Original Article

Comparing Four Different Risk Malignancy Indices in Differentiating Benign and Malignant Ovarian Masses

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Abstract

Background: Accurate prediction of ovarian masses preoperatively is crucial for optimal management of ovarian cancers. **Objective:** The objective of this study was to identify the risk of malignancy index (RMI) incorporating menopausal status, serum carbohydrate antigen 125 levels, and imaging findings for presurgical differentiation of benign from malignant ovarian masses and to evaluate the diagnostic ability of four different RMIs. **Materials and Methods:** Women presenting with ovarian masses from August 2018 to January 2020 were evaluated preoperatively with detailed history, examination, imaging, and tumor markers. RMI 1–4 was calculated for all patients. Evaluation of the diagnostic utility of four different RMIs for preoperative identification of malignancy was based on the increment of the area under the receiver operating characteristic curve. Histopathological diagnosis was used as the gold standard test. **Results:** One hundred and twenty-one patients fulfilling the eligibility criteria were enrolled in this study. Benign tumors constituted 61 (50.4%) out of 121 cases, followed by malignant tumors and borderline tumors constituting 49 (40.49%) cases and 11 (9.09%) cases, respectively. The sensitivity of RMIs 1, 2, 3, and 4 was 77.0%, 63%, 77.0%, and 77.0%, respectively, and the specificity was 84%, 86%, 77%, and 71%, respectively. The RMI 2 had higher specificity at predicting malignancy than other RMIs while diagnostic accuracy was highest in RMI 1. **Conclusion:** The RMI method is a simple and cost-effective technique in preoperative differentiation of ovarian masses.

Keywords: *Adnexal masses, ovarian masses, risk of malignancy index*

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Introduction

Ovarian cancer is the third most common cancer in females.[1] Ovary is subjected to monthly ovulatory insults with subsequent rupture and repair making them susceptible to tumorigenesis. Based on tissue of origin, ovarian tumors can be surface epithelial (65%), germ cell (15%), sex cord stromal (10%), metastasis (5%), or miscellaneous (5%).[2] The frequency of ovarian masses to be malignant is almost 30% and 7% in postmenopausal and premenopausal women, respectively.[3]

Ovarian cancer is a silent killer in true sense as the presenting features are mostly nonspecific gastrointestinal symptoms, resulting in late diagnosis and poor survival. The overall 5-year survival rate is only 46%.[4] The nonspecific clinical presentation with varied morphological spectrum results in diagnostic dilemma and thus histopathological evaluation serves a major role in diagnostic and therapeutic intervention.[5]

Absence of any screening test and late presentation associated with malignant ovarian masses is a matter of concern. There is an utmost need to correctly characterize these masses preoperatively for better management. If detected early, the 5-year survival reaches up to 90%.[6] Ultrasound remains the most

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common imaging modality done preoperatively for characterizing adnexal masses. The Simple Rules given by the International Ovarian Tumor Analysis (IOTA) in 2008 classifies adnexal masses as benign, malignant, and inconclusive based on ten ultrasound findings.[7] IOTA ADNEX Model developed in 2014 characterizes adnexal masses into benign, borderline, Stage I, Stage II–IV, and metastatic in nature based on three clinical and six ultrasound variables.[8] Ovarian Adnexal Report Data System (O-RADS) given by the American College of Radiology in 2020 characterizes adnexal masses with 0% risk of malignancy in O-RADS 1 to more than 50% malignancy risk in O-RADS 5.[9]

Certain serum biomarkers done preoperatively predict ovarian malignancy. With a cutoff value as 35 U/ml when suspecting malignancy, the carbohydrate antigen (CA) 125 is a commonly utilized biomarker in evaluating ovarian tumors.[10] However, in the early stages of ovarian cancer (elevated in 23%–50% of Stage I patients), this is not highly sensitive.[11] Studies have demonstrated that the human epididymis protein 4 (HE4), a relatively new biomarker, has better efficacy in characterization of ovarian cancer compared to CA-125, but cost is still a significant barrier to its use.[12,13] Models combing biomarkers with imaging findings are also available to preoperatively predict ovarian malignancy. Risk of ovarian malignancy algorithm (ROMA) combines serum CA-125 level with serum HE4 level and menopausal status.[14] The menopausal status, ultrasonography, and serum CA-125 concentrations multiplied together calculates the risk of malignancy index (RMI). Till now, we have four versions of RMI, with RMI 1 and 2 being the commonly used ones.

This study sought to compare the diagnostic value of four RMI score.

