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Original Research Article

Risk of malignancy index 4 in preoperative evaluation of patients with ovarian tumours

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ABSTRACT

Background: Ovarian tumors usually presents as adnexal masses which may be benign or malignant. Accurate and timely diagnosis of an adnexal mass is a challenge for the gynecologists. Currently clinical examination, ultrasonographic assessment and ovarian tumour markers (CA 125, beta hCG, AFP, LDH) are routinely done at our centre to evaluate patients with ovarian tumours. The study was designed to evaluate the ability of RMI 4 to discriminate benign ovarian tumor from malignant ovarian tumor in patients attending Department of Obstetrics and Gynaecology, S.M.S. Medical College, Jaipur.

Methods: 200 patients diagnosed to have ovarian tumours were included in the study after obtaining written consent. Ultrasonographic characteristic, menopausal status and serum CA 125 levels were documented preoperatively. Risk of malignancy index 4 was calculated and correlated with histopathological diagnosis.

Results: At a cut-off point of 450, RMI 4 had a sensitivity of 67.5% (95% CI: 50.87-81.43%), specificity of 98.75% (95.56-99.85%), positive likelihood ratio of 54, negative likelihood ratio of 0.33, a positive predictive value of 93.1%, negative predictive value of 92.4% and diagnostic accuracy of 92.5%.

Conclusions: RMI 4 is a simple, cost effective, reliable scoring system that is easily applicable method in primary evaluation of patients with ovarian tumours with a sensitivity of 67.5% and specificity of 98.75%.

Keywords: CA 125, Malignancy, Ovarian tumour, Risk of malignancy index, Ultrasonography

INTRODUCTION

Ovarian malignancy is third most common cancer in females after cervical and breast carcinoma and unfortunately it remains clinically silent until advance stage of disease leading to higher mortality rate.^{1,2} Up to 60% ovarian tumours in postmenopausal women are malignant as compared to 24% ovarian tumours in premenopausal women.³⁻⁵

Ovarian tumors usually presents as adnexal masses which may be benign or malignant. Accurate and timely diagnosis of an adnexal mass is a challenge for the

gynecologists, because the type of surgical procedure and the experience of the surgeon are important for the prognosis of ovarian carcinoma. Apart from clinical evaluation, ultrasonography, tumour markers and radiological investigations have been proposed to evaluate ovarian tumours. Unfortunately, none of these methods has shown significantly better performance in discriminating malignant tumors from benign tumors. Risk of malignancy index is a mathematical formula which incorporates menopausal status, serum level of CA125 and ultrasonographic score. RMI was first developed by Jacob et al, in 1990 to discriminate between malignant and benign ovarian tumours.⁶ Using an RMI cut-off level of 200, they observed sensitivity to be 85%

and the specificity 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. Tingulstand et al, in 1996 developed RMI 2 and in 1999 developed RMI 3 to discriminate between malignant and benign pelvic masses.^{7,8} In 2009 Yamamoto et al, developed RMI 4 by adding tumour size in previous criteria and found that the accuracy of the RMI 4 with a cut off level >450 was better than RMI 1 (P=0.0013), RMI 2 (P=0.0009) and RMI 3 (P=0.0013).⁹

Currently clinical examination, ultrasonographic assessment and ovarian tumour markers (CA 125, beta hCG, AFP, LDH) are routinely done at our centre to evaluate patients with ovarian tumours. The study was designed to evaluate the ability of RMI 4 to discriminate benign ovarian tumor from malignant ovarian tumor in patients attending Department of Obstetrics and Gynaecology, S.M.S. Medical College, Jaipur.

METHODS

200 patients diagnosed to have ovarian tumours were included in the study. All patients were informed about the nature of the study and a written informed consent was obtained prior to enrollment in the study. Clearance from ethical committee was also taken. Patients who had advanced ovarian malignancies, secondary ovarian malignancies, history of unilateral oophorectomy were excluded from the study. A detailed history was obtained from all patients. A complete general physical, systemic and gynecological examination was performed. All patients were evaluated by transabdominal or transvaginal ultrasound by ultrasound machine Prosound ALOKA ALFA 6 using abdominal (3.75MHz) and vaginal probes (7.5MHz). On ultrasonographic examination, findings of ovary particularly multilocularity, solidity, bilaterality, ascites and presence of metastasis were noted. 1 point was given to each criteria. USG score was assigned as U = 1 if 0 or 1 criteria fulfilled and U=4 if 2 or more criteria are fulfilled.

