Original Research Article

Study of validity of risk of malignancy index in perimenopausal women with ovarian mass in a tertiary care hospital in India

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ABSTRACT

Background: Ovarian carcinoma is a silent killer because it presents in advanced stage. In India, it ranks third after carcinoma cervix and breast. Incidence of ovarian cancer is 5.4-8.0 per 100,000 in India. Various versions of risk of malignancy index have been studied to show its validity in different settings. We have studied third version of risk of malignancy index in a resource poor setting in India.
Methods: In this prospective observational study 74 perimenopausal and postmenopausal women with ovarian mass were recruited. Menopausal score (M), Ultrasonography score (U) and CA-125 are components of Risk of Malignancy Index 3. Patients underwent preoperative ultrasonography and CA-125 level was assessed. Scores of M 1-3, U 1-3 and absolute value of CA-125 was multiplied. This product was value of Risk of Malignancy Index 3. If it is less than 250 it suggests absence of malignancy and more than 250 strongly suggests malignancy. Results were confirmed by histopathology.
Results: Fifty six percent women were cancer positive. Ovarian malignancy was more common in postmenopausal age group. Ultrasonography and CA-125 had high sensitivity of 90% but poor specificity. Risk of malignancy index 3 had a sensitivity, specificity, positive predictive value and negative predictive value of 90%, 91%, 78% and 96% respectively at a cut off value of 250.
Conclusions: Risk of malignancy index was concluded to be a multimodal approach with better diagnostic scoring index in preoperative stage in women of ovarian masses. It is simple and easily applicable clinical tool in resource poor setting.

Keywords: Menopause, Ovarian cancer, Risk of malignancy index, Serum CA-125, Ultrasonography in carcinoma ovary

INTRODUCTION

Ovarian cancer is the most lethal malignancy as 70 % are diagnosed only in advanced stage.[1] The lifetime risk of ovarian cancer in women is 1 % to 1.5%. It has the highest case fatality ratio of all gynaecological malignancies.[2] In India, ovarian cancer (OC) ranks third after carcinoma cervix and breast in most of the population-based cancer registries. Age-adjusted incidence rates of ovarian cancer vary between 5.4 and 8.0 per 100,000 population in different parts of our country.[3] Projected number of cases for this cancer for 2015 and 2020 are 45,231 and 59,276, respectively.[4] This statistic efficiently demonstrates OC as a major concern. Preoperative detection of OC is a challenge in the eyes of gynaecologist as the anatomical location of the ovary is deep into the peritoneum which makes them less accessible for satisfactory screening test unlike cervix, endometrium and breast which can be easily examined. Vague presenting symptoms, low prevalence and contraindication of biopsy as it can lead to dissemination of tumour cells and change in surgical staging further enhance the difficulty. Preoperative detection is imperative from intervention point of view because in

stage Ia (FIGO 2014) ovarian tumour the cure rate is more than 80%.[5] Moreover, it will prevent morbid surgeries and cost of therapy in benign ovarian tumour. The screening tests available are tumour markers (CA-125), Ultrasonography (USG), multimodality screening (CA-125 followed by USG), CT scan and MRI. CA-125 elevation is significant in postmenopausal age group as it may be falsely elevated in benign conditions in premenopausal women. The prostate, lung, colorectal and ovarian cancer screening (PLCO) trial concluded its positive predictive value as < 4% which is unacceptable for screening test of OC and thus US preventive services task force gave it the lowest ranking.[6,7] Various morphological features in USG are suggestive of malignancy like irregular solid mass or multilocular cystic mass, solid components, papillary projections on the cyst wall, ascites, peritoneal nodules and any evidence of metastases. Papillary projections are defined as small solid areas projecting $\geq$ 3 mm from the cyst wall.[8]

