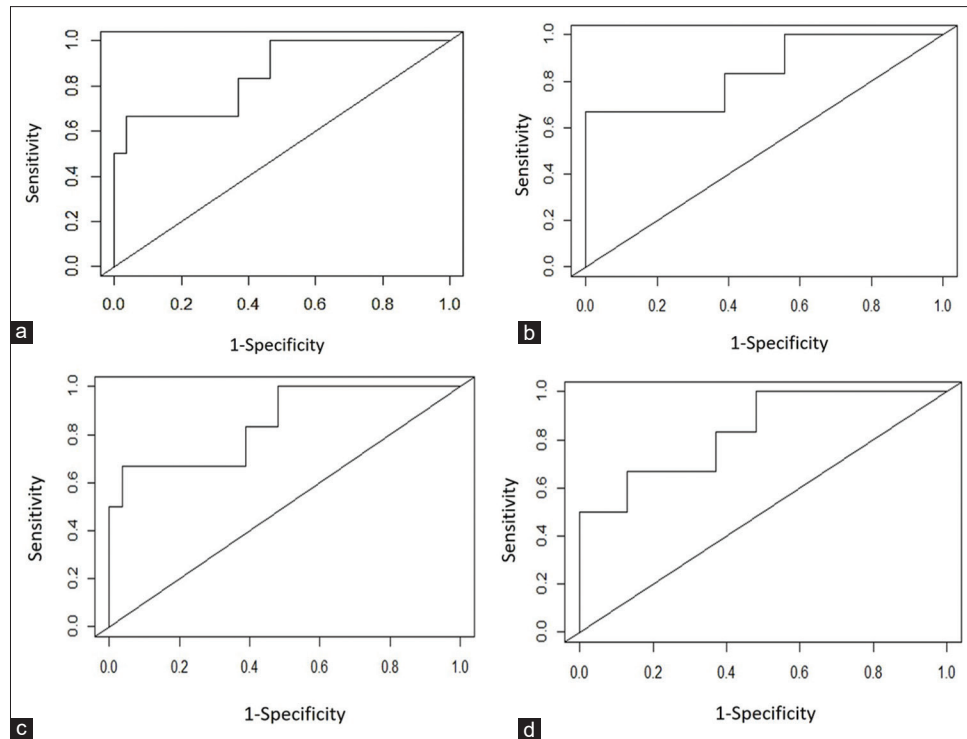


Figure 1: ROC curves of (a) RMI 1, (b) RMI 2, (c) RMI 3 and (d) RMI 4. ROC: Receiver operating characteristic, RMI: Risk of malignancy index

Table 3: Association of risk of malignancy indices with number of patients exhibiting the type of tumor along with comparing the efficacy of risk of malignancy indices at the universally recommended cut-off values

Score	Cut-off	Number of patients		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
		Benign	Malignant				
RMI 1	≥200	6	4	66.7	88.9	40.0	96.0
	<200	48	2				
RMI 2	≥200	9	4	66.7	83.3	30.8	95.7
	<200	45	2				
RMI 3	≥200	6	4	66.7	88.9	40.0	96.0
	<200	48	2				
RMI 4	≥450	7	4	66.7	87.0	36.3	95.9
	<450	47	2				

RMI: Risk of malignancy index, PPV: Positive predictive value, NPV: Negative predictive value

Table 4: Median (interquartile range) for risk of malignancy indices regarding the type of tumor

Score	Median (IQR, 1 st -3 rd quartile)		P
	Benign	Malignant	
RMI 1	40.5 (17.2-83.5)	287.3 (106-2050)	0.005*
RMI 2	54.0 (21.9-128)	434.9 (167-3606)	0.006*
RMI 3	42 (20.6-84.4)	287.3 (106-2050)	0.005*
RMI 4	77 (40.2-219)	642.2 (241-7191)	0.007*

*Significant. RMI: Risk of malignancy index, IQR: Interquartile range

Initially, the patients' menopausal status, ultrasound report (transabdominal sonogram and/or transvaginal sonogram), and the CA-125 levels were noted. The four RMI scores were calculated for all the patients, and the results were compared with postoperative HPE reports. As per the HPE report, 90% of patients were

diagnosed with benign and 10% with malignant ovarian masses. The comparison of the mean age between the benign (38.8 ± 12.7) and malignant (39.5 ± 18.0) was insignificant (P = 0.77). Similar observations were reported by Aktürk *et al.*^[11] Though some studies have reported a higher percentage of benign masses, the comparison of age between the two groups was noted to be significant.^[16,20,21] The difference in the menopausal distribution between the benign and malignant groups in this study was insignificant (P = 0.58). A few studies have contrasting reports in this aspect.^[16,21,22] The levels of CA-125 was noted to be below the cutoff point (≤35 U/ml) in a large number of patients, comparable to earlier studies.^[5,19,23] The median levels of CA-125 were significant (P = 0.014), which was also in concurrence with the earlier studies.^[5,20] However, the tumor size was

