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A prospective observational study on the effectiveness of risk of malignancy index score (RMI 3) in a tertiary care centre in Eastern India

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ABSTRACT

Background: Adnexal mass is a common presentation in today's gynecological practice. The incidence of ovarian cancer is increasing day by day and diagnosis is often difficult to be made pre operatively with inadequate surgical exploration is a regular occurrence. **Aims and Objectives:** To assess and validate the importance of RMI-3 score as pre-operative diagnostic tool of differentiating benign from malignant adnexal mass for starting first line therapy of ovarian cancer and to find out the incidences of ovarian malignancy among study population. **Materials and Methods:** The study was conducted in the Department of Gynecology and Obstetrics on (n = 115) patients attending GOPD and indoor with adnexal mass fulfilling the inclusion and exclusion criteria using purposive sampling technique. All the selected cases underwent ultrasonography and serum CA- 125 level estimation necessary for calculating RMI score. A score of >200 was taken as suggestive of malignancy and confirmatory diagnosis was performed by histopathological examination obtained from staging laparotomy of adnexal mass. The individual scores were then correlated with final outcomes with statistical analyses. **Results:** The study revealed benign ovarian tumors are more under 50 years (78.46%) and patients with normal BMI are diagnosed with maximum of malignancy (n = 28). History of tubal ligation carried less risk of malignancy ($p < 0.0001$). Histologically malignant tumors found mostly in 71.4% postmenopausal group whereas 94.1% benign pathology were present in perimenopausal group and there is no association found between parity and histopathology ($p = 0.058$). Bilateral ($p = 0.013$), multilocular($p = 0.000$) tumors with solid areas($p < 0.0001$) and thick papillary projections ($p < 0.0001$) had statistically significant association with malignant lesions. RMI score (>200) had more efficacy than serum CA-125 level (>46) in differentiating malignant lesions from benign one in terms of specificity (96% vs 83.87%) and positive predictive value (95% vs 79.17%). **Conclusions:** RMI-3 score is a simple, reliable and effective tool in differentiating benign from malignant adnexal masses thereby help in quick referral and management of cases with increase chances of survival of the patients.

Key words: Adnexal mass; Ovarian malignancies; Serum CA-125; Risk of Malignancy Index-3

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INTRODUCTION

An adnexal mass is a common problem encountered in gynecological practice. The differential diagnosis of an adnexal mass varies from functional cysts to benign tumors to malignant tumors of various abdominal and pelvic organs.[1] Of all the gynecologic cancers, ovarian malignancies represent the greatest clinical challenge as

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they have high mortality.[2] Benign masses can be treated conservatively or by minimal invasive surgical procedures. According to WHO, epithelial ovarian cancer is the most common (65%) among all others and patients often present in the advanced stages.[3] This is because most of the patients do not experience any signs and symptoms until the disease spreads to upper abdomen.[4] Early identification of a lurking malignancy carries a more favorable prognosis [5] and this requires a high index of suspicion. A percutaneous biopsy is not recommended during the initial evaluation as this can result in cyst rupture and spillage of malignant cells into the peritoneal cavity.[6] Used alone, the diagnostic accuracy of demographics, ultrasound (US), and biochemical variables is inadequate as sensitive and specific method for clinical application. Various combined methods for evaluating the risk of ovarian cancer have been proposed. The risk of-malignancy index (RMI) is a simple scoring method based on menopausal status, ultrasound findings, and the serum CA 125 level.[7] This method has given significantly better results than the use of a single parameter. The RMI can be applied in less-specialized centers. The RMI score is the product of the ultrasound imaging scores (U), the menopausal score (M), and the absolute value of the serum CA 125 i.e. RMI = U x M x CA 125. The original RMI (RMI-1) has been modified in 1996 Tingulstad et al [8] known as RMI-2 and again modified in 1999 known as RMI-3. [9] The difference between the new indices lies in the different scoring of ultrasound characteristics and menopausal status. [10,11] Till date there is no universally accepted test or criteria to exclude cancer with certainty.[12] And often, surgery is required solely to exclude the possibility of malignancy. Screening of ovarian malignancy is not recommended in women who are at average to high risk as evidence does not support a reduction in death and the high rate of false positive tests may lead to unneeded surgery which is accompanied by its own risk.[13] Few studies[14,15] done earlier have shown highly sensitive and specific results and there is still ample scope to further validate those findings so that timely referral of appropriate cases to gynecological oncologists can be made for initiating management. Therefore, this study was planned to find out the incidences of ovarian malignancy among study population and to evaluate and validate RMI-3 score as a pre-operative diagnostic tool of differentiating benign from malignant adnexal mass for starting first line therapy of ovarian cancer.