In a health care resource limited developing country like India we need to adopt a feasible and economical screening test which identifies OC and differentiate between benign and malignant ovarian neoplasm. Risk of malignancy index (RMI) is a scoring system which was first introduced by Jacob et al in 1990 as RMI1.[9] It was modified by Tingulsted in 1996 which was named as RMI2 and later in 1999 as RMI3.[10,11] The difference between the three indices lies in the different scoring of ultrasound parameters and menopausal status. It incorporates absolute value of CA-125, USG and menopausal status in preoperative period for the likelihood of ovarian malignancy. Through this study we intend to evaluate the validity of RMI3 in its application in daily clinical practise to facilitate screening in women suspected with pelvic mass, to plan appropriate treatment protocol and triage management.

METHODS

This was a prospective observational study conducted at department of obstetrics and gynecology, R.D. Gardi Medical College Ujjain from 2017 to 2019. Seventy-four perimenopausal and postmenopausal women who were clinically diagnosed as pelvic tumour were recruited in the study. Patients who were unfit for surgery due to medical comorbidities and OC in advanced stage were excluded. Detailed clinical history was taken pertaining to age, parity, symptoms, menstrual history and consumption of oral contraceptive pills (OCPs) for more than five years. After recording demographic information, general examination with height and weight was recorded to calculate body mass index (BMI). BMI is the metric currently in use for defining anthropometric height/weight characteristics in adults and for classifying them into groups.[12] It is calculated as weight (kg)/ height x height (m^2) and the patients were categorized into underweight (> 18 kg/m^2), normal weight (18-24.9 kg/m^2), overweight (24.9-29.9 kg/m^2)and obese (> 30

kg/m^2). Thorough clinical examination was performed to derive provisional diagnosis. In all women serum CA-125 estimation was done. Ultrasonography (abdomen and pelvis) was performed with full bladder technique with 3-5 MHz probe frequency by an experienced radiologist. Based on these three parameters RMI was calculated.

Ultrasound scoring (U)

It was based on one point for each of the following - bilateral lesion, multilocular cyst, solid areas, evidence of metastasis and ascites. Among them solid component is the most significant predictor of malignancy.[13,14] Cystic ovarian mass with septa is a strong evidence of neoplasm and if it measures > 2-3 mm is suggestive of malignancy.[10] For RMI, U = 1 for ultrasound point 0/1, U = 3 for ultrasound point $\geq$ 2. Ultrasound scoring was done one week prior to laparotomy.

Serum CA-125 level estimation

Peripheral venous blood sample (5 ml) was withdrawn from each patient prior to surgery for estimation of serum CA-125 level. It was determined by radioimmunoassay using 2 monoclonal antibodies with specificities against CA-125's two major antigenic domains, OC125 and M11.5 (VITROS ECi/ECiQ/3600 Immunodiagnostic systems and the VITROS 5600/XT 7600 integrated systems). The cut off value of CA-125 was accepted as 35 IU/ml as the upper limit of normal (ULN).[15]

Menopausal scoring (M)

Postmenopausal status was defined as more than one year of amenorrhea or an age of 50 years in women who had hysterectomy while all other women were considered premenopausal. For premenopausal women M = 1 and for postmenopausal women M = 3. RMI was calculated for each subject

$$RMI = M \times U \times CA\text{-}125 \ (U/ml)$$

Operative finding during surgery of all cases were obtained. Specimen was sent for histopathology in the department of pathology. Histopathology was considered the gold standard for defining the outcomes.[16] Results of RMI were validated against histopathology confirmed malignancies.

Statistical analysis

Statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 23.0 statistical Analysis Software. Chi square test was used for data analysis. Univariate analysis to determine the association of each parameter was performed using Student's t test. The predictive power of each factor and their combinations were assessed by the goodness of fit test at 1% significance. To determine the best cut off value to differentiate between benign and malignant pelvic mass,

receiver operating characteristic curves (ROC) of CA-125 and RMI were plotted. The best cut off was chosen according to the highest sensitivity with the lowest false-positive rate. Diagnostic performances of each test were reported as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) with 95% confidence interval. Sensitivity is the percentage of patients with malignant ovarian mass having a positive test result. Specificity is the percentage with benign ovarian mass showing negative results. Positive predictive value is the percentage of patients with a positive test result having malignant ovarian mass.