Materials and Methods

In this prospective observational study, women with ovarian tumors scheduled for surgery at our institution between August 2018 and January 2020 provided clinical data. The institutional ethics committee gave its approval to the project. We enrolled all women with ovarian masses planned for surgery and excluded those having nonneoplastic ovarian lesions like simple ovarian cyst not planned for surgery, tubo-ovarian masses, and endometriomas. Informed consent was taken from all included subjects. Baseline demographic details were recorded. The presurgical value of serum CA 125, imaging finding were noted. For identifying ovarian masses, every patient had to undergo a pelvic ultrasound, computed tomography, or magnetic resonance imaging. Operative details along with gross appearance of the mass were noted. The sample obtained from surgery was sent for histopathological examination.

Risk of malignancy index calculation

RMI was calculated based on formula: RMI = U × M × CA-125. Five features were used to calculate the ultrasound score (U). Multilocular tumor, bilateral tumor, solid components in the tumor, metastases, and ascites all received one point each. Each patient's tumor size was assessed using ultrasonography. The absolute value of CA-125 was noted. Currently, there are four RMI. RMI 1–3 takes into account ultrasound score (U), menopausal status (M), and CA 125 values. RMI-4 also includes size of the tumour along with other three parameters.[15-18]

Statistical analysis

All the above collected details were noted on a structured pro forma and entered into MS Excel datasheet. The qualitative data were analyzed as proportions and percentages and expressed in tabular form. The quantitative data were analyzed as mean and standard deviation. Based on increment in area under the receiver operating characteristic curve (AuROC), four distinct RMIs were evaluated for their diagnostic value taking histology as the gold standard.

Results

During the study period, surgery was performed on 121 patients who had ovarian masses. Surface epithelial tumors were the most prevalent histological type (n = 81, 66.9%), followed by germ cell tumors (n = 30, 24.8%). There was one case each of metastatic Krukenberg tumor, malignant round cell tumor, malignant mesenchymal tumor, and carcinoid tumor [Figure 1].

Table 1 shows the baseline variables of study participants based on different histological types. The mean age

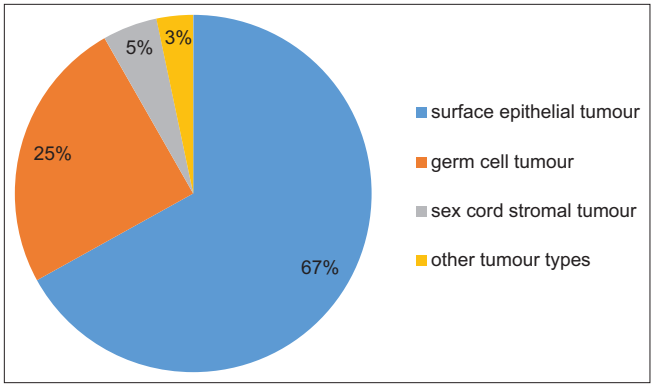

Figure 1: Histological types seen in the study cohort

Table 1: Baseline characteristics of study population based on different histological types

Parameter	Surface epithelial tumor (*n*=81)	Sex cord stromal tumor (*n*=6)	Germ cell tumor (*n*=30)	Other tumor types (*n*=4)
Age (mean±SD)	43.62±14.19	48.50±10.82	31.57±11.30	28.25±11.09
Parity*				
Nullipara	13 (16.0)	0	14 (46.7)	2 (50)
P1	3 (3.7)	1 (16.7)	2 (6.7)	0
P2	21 (25.9)	2 (33.3)	5 (16.7)	1 (25)
P3	20 (24.7)	2 (33.3)	7 (23.3)	0
≥ P4	24 (29.6)	1 (16.7)	2 (6.7)	1 (25)
Mean duration of symptoms (mean±SD)	8.02±10.15	6.83±8.45	5.47±7.08	5.25±4.99
Menopausal status*				
Premenopausal	54 (66.7)	2 (33.3)	25 (83.3)	4 (100)
Postmenopausal	27 (33.3)	4 (66.7)	5 (16.7)	0

*Represented as *n* (%). BMI: Body mass index, SD: Standard deviation

of occurrence of surface epithelial tumors, germ cell tumors, and sex cord stromal tumors in our study was 43.62 ± 14.19, 31.57 ± 11.30, and 48.5 ± 10.82 years, respectively. The mean duration of presentation of symptoms was lowest in germ cell tumors and highest in surface epithelial cell tumors. 70.2% of patients were premenopausal, and 29.8% of patients were postmenopausal.

In Table 2, benign tumors made up most of the cases of ovarian neoplasm constituting 61 out of 121 cases (50.4%), followed by malignant tumors and borderline tumors constituting 49 cases (40.49%) and 11 cases (9.09%), respectively.