MATERIAL AND METHODS

A prospective, observational study was conducted at Department of Obstetrics and Gynecology, Nil Ratan Sirkar Medical College &Hospital (NRSMCH), Kolkata, West Bengal, India during1st April 2018 to 31st March 2019 (1 year) after prior approval from institutional ethics committee (No/NMC/449 dated 30/01/2018) on (n=115) consecutive patients aged ≥ 40 years, having clinically palpable as well as USG suggesting adnexal mass ≥ 8 cm and gave written informed consent for participation in the study. Patients with past history of ovarian malignancy, past treatment for ovarian malignancy, age < 40 years (incidence of ovarian malignancy is more in women >20 years) and pregnancy were excluded from the study. By adopting a purposive sampling technique (n=115) patients attending the OPD/ER were selected for this study. A thorough history with special emphasis on the age, menopausal status and clinical examination of palpable adnexal mass ≥ 8 cm followed by USG of whole abdomen using Philips HD-7 Ultrasound machine with Color Doppler facility, equipped with a 3.5-MHz TAS probe and 7.5-10-MHz TVS probe to confirm the mass and serum CA 125 protein (monoclonal antibody technique) estimation was done with a cut off value of >46 U/ml[16] was considered to be confirmatory for malignancy. The presence of bilateral lesions, multi-locular cystic lesions, solid areas, ascites and metastasis were recorded. RMI score >200[7, 8] was taken as suggestive of malignancy. The confirmatory diagnosis was performed by the histopathological examination (HPE) reports of specimen obtained from laparotomy of adnexal mass. The individual scores were then correlated with the final outcomes. Descriptive statistical analysis has been carried out in the present study. Results on categorical measurements are presented in number (%). Significance is assessed at 5 % level of significance. Two - tailed hypothesis with z- score has been used to find the significance of study parameters (p- value) on categorical scale between two or more groups. A p value < 0.05 is considered statistically significant. Receiver Operating Characteristic (ROC) curve was constructed to find the best cut-off of predictors along with the sensitivity and specificity. The Statistical software SPSS 21.0 was used for the analysis of the data and Microsoft word and Excel 2010 have been used to generate graphs, tables.

RESULTS

This prospective observational study was done to demonstrate primarily the importance of RMI as a pre-operative diagnostic tool of an adnexal mass and secondarily the incidence and prevalence of ovarian malignancy in a tertiary care hospital in eastern India. Initially (n =115) patients were taken, among those (n = 2) patients had pregnancy which was diagnosed later and (n=13) patients were lost to follow up (Figure 1). Finally (n =100) patients were included in this study of which (n= 59) patients had a past history of tubal ligation. Nobody gave a history of smoking. RMI scores were calculated, compared in all the

patients and were correlated with histology findings. The demographic profile of the study participants was depicted in Table 1 according to the type of tumor diagnosed by HPE.

The clinical and pathological characteristics of the tumor observed along with level of serum CA -125 marker in both the study groups are mentioned in Table 2.

The association between the serum CA-125 level and results of histopathological examination were shown in Table 3. It was found that 79.17% of the malignant cases had a CA-125 level more than the cut off value 46 U/ml. Whereas all of the benign cases (100%) had their level of CA-125 under 46U/ml. The association was statistically just significant (p = 0.047).

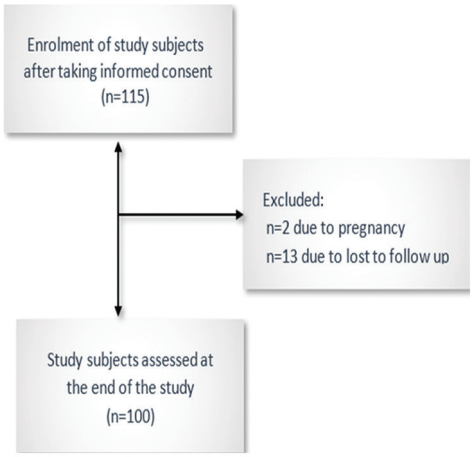

Figure 1: Flow short of study

Out of 100 study subjects it was found that 60 (60%) had RMI scoring <200 and 40 (40%) had RMI scoring >200. The association between the serum RMI and results of histopathological examination were shown in Table 4. The association was also just statistically significant (p= 0.029).