Negative predictive value is the percentage of patients with a negative test result having benign ovarian mass, p-value < 0.05 was considered to be significant.

RESULTS

A total of 74 perimenopusal and postmenopausal women with pelvic tumour suspected to be ovarian neoplasm were enrolled. Based on histopathological examination of the specimen after surgery 54 patients (72.9%) had benign tumour and 20 patients (27%) had malignant tumour.

Table 1: Clinical profile of study participants and their distribution as benign and malignant tumor.

Characteristics of study participants		Histopathology		p-value
		Benign (n = 54)	Malignant (n = 20)	
Age (years)	≤ 50 (n = 53)	81.1% (43)	18.9% (10)	p = 0.012
	> 50 (n = 21)	52.4% (11)	47.6% (10)	
Parity	Nulliparous (n = 6)	33.3% (2)	66.7% (4)	p = 0.02
	Multiparous (n = 68)	76.5% (52)	23.5% (16)	
OCP use	Yes (n = 15)	93.3% (14)	6.7% (1)	p = 0.041
	No (n = 59)	67.8% (40)	32.2% (19)	
BMI	Underweight (n = 5)	80% (4)	20% (1)	p = 0.399
	Normal weight (n = 33)	81.8% (27)	18.2% (6)	
	Overweight (n = 33)	63.6% (21)	36.4% (12)	
	Obese (n = 3)	66.7% (2)	33.3% (1)	

Table 2: Correlation of RMI and its individual parameter with histopathology.

Parameter		Histopathology		p-value
		Benign	Malignant	
Menstrual status (M)	1 (n = 45)	84.4% (38)	15.6% (7)	p = 0.006
	3 (n = 29)	55.2% (16)	44.8% (13)	
CA-125 (IU/ml)	< 35 (n = 42)	95.2% (40)	4.8% (2)	p = 0.000
	> 35 (n = 32)	43.8% (14)	56.3% (18)	
USG Score (U)	1 (n = 32)	93.8% (30)	6.3% (2)	p = 0.000
	3 (n = 42)	57.1% (24)	42.8% (18)	
RMI	< 250 (n = 51)	96.1% (49)	3.9% (2)	p = 0.000
	>250 (n = 23)	21.7% (5)	78.3% (18)	

According to (Table 1) the study included 53 patients with age < 50 years and 21 patients with age > 50 years. OC was seen in 47.6 % among patients > 50 years and 18.9 % in patients with age < 50 years. The occurrence of OC in the age group > 50 years is statistically significant (p = 0.012) demonstrating that ovarian tumour in advanced age is more likely to be malignant. Number of nullipara women in our study were 6 and multipara were 68. The percentage of OC was 66.7 % (4) in nullipara and 23.5 % (16) in multipara women. Our study comprised of 15 patients who were consuming OCPs for > 5 years and 59 patients who did not use OCPs or consumed it for less than 5 years. Malignancy was seen in 32.2 % (19) of patients who did not use OCPs or used it for less than 5

years and only in 6.7 % (1) of patients who were on OCPs for >5 years. Statistically it is shown that both number of pregnancies (p = 0.02) and use of OCPs > 5 years (p = 0.041) are protective factors for OC. There were 5 patients in the underweight category, 33 patients of normal weight, 33 patients in overweight category and 3 patients in obese category. OC was seen in 20 % (1) of underweight patients, 18.2 % (6) of normal BMI, 36.4 % (12) of overweight and 33 % (1) of obese patients. This data was statistically insignificant (p = 0.399).