Size of ovarian tumour was also measured. Score 1 was given for tumour less than 7cm and score 2 for tumour more than 7 cm in size.

For estimation of serum CA 125 levels, 5ml of venous blood was collected and assayed by MEIA (micro particle enzyme immunoassay) technique for quantitative measurement. The optimal cut off value of serum CA 125 was 35U/ml.

Postmenopausal status is defined as amenorrhea of more than one year or age older than 50 years in women who had a hysterectomy. Women who did not meet these criteria were classified as premenopausal. Menopausal score was assigned as M=1 for premenopausal and M=4 if postmenopausal.

Risk of malignancy index 4 was calculated as a product of $U \times M \times S$ (size in centimeters) \times S. CA-125. A cutoff value of 450 was used to differentiate between benign and malignant ovarian tumours.

All women underwent laparotomy/staging laparotomy after PAC clearance. Surgically removed specimens were sent for histopathological examination. Risk of malignancy index 4 was correlated with histopathological diagnosis considered as gold standard.

Statistical analysis was done by standard statistical methods and a p value <0.05 was considered significant. Performance of RMI 4 was analyzed in the form of sensitivity, specificity, positive predictive value, negative predictive value and diagnostic ability.

RESULTS

Out of 200 patients, 160 patients (80%) had benign and 40 (20%) had malignant ovarian tumour. Disease prevalence in our study was 20%. The distribution of patients by age, menopausal status, ultrasound score, tumour size score and serum Ca-125 level is shown in Table 1.

Table 1: Distribution of patients by age, menopausal status, serum CA125 levels, ultrasound score and tumour size score.

Variables	Benign (n = 160)		Malignant (n = 40)		p value
	No.	%	No.	%	
Age (years)					
<30	88	55	8	20	0.00007
>30	72	45	32	80	significant
Menopausal status					
Premenopausal	135	84.4	24	60	0.0006
Postmenopausal	25	15.6	16	40	significant
USG Score					
1	151	94.4	8	20	0.0000
4	9	5.6	32	80	significant
Serum CA 125(U/ml)					
<35	144	90	10	25	0.000
>35	16	10	30	75	significant
Tumour Size score					
1	83	51.9	12	30	0.01
2	77	48.1	28	70	significant

80% patients with malignant tumours were above 30 years of age in contrast to 45 % patients with benign tumours. The association of patient's age with disease status was statistically significant (p 0.00007). 40% patients with malignant ovarian tumours were postmenopausal as compared to 15.6% patients with benign ovarian tumour and the difference was statistically significant (p .0006). The association between ultrasound score and disease status and tumour size score and disease status was statistically significant at a p value of

0.0000 and .01 respectively. 75 % patients with malignant ovarian tumours had a CA 125 level >35U/ml as compare to 10% patients with benign tumours. The difference in the level of CA 125 in benign and malignant ovarian tumours was statistically significant (p - 0.000).

Performance of RMI 4 is shown in Table 2. Out of 29 patients having RMI 4 of >450, 27 (93.1%) had malignant tumour and 6.9% had benign tumour. 171 patients had RMI 4 score <450, of which 158 (92.4%) had benign tumour and 7.65 had malignant tumour. 40

patient had malignant ovarian tumours on histopathological examination, out of which 27 were malignant by RMI 4 (True positive). 160 ovarian tumours were benign on histopathological examination, out of which 158 were benign by RMI 4 (True negative). At a cut-off point of 450, RMI 4 had a sensitivity of 67.5% (95% CI: 50.87-81.43%), specificity of 98.75% (95.56-99.85%), positive likelihood ratio of 54, negative likelihood ratio of 0.33, a positive predictive value of 93.1%, negative predictive value of 92.4% and diagnostic accuracy of 92.5% (Table 3).