The ROC curve for CA-125, has obtained an AUC (area under the curve) value of 0.919 which tends to 1 (Figure 2).

The ROC curve for RMI score, has obtained an AUC (area under the curve) value of 0.984 which tends to 1(Figure 3).

The acceptability and validity of the two parameters i.e. serum CA-125 and RMI score in detecting appropriate ovarian tumors are compared in Table 5 which depicts although there are no statistically significant difference in sensitivity and specificity of the parameters (p = 0.254) but the positive predictive value has some significant differences (p= 0.030) and negative predictive value has a highly statistically significant difference (p<0.001).

DISCUSSION

Ovarian cancer is the 5th worldwide leading cause of death of women due to cancer.[17] Early diagnosis of ovarian cancer has been a challenge for the physician since decades. Patients are usually diagnosed at an advanced stage due to absence of suitable screening tests. This prospective, observational

Table 1: Demographic profiles distribution of study participant according to type of tumor (n=100)

Sl No.	Parameters	Histopathology		P- value•
		Benign	Malignant	
1	Age group (years)			
	40-49	51 (78.46%)	14 (21.54%)	< 0.0001
	50-59	3 (18.75%)	13 (81.25%)	< 0.0001
	60-69	4 (30.77%)	9 (69.23%)	0.012
	70-79	4 (66%)	2 (34%)	0.810
2	BMI			
	Underweight (<18.5)	2 (50%)	2 (50%)	0.617
	Normal (18.5 - 24.9)	52 (65%)	28 (35%)	0.214
	Overweight (25 - 29.9)	2 (33.33%)	4 (66.66%)	0.136
	Obese (>30)	6 (60%)	4 (40%)	0.888
3	Place of residence			
	Rural	27 (62.79%)	16 (37.21%)	0.888
	Urban	35 (61.40%)	22 (38.60%)	
4	Menopausal status			
	Perimenopausal	48 (94.12%)	3 (05.88%)	< 0.0001
	Postmenopausal	14(28.57%)	35(71.43%)	
5	Parity			
	Multipara	36 (54.55%)	30 (45.45%)	0.058
	Nullipara	26 (76.47%)	8 (23.53%)	
6	H/O Tubal ligation			
	Present	57 (96.61%)	2 (03.39%)	< 0.0001
	Absent	5 (12.19%)	36 (87.81%)	

* Two-tailed hypothesis with significance level =0.05

Table 2: Clinico-pathological characteristics of ovarian tumors in the study participants (n=100)

Sl. No.	Parameters	Histopathology		P- value•
		Benign	Malignant	
1	Bilateral tumours			
	Yes	30 (51.72%)	28 (48.28%)	0.013
	No	32 (76.19%)	10 (23.81%)	
2	Multilocular			
	Yes	18 (40.91%)	26 (59.09%)	< 0.0001
	No	44 (78.57%)	12 (21.43%)	
3	Metastasis			
	Present	2 (20.00%)	8 (80.00%)	0.004
	Absent	60 (66.67%)	30 (33.33%)	
4	Ascites			
	Present	12 (40%)	18 (60%)	0.03
	Absent	50 (71.43%)	20 (28.57%)	
5	Solid areas			
	Present	22 (37.93%)	36 (62.07%)	< 0.0001
	Absent	40 (95.24%)	2 (4.76%)	
6	Thick papillary projections:			
	Present	6 (27.27%)	16 (72.73%)	< 0.0001
	Absent	56 (71.79%)	22 (28.21%)	
7	Serum CA 125 level			
	<46	52 (100%)	0 (0%)	0.047
	>46	10 (20.83%)	38 (79.17%)	
8	RMI score			
	<200	60 (100%)	0 (0%)	0.029
	>200	2 (5%)	38 (95%)	

* Two-tailed hypothesis with significance level =0.05

Table 3: Association between serum CA-125 level and type of tumor based on results of histopathological examination