Table 2 shows in our study 29 patients were postmenopausal and 45 were premenopausal. Ovarian malignancy was detected in 44.8% (13) of

postmenopausal women and 15.6% (7) of premenopausal patients. Statistically it was shown that malignancy was more common in postmenopausal group (p = 0.006). The CA-125 is analysed with a cut off value of 35 U/ml. The normal range is 0-35 U/ml. Out of 32 patients with CA-125 > 35 U/ml, 56.3% (18) were malignant and 43.8% (14) patients had benign ovarian tumour. Among 42 patients with CA-125 < 35 U/ml, 95.2% (40) were benign and 4.8% (2) were ovarian malignancy. It is statistically significant that CA-125 below it cut off clearly demarks the benign nature of ovarian mass but it elevation > 35 IU/ml is inconclusive (p = 0.000). There were 32 patients

with U = 1 while 42 patients with U = 3. Among patients with U = 3, 42.9% (18) were malignant and 57.1% (24) were benign while patients with U = 1, 6.3% (2) had OC and 93.8% (30) had benign ovarian tumour. It was statistically significant (P = 0.000). With the cut off value of 250, 51 patients had RMI < 250 and 23 patients had RMI > 250. With RMI < 250, 96.1% (49) patients had benign ovarian tumour and 3.9% (2) had OC and patients with RMI > 250 have 21.7% (5) had benign neoplasm and 78.3% (18) of patients had OC. It is statistically significant (p = 0.000).

Table 3: Diagnostic efficacy of individual parameter of RMI and RMI as marker of malignancy in histopathology positive malignant patients.

Measures	U ≥ 3 (%)	CA-125≥35 IU/ml (%)	M ≥ 3 (%)	RMI ≥250 (%)
Sensitivity	90	90	65	90
Specificity	56	74	70	91
Positive predictive value (PPV)	43	56	45	78
Negative predictive value (NPV)	94	95	84	96
False positive rate	44	26	30	9
False negative rate	10	10	35	10
Diagnostic accuracy	65	78	69	91

Table 4: Area under the curve.

Test result variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
RMI	.918	.045	.000	.829	1.000
CA-125	.860	.056	.000	.751	.970

[a]Under the nonparametric assumption, [b]Null hypothesis: true area = 0.5.
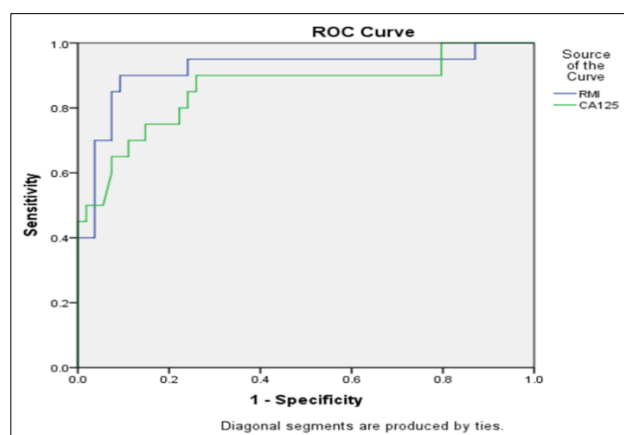

Figure 1: Receiver operating characteristic curves of RMI and CA-125 for predicting malignancy.

Table 3 demonstrate that the sensitivity of menopausal score in our study was 65%, specificity 70%, PPV 45% but had a high NPV of 84 % with the accuracy of 69%. The sensitivity of ultrasound in differentiating benign and malignant tumor was 90%, specificity 56%, PPV 43%,

NPV 94% and accuracy 65 %. The sensitivity of CA-125 with a cut off value of 35 U/ml was 90%, specificity 74%, PPV 56% and NPV 95% with the diagnostic accuracy of 78%. The sensitivity and NPV of CA-125 and USG is comparable in diagnosing OC. The sensitivity, specificity, PPV and NPV of RMI at cut off value of 250 were 90%, 91%, 78%, 96% respectively. We found that RMI has the maximum diagnostic accuracy of 91% and better performance than the individual parameter i.e. CA 125, ultrasound score and menopausal score as a predictor of OC.