Table 2: Analysis of performance of risk of malignant index 4.

		Benign on HPR		Malignant on HPR		Total		p value
		No	%	No	%	No	%	
RMI 4	Benign (<450)	158 (TN)	98.8	13 (FN)	32.5	171	85.5	X ² -72.84 p-<.00001
	Malignant (>450)	2 (FP)	1.2	27 (TP)	67.5	29	14.5	
	Total	160		40		200		

Table 3: Evaluation of RMI 4.

Statistic	Formula	Value	95% CI
Disease Prevalence	TP+FN/TP+FP+FN+TN	20%	14.69-26.22%
Sensitivity	TP/TP+FN	67.5%	50.87-81.43%
Specificity	TN/TN+FP	98.75%	95.56-99.85%
Positive likelihood Ratio	Sensitivity/1-Specificity	54.0	13.40-217.65
Negative likelihood Ratio	1-Sensitivity/Specificity	0.33	0.21-0.51
PPV	TP/TP+FP	93.1%	77.01-98.2%
NPV	TN/FN+TN	92.4%	88.6-95%
Accuracy	TP+TN/TP+FP+FN+TN	92.5%	87.93-95.74%

Table 4: Performance of RMI 4, menopausal status, USG score, tumour size score and serum CA 125 levels.

Variables	RMI	Menopausal status	USG score	Tumour size score	S. CA 125
Sensitivity (95% CI)	67.5 (50.87-81.43)	40 (24.86-56.67)	80 (64.35-90.95)	70 (53.4-83.44)	75 (58.80-87.31)
Specificity (95% CI)	98.7 (95.56-99.85)	84.3 (77.80- 89.63)	94.38 (89.59-97.40)	51.88 (43.85-59.83)	90 (84.27-94.18)
Positive likelihood ratio (95% CI)	54.0 (13.40-217.65)	2.56 (1.52 to 4.32)	14.22 (7.40-27.33)	1.45 (1.12-1.88)	7.50 (4.56-12.34)
Negative likelihood Ratio (95% CI)	0.33 (0.21-0.51)	0.71 (0.55 to 0.92)	0.21 (0.11-0.39)	0.58 (0.35-0.95)	0.28 (0.16-0.48)
PPV (95% CI)	93.1 (77.01-98.2)	39.02 (27.50-51.92)	78.05 (64.91-87.23)	26.67 (21.92-32.02)	65.2 (53.26-75.52)
NPV (95% CI)	92.4 (88.6-95)	84.91 (81.24-87.96)	94.97 (91.03-97.23)	87.37 (80.81-91.91)	93.5 (89.36-96.11)
Diagnostic accuracy (95% CI)	92.5 (87.93-95.74)	75.5 (68.94-81.29)	91.5 (86.74-94.97)	55.5 (48.32-62.51)	87 (81.53-91.33)

Table 4 compares performance of RMI with menopausal status, USG score, tumour size score and S CA 125 level used individually to discriminate benign and malignant ovarian tumours. RMI at a cutoff point of 450 had a sensitivity of 67.5%, specificity of 98.75%, positive likelihood ratio of 54, negative likelihood ratio of 0.33, a

positive predictive value of 93.1%, negative predictive value of 92.4% and diagnostic accuracy of 92.5%. Menopausal status had a sensitivity of 40%, specificity of 84.3%, positive likelihood ratio of 2.56, negative likelihood ratio of 0.71, a positive predictive value of 39.02%, negative predictive value of 84.91% and

diagnostic accuracy of 75.5%. Ultra sound score had a sensitivity of 80%, specificity of 94.38%, positive likelihood ratio of 14.22, negative likelihood ratio of 0.21, a positive predictive value of 78.05%, negative predictive value of 94.97% and diagnostic accuracy of 91.5%. Tumour size score had a sensitivity of 70%, specificity of 51.88%, positive likelihood ratio of 1.45, negative likelihood ratio of 0.58, a positive predictive value of 26.67%, negative predictive value of 87.37% and diagnostic accuracy of 55.5%. Serum CA 125 level had a sensitivity of 75%, specificity of 90%, positive likelihood ratio of 7.5, negative likelihood ratio of 0.28, a positive predictive value of 65.2%, negative predictive value of 93.5% and diagnostic accuracy of 87% (Table 4).