CA -125 (U/ml)	Histopathological examination			P-Value
	Benign	Malignant	Total	
<46	52 100%	0 0%	52	0.047
>46	10 20.83%	38 79.17%	48	
Total	62	38	100	

Table 4: Association between RMI score and type of tumor based on results of histopathological examination

Risk of Malignancy Index (RMI)	Histopathological examination		Total	p-value
	Benign	Malignant		
<200	60 100%	0 0 %	60	0.029
>200	2 5 %	38 95 %	40	
Total	62	38	100	

study was conducted on (n = 100) cases with adnexal mass ≥ 8cm diagnosed clinically and USG supported. Each and every patient was evaluated by using RMI scoring system. All underwent laparotomy and specimen were sent for histopathology. Scores allotted by the scoring system were then compared with histopathology reports.

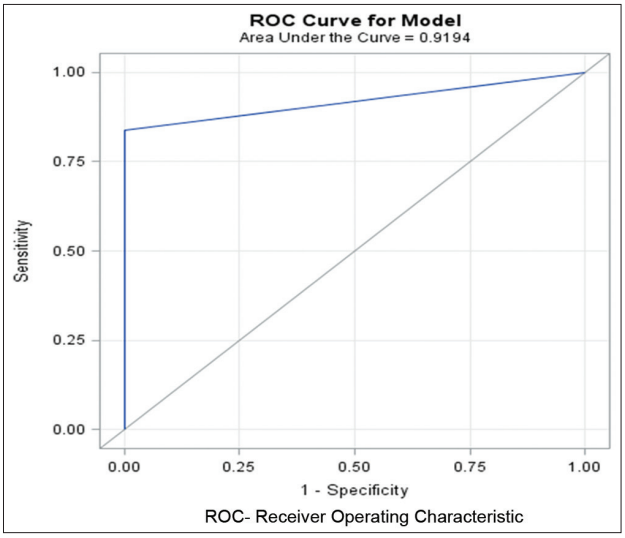

Figure 2: ROC curve of CA-125 for predicting malignancy

Ovarian cancer is usually a disease of older women. Our study showed benign ovarian tumors are more common below 50 years of age (78.46%) and patients with normal BMI are diagnosed with maximum (n = 28) of malignancy (Table 1). In the study by Singh et al. 2006[18] and Van Gorp et al. 2012[19] cut off age for malignancy was ≥ 40 years ($p<0.05$). The BMI of 80% subjects was normal out of which 35% were malignant following HPE (Table 1). Ferraro S et al. 2015[20] showed also that BMI does not influence human epididymis protein (HE4) and CA-125

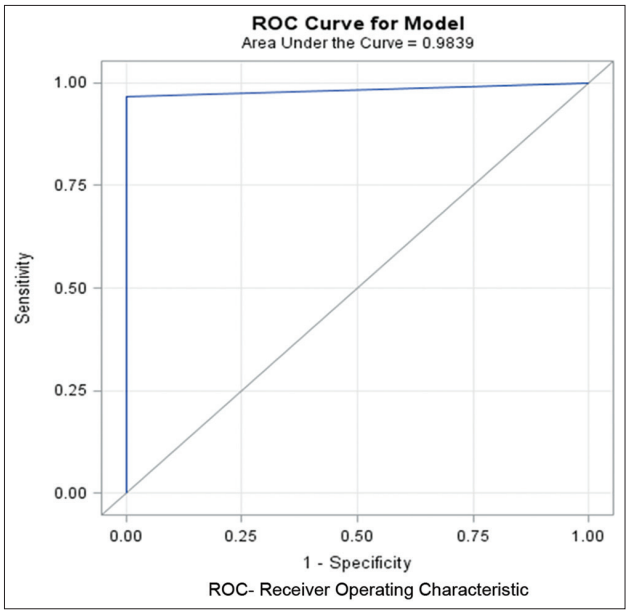

Figure 3: ROC curve showing RMI scoring for predicting malignancy

Table 5: Comparison of efficacy and validity between RMI score and CA-125 marker

Parameters	RMI score	CA125 level	P value•
1.Sensitivity	100%	100%	0.254
2.Specificity	96.77%	83.87%	0.254
3.PPV	95%	79.17%	0.030
4.NPV	100%	100%	<0.0001