Figure 1 depicts the ROC curves of RMI and CA-125.The performance of CA-125 and RMI is shown in ROC curves. Area under cover in ROC determines the diagnostic power of test. The curve is obtained from sensitivity versus specificity. Its application for evaluation of a screening test for differentiating benign and malignant mass is based on this curve. The cut-off point is the shortest distance between peak of the curve and point 1. Best performance of CA-125 was seen at level of 35 IU/ ml (highest area under the ROC curves i.e. 86%). As we increase the cut off value specificity increase but the sensitivity decreases. The best

performance obtained for RMI was at the cut off of 250. There was 91% increase in the odds of diagnosing OC with use of RMI when compared to not using RMI. Taking into account the best obtained cut-off point for RMI, 5 cases were false positive (RMI ≥ 250 benign tumours) among which 60% (3) was contributed by serous cystadenoma and 40% (2) by the mucinous cystadenoma. Eighteen cases were true positive (RMI ≥ 250 malignant tumours) while 49 cases were true negative (RMI < 250 benign tumours) and 2 cases were false negative (RMI < 250 malignant tumours), that were mucinous cystadenocarcinoma.

DISCUSSION

This study addresses validity of RMI- version 3 to correlate presumptive diagnosis of ovarian carcinoma in women of perimenopausal and postmenopausal age having ovarian masses. As five-year survival in stage Ia is 80% we assume that this score will help in preoperative provisional diagnosis with early intervention.[5] The most common benign ovarian tumour was serous cystadenoma and malignant OC was serous cystadenocarcinoma.

Mean age of women in this study for OC was 47.36 years. This study shows that among nulliparous women 66.7% had malignant tumour when compared to 23.5% in multiparous women (p = 0.012). It is concluded that nullipara have higher incidence compared to multipara. Pregnancy causes anovulation and suppresses secretion of pituitary gonadotropins. Each full-term pregnancy lowers risk by approximately 15%.[17,18] Studies in African, American and Asian populations have yielded similar results.[19,20] While considering relation of OC to contraceptive pills our findings are consistent with other authors.[21] The protective effect of OCP on OC is an interesting finding. As such OCP use is less common in India compared to other countries with high literacy rate. In this study OC was reported in 32.2% of women not using OCPs or consuming it for less than 5 years and 6.7% of women who were regularly using OCPs (p = 0.041). Epidemiological literature over past several decades has consistently reported that consumption of OCPs causes a state of anovulation and is inversely associated with the risk of ovarian cancer with protective action increasing with duration of use.[21] There is an increased risk of OC in obese women, which could be due to aromatisation of androgens into oestrogen in peripheral fat.[22] Association of obesity and OC is a well-accepted phenomenon in all populations. We correlated BMI with presence or absence of malignancy. OC was documented in 20%, 18.2%, 36.4% and 33.3% of underweight, normal weight, overweight and obese patients respectively in this study. While, ovarian cancer association consortium (OCAC) and the collaborative group on epidemiological studies of ovarian cancer observed that obesity is a risk factor for borderline and non- epithelial ovarian tumour and did not influence high grade serous cancers.[23,24] We have a little different observation, we found serous cystadenocarcinoma as a major contributor of OC in our study, these authors concluded presence of obesity association with non-epithelial OC (Table 1), (p = 0.399). Prevalence of OC is more in postmenopausal age than premenopausal age. This was observed from presence of malignancy in 44.8% of patients in postmenopausal age group and 15.6% of premenopausal patients. Presence of premenopausal status (M-1) appears to have less likelihood of malignancy than postmenopausal (M-3) status (Table 2) (p = 0.006).Other various studies have also concluded that OC is more common in postmenopausal age group.[16,25-27] The main focus of this study is on RMI which is an integration of menopausal score, CA-125 level and USG score. In the present study menopausal score was the weakest constituent of RMI with sensitivity of 65% and specificity of 74% which is comparable with Jenitha B et al.[28] Menopausal status alone cannot be used as an indicator of malignancy.