Table 5: Association of risk of malignancy indices with number of patients exhibiting the type of tumor along with comparing the efficacy of risk of malignancy indices at the suggested cut-off value from the study

Score	Cut-off	Number of patients		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC (95% CI)
		Benign	Malignant					
RMI 1	≥380.14	0	2	66.6	96.2	100.0	93.1	0.854 (0.659-1)
	<380.14	54	4					
RMI 2	≥549.2904	0	2	66.6	100.0	100.0	93.1	0.842 (0.64-1)
	<549.2904	54	4					
RMI 3	≥380.8428	0	2	66.6	96.2	100.0	93.1	0.848 (0.649-1)
	<380.8428	54	4					
RMI 4	≥1172.208	0	2	66.6	87.03	100.0	93.1	0.836 (0.636-1)
	<1172.208	54	4					

RMI: Risk of malignancy index, PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under curve, CI: Confidence interval

noted to be ≥ 7 in a majority of the patients, with similar observations reported earlier.^[21,22]

Majority of the patients diagnosed with benign tumors had RMI scores lesser than the universally recommended cutoff values. Statistical parameters at these cutoff values, such as sensitivity was 66.7%, specificity ranged from 83.3% to 88.9%, PPV from 30.8% to 40.0%, and NPV from 95.7% to 96%. Similar observations were reported earlier.^[11,19,22,24] The median values for the benign group ranged from 40.5 to 77 and that of the malignant group from 287.3 to 642.2 for all four RMIs. The association of RMI 1 and RMI 3 scores with the benign and malignant groups was significant ($P = 0.005$).

After plotting ROC curves as per the RMI scores obtained for the study, the cut-off values for RMI 1 was 380.314, RMI 2 was 549.2904, RMI 3 was 380.8428 and RMI 4 was 1172.208. The statistical parameters such as sensitivity were 66.6%, specificity ranged from 87.03% to 100.0%, PPV was 100.0% and NPV was 93.1%, which was higher than the universally recommended values mentioned earlier. The AUC ranged from 0.836 to 0.854, comparable to that reported earlier.^[16,22,25] Overall, 54 patients diagnosed with benign and 4 with malignant tumor had lower suggested cutoff values, whereas only two patients with malignant tumor had higher suggested cutoff values. All four RMIs had similar performance in predicting benign and malignant ovarian tumors; however, in the study, the suggested cut-off values showed better diagnosis.

Hada *et al.* employed Human Epididymis Protein 4 (HE4) and the risk of malignancy algorithm along with RMIs in differentiating the adnexal mass into benign and malignant.^[24] However, they reported that none of the tests were significantly better than the other in differentiating adnexal masses. Similarly, Mulder *et al.* reported that the International Ovarian Tumor Analysis Simple Rules and RMI (cutoff ≥ 200) diagnostic tests were not discriminative enough with respect to benign and malignant ovarian tumors.^[26] This is suggestive of an alternative diagnostic model for better accuracy and consistency in the future.

With the increase in the incidences of gynecologic malignancies, it is imperative to diagnose it an earlier

stage, which could result in better prognosis and survival.^[15] The major diagnostic tools for the preoperative assessment of ovarian masses are clinical impression and examination by ultrasound. However, there are still chances of misdiagnosis because many times, the gynecologists/surgeons detect unexpected malignancy intraoperatively. Therefore, the application of a scoring system can improve the chances of preoperative counseling and management.^[27] The study attempted to accurately assess the status of the ovarian mass and to reduce any unnecessary referrals for the low-risk patients to approach the gynecologist. Since RMIs are multiparametric, they have been used as an objective tool and has been widely accepted for the same purpose globally during the past decade, especially in low-resource settings.

The limitation of this study was the smaller sample size because of which age and menopausal distribution were insignificant. The ultrasound parameters were not assessed by a single examiner, which lead to inter-observer discrepancies. Since RMI is more reliable for epithelial ovarian tumors, the efficacy of RMI in the case of nonepithelial malignant ovarian tumors is questionable, as this study includes two cases of malignant germ II tumors. In this study, relatively a smaller number of postmenopausal women were included since the malignant epithelial ovarian tumors are more common in them. The inclusion of more postmenopausal women would increase the efficacy of RMI in detecting malignancy. The small sample size could be one of the reasons which contributed to better diagnostic results in comparison to the universally recommended values. To overcome these limitations, more research in this path is recommended.

Conclusion

RMI uses simple clinical and ultrasound parameters that can be practiced in most gynecologic clinics for identifying patients with high risk for malignant ovarian tumors. In the study, the universally recommended cutoff values of 200 (RMI 1, 2, and 3) and 450 (RMI 4) was shown to discriminate benign and malignant ovarian masses in majority of the patients. The suggested cutoff values from

this study showed good sensitivity, specificity, PPV, and NPV. Hence, RMIs are decisive tools that may be suitable in developing countries.

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Conflicts of interest

There are no conflicts of interest.

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