DISCUSSION

The present study was done to evaluate RMI 4 in discriminating benign from malignant ovarian tumours. 200 patients with ovarian tumours were recruited out of them 40 (20%) patients were diagnosed to have malignant tumours.

Occurrence of malignant ovarian tumours was lower (20%) in our study than that (35%) observed by G O Abdulrahman Jr et al, in their study and higher than that (15%) observed by Abdel Baset F. Mohammed et al.^{10,11}

Mean age of patients with benign tumour (33.93±13.67 yrs) was lower than that for malignant ovarian tumour (44.07±14.17 yrs). Our results were consistent with that observed by Ashrafangooei T et al, Dora et al 2017.^{12,13} The association of patient's age with disease status was statistically significant (p 0.00007).

There was highly significant difference among benign and malignant ovarian tumours regarding menopausal status of the patients (p -0.0006) with 40% women with malignant tumours were post-menopausal as compared to 15.6% women with benign tumours. Our results were similar to that observed by Radhamani and Akhila, who in their study observed that majority of the tumours belonged to postmenopausal group, Dora et al who observed that among the postmenopausal patients, 81.6% had malignant disease as compared to premenopausal women and Arun-Muthuvel V who observed that 61% of the ovarian tumours in postmenopausal women were malignant.¹³⁻¹⁵

High false positive rates was observed for ultrasound (5.6%), tumour size score (48.1%) and CA 125 levels (10%) when used individually as compared to low false positive rate (1.2%) observed with RMI 4. In our study, at a cut-off point of 450, RMI 4 had a sensitivity as 67.5%, specificity as 98.75%, PPV as 93.1%, NPV as 92.4% and diagnostic accuracy of 92.5%. Our results were comparable with various studies done in the past. Yamamoto et al, developed RMI 4 by using tumor size along with other parameters.⁹ They observed that at a cut-

off level of 450 the sensitivity, specificity, positive predictive value, negative predictive value and accuracy were respectively, 86.8%, 91.0%, 63.5%, 97.5%, and 90.4%. Aktürk E et al, in their study reported that RMI 4 has a sensitivity, specificity, PPV, NPV and diagnostic accuracy as 84%, 87%, 60%, 95% and 86% respectively.¹⁶ Jung-Woo Park et al, observed that for RMI 4, sensitivity, specificity, PPV, NPV and diagnostic accuracy was 75.2%, 87.5%, 61.2%, 93.1% and 85% respectively.¹⁷

Mohammed ABF et al, in their study stated that RMI 4 has a sensitivity, specificity.¹¹ PPV, NPV and diagnostic accuracy as 76.9%, 93.8%, 71.4%, 95.3% and 91% respectively.

The prevalence of ovarian neoplasm has been rising during last decades. Silent occurrence, slow progression, makes its mortality rate the highest among gynecological malignancies. There is no universal screening method for discriminating between benign and malignant ovarian tumours yet. So many authors have tried for earliest diagnosis of malignant ovarian tumours by various parameters. These may be earliest clinical features, tumour markers, imaging studies, cytology but no one yet is a definite method for screening of cancer ovary. The present study demonstrated that in the absence of a definite biomarker, the multi parametric risk of malignancy index, RMI 4 is better tool in discriminating benign and malignant tumours. The sensitivity of RMI 4 was 67.5% and specificity of 98.75%.

CONCLUSION

In conclusion, the RMI 4 is a simple, cost effective, reliable scoring system that is easily applicable method in primary evaluation of patients with ovarian tumours in daily clinical practice by all gynecologists. Use of RMI 4 in discriminating between benign and malignant ovarian tumour will help in timely referral of patient to specialized oncologist/gynecologists for effective surgical intervention/ management.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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