The AuROC for RMI 1–4 was 0.874, 0.788, 0.812, and 0.823 respectively. The AuROC for RMI 1 in predicting malignant ovarian masses was 0.874 (95% confidence interval: 0.809–0.939), showing good diagnostic performance. It was statistically significant ($P < 0.001$). With a sensitivity of 77% and a specificity of 84%, RMI 1 predicts malignancy at cutoff ≥112. At a cutoff of RMI 2 ≥218.8, it predicts malignant ovarian masses with a sensitivity and specificity of 63% and 86%, respectively. RMI 3 ≥112 predicts malignancy with a sensitivity and specificity of 77% each. At a cutoff of RMI 4 ≥224, it predicts malignancy with a sensitivity of 77% and a specificity of 79%. RMI 1 had significantly better diagnostic performance (81%) as compared to other three RMIs. RMI 2 had better specificity as compared to other RMIs [Table 3 and Figure 2].

Discussion

Triage of adnexal masses presenting in terms of benign and malignant etiologies is crucial for optimal management of ovarian cancers. Characterization of these masses not only helps determine the need for higher center referrals but also guides in the management resulting significant impact on overall prognosis. Absence of any screening test and late presentation associated with malignant masses is a matter of concern. However, there remains a lack of universally accepted screening methodology. Jacobs *et al*. originally developed the RMI and presently we have four versions.[15] With this study, we planned to evaluate the diagnostic utility of four different RMIs in presurgical characterization of ovarian masses and found that all were able to differentiate between benign and malignant masses.

In our analysis of 121 ovarian masses, benign tumors made up most of the cases constituting 61 out of 121 cases (50.4%), followed by malignant tumors and borderline tumors constituting 49 cases (40.49%) and 11 cases (9.09%), respectively. In terms of histopathological pattern, surface epithelial tumors were the most common variety (n = 81, 66.9%).

Narang *et al*. in their analysis of 158 ovarian masses found benign (62.65%), borderline (3.79%), and malignant (33.55%) masses. Similar to our findings, they discovered that surface epithelial tumors made up 74.06% followed by germ cell tumors (15.82). The prevalence of teratoma was 11.40% in their study.[19] Similar findings were made by Agrawal *et al*.[20] in their investigation of 226 patients, which revealed that surface epithelial tumors accounted for 163 cases (72.1%) of ovarian cancers, with germ cell tumors accounting for 45 cases (19.9%).

In this study, we compared the diagnostic performance of four RMIs for presurgical differentiation of ovarian tumors. Yamamoto *et al*. in their evaluation of 296 pelvic masses discovered that RMIs 1, 2, 3, and 4 were, respectively, 73.0%, 81.1%, 73.0%, and 77.0% sensitive. RMIs 1, 2, 3, and 4 were, respectively, 93.7%, 89.6%, 93.7%, and 92.3% specific for identifying malignant ovarian masses.[18] In our study, the specificity of RMIs 1, 2, 3, and 4 was 84%, 86%, 77%, and 79%,

respectively, which were lower as seen by Yamamoto *et al.*[18] In our study, RMI 1 had significantly better diagnostic performance (81%) as compared to other three RMIs. RMI 2 had better specificity as compared to other RMIs. In contrast to our findings, no statistically significant differences between the capacities of four different RMIs to identify malignancy were found by Aktürk *et al.*[21]

RMIs when compared to other models have different results. In a recent systematic review and meta-analysis involving 2662 women, the authors reported similar diagnostic accuracy for both RMI-1 and ROMA, but for premenopausal women, RMI-I showed better specificity compared to ROMA (89% vs. 78%, $P = 0.022$).[22] Another study involving 168 women with ovarian masses found RMI to be better than IOTA Simple Rules with higher specificity (90.7% vs. 68.6%), but the authors concluded that both these models were

Table 2: Distribution of the participants in terms of type of tumor (n=121)

Type of tumor	Frequency (%)
Benign	61 (50.4)
Borderline	11 (9.1)
Malignant	49 (40.5)
Total	121 (100.0)

Table 3: Comparison of diagnostic performance of different risk of malignancy index in predicting malignant versus benign/borderline ovarian masses

Predictor	Cutoff	AUROC	95% CI	Sn (%)	Sp (%)	PPV (%)	NPV (%)	DA (%)
RMI 1	112	0.874	0.809–0.939	77	84	77	84	81
RMI 2	218.8	0.788	0.696–0.88	63	86	76	78	77
RMI 3	112	0.812	0.725–0.899	77	77	69	83	77
RMI 4	224	0.823	0.741–0.905	77	79	71	84	78

RMI: Risk of malignancy index, AUROC: Area under receiver operating characteristic curve, CI: Confidence interval, Sn: Sensitivity, Sp: Specificity, PPV: Positive predictive value, NPV: Negative predictive value, DA: Diagnostic accuracy