In our study CA-125 level has a varied range of 5.5-6680.0 U/ml and the mean value was 275.45 U/ml in all women with ovarian masses. In women with OC CA-125 had a high sensitivity of 90% with poor specificity of 74% (Table 3). Similar results were also obtained by several other studies.[25,29,30] Thus, if the level of CA-125 is increased beyond 35 U/ml does not necessarily infer that the ovarian mass is malignant but if it is < 35 U/ml clearly denotes it is not malignant. The low specificity could be due to other benign causes of raised CA-125 in premenopausal women which increase its false positive rate. At the same time it is a good predictor and prognostic marker of OC.

USG is a widely accepted diagnostic modality which can accurately characterize 90% of ovarian masses. In the present study USG has a high sensitivity of 90% but poor specificity of 56% (Table 3) which is in accordance with Kestane I et al.[30] It has a high false positive value which can lead to misdiagnosis of benign or borderline ovarian tumour as OC as the radiological findings between them show considerable overlap.[31] If used as a single diagnostic indicator of OC it may cause unnecessary and morbid surgeries in malignant negative patients.

RMI is a multiparametric tool used to predict malignant ovarian disease. It overcomes high false positive rates of individual contributor of RMI i.e. menopausal score, USG score and CA-125 level. It transforms the morphological description of ovarian mass into objective numerical data.[32] In benign tumours, the RMI had a range from 5.5 to 954. Among the malignant tumours the range is from 10.90 to 44597.9. Average RMI for OC was 5717.3. Several studies have investigated the most accurate cut off value of RMI and found that value of > 200 has the best sensitivity, specificity, PPV and NPV of 89% - 92%, 82% - 96%, 62% - 98% and 77% - 98% respectively.[33,34] In our study the cut off value of RMI was derived to be 250 (Figure 1) and the sensitivity, specificity, PPV and NPV of RMI were 90%, 91%, 78% and 96% respectively (Table 3). In order to exclude

malignancy, the false negative rate of scoring system should be 0 or near to 0.[35] In our study among 74 cases, 2 patients had score < 250 but were diagnosed with mucinous cystadenocarcinoma because the level of CA-125 was within normal range which contributed to 2.7 % of false negative rate. CA-125 has a limited role in diagnosing mucinous tumours when compared with non-mucinous epithelial tumor.[30] Various prospective and retrospective studies have reported it to be best tool for triage and management of OC.[29,30] The minimum USG score was 0 in previous other studies which brought the product of RMI = 0.[5,29] It was the major contribution of high false negative rate and low sensitivity of RMI in these studies. But in present study ovarian neoplasm with no USG parameters the U = 1 similar to various other studies.[16,28,30,34,36] Its utility as diagnostic tool has been found to be statistically significant (Table 2, P = 0.00). In India patients defer repetitive radiological investigations due to lack of knowledge and financial limitations. RMI is a feasible and easily applicable device even in centres which do not have facilities of CT scan and MRI. Referral of patients with RMI ≥ 250 to specialized oncology centres is essential as the primary debulking surgery plays a great role in deciding prognosis of OC.[5]

CONCLUSION

Risk of malignancy index is a simple tool and with its high diagnostic efficiency can be used in daily clinical practise for preoperative evaluation of ovarian masses. With the high specificity it can not only discriminate benign from malignant OC but also decide for referral of malignant masses to gynaecology oncosurgeon when it is in operable state. The study findings clearly withstand that the validity of RMI is higher than its individual parameter in diagnosing ovarian tumour.

ACKNOWLEDGMENTS

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