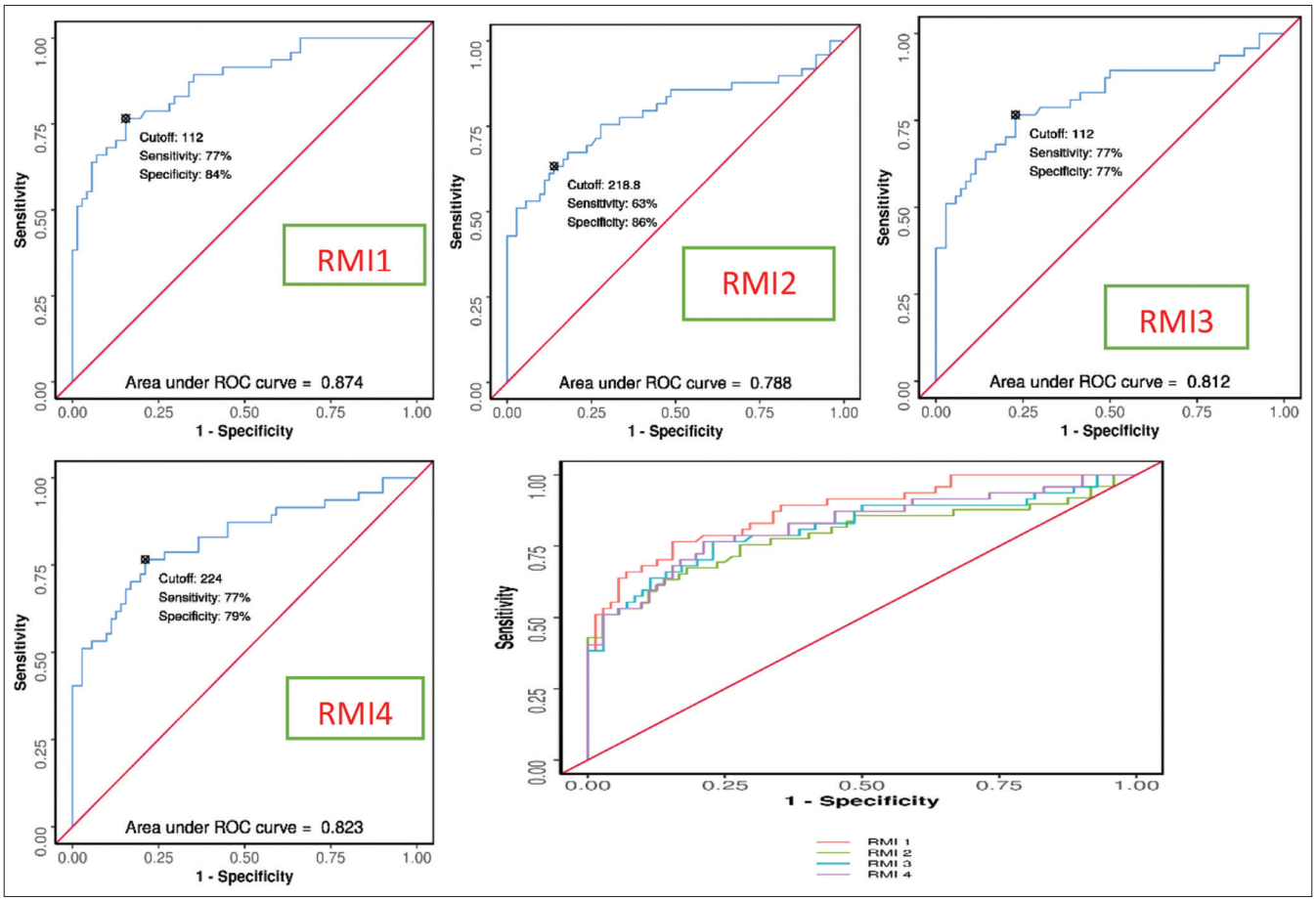

Figure 2: Receiver operator characteristic curve showing diagnostic performance of risk of malignancy index 1–4 in predicting malignant versus benign/borderline tumor. RMI: Risk of malignancy index, ROC: Receiver operating characteristic

not much discriminatory owing to low sensitivity of RMI and high chances of inconclusive results by IOTA Simple Rules.[23] In a recent Cochrane database systematic review involving 59 studies, ADNEX model with posttest probability 10% had higher sensitivity of 97.6%, compared to 78.4% for RMI in postmenopausal women.[24] In another diagnostic study comparing IOTA ADEX, O-RADS, and RMI-2, the authors reported both IOTA ADEX and O-RADS to be better compared to RMI-2.[25]

Strengths and limitations

Although this study compared all four RMIs in detecting malignant masses, we did not analyze them based on the menopausal status, which could further enhance the diagnostic utility of these easily applicable cost-effective tools. Second, the small sample size is a major limitation of this study.

Conclusion

RMI method can serve as a simple and cost-effective screening tool, particularly in less-specialized gynecology clinics facilitating early referral to an oncological unit, thereby improving patient outcome.

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Conflicts of interest

There are no conflicts of interest.

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