PPV- Positive Predictive Value, NPV – Negative Predictive Value
*Two-tailed hypothesis with significance level =0.05

level in serum. No significant association was seen between malignancy and place of residence whether it is rural or urban. In our study menopausal status and ovarian neoplasm was found to have a very significant association with a p value of 0.0001. Other studies like Singh et al. 2006,[18] Jacobs et al. 1990[7] showed similar significant association with malignancy. Malignant tumors are significantly more in multipara than nullipara (p=0.058) as also suggested by Ali Yavuzcan et al. 2014.[21] History of tubal ligation has significant protective effect against ovarian malignancy (p<0.0001) in our study as seen in studies by Weiva Sieh et al. 2013[22] and Madsen et al.2015[23] showing less occurrence of epithelial and borderline ovarian cancer.

In our study presence of bilateral adnexal mass (p =0.013) and multilocular lesions(p<0.0001) has a significant association with malignancy (Table2). In a study conducted by Sinha et al. 2013[24] the association of bilateral tumors with malignancy was significant with p<0.0001. Similar findings were also seen in studies by Jacobs et al. 1990,[7] Leelahakorn et al. 2005. [25] Benign as well as malignant tumors may present with ascites and metastasis indicating an advanced stage of the disease but the incidences are much more in cases of malignancy and this finding is statistically significant with p value of 0.03 and 0.004 respectively (Table 2) in the current study. In our study, solid component detected in the tumors was statistically highly significant (p<0.0001) in the differentiation of benign from malignant ovarian mass (Table 2). In other studies, conducted by Alcazar et al. 2003[26] and Brown et al. 1998 [27] solid components found was statistically significant (p<0.05, p<0.001) similar to this study. In the current study, thick papillary projections (≥ 3mm) was found to be statistically significant (p<0.0001) in the differentiation of benign from malignant mass. In the study by Sinha and co-workers (2013),[24] papillary thickness ≥ 3 mm was found to be significant with p<0.02.

A direct correlation was observed with level of CA -125 and HPE suggested malignancy which was found to be significant with p = 0.047 (Table 3). In the present study CA-125 level was found to be a fair to good predictor in the diagnosis of malignant adnexal mass with regard to differentiating from the benign group. In this study, the CA-125 at a cut-off level of 42 showed 100% sensitivity but a lower specificity of 83.87% (Table 5). The best cut-off for Serum CA-125 was found to be 55 U/ml with a sensitivity of 97.37% and specificity 100% for the current study. In the study by Hossain and colleagues (2010),[28] the best cut off for CA-125 was obtained as 55 U/ml, with a sensitivity of 96.67%, specificity 96.77%. Sinha and colleagues (2013) [24] used a cut off value >35 U/ml as a criterion of malignancy and obtained a sensitivity of 92.5% and specificity of 83%. In the current study the ROC for CA-125 showed an AUC of 0.919 (Figure 1) which was comparable with Sinha and colleagues (2013)[24] work, with an AUC of 0.90. At lower cut off values the sensitivity increases at the expense of specificity, while at a higher cut off values the specificity increases at the expense of sensitivity and more benign cases are likely to be referred as malignant. We can infer from the above that the CA-125 determined the true positive and false negative cases, i.e. the benign cases as benign and malignant cases as malignant with an accuracy of 91.9% for a threshold value of 42.

A direct correlation was also observed with RMI score and HPE suggested malignancy which was found to be significant (p = 0.029) [Table 4]. The cut-off levels of RMI score in many previous studies ranged from 25 to 250 as concluded by Geomini et al.[29] Most studies reported an increased diagnostic accuracy and performance with a RMI score of >200.[7,8] In our study, RMI at a cut-off 200 shows 100% sensitivity, but a lower specificity of 96.00% (Table 5). The best cut-off for the RMI was found to be 450 with a sensitivity of 100% and specificity of 100% for the current study. In study by Jacobs et al.1990 [7,8] a RMI cut-off level of 200 had a sensitivity of 85.4% and a specificity

of 96.9%. Davies et al.1993[30] found a sensitivity of 87% and specificity 89% for this index. Sinha and colleagues (2013) [24] study showed a cut-off of 190 of RMI score had a sensitivity of 86.67%, specificity of 92.5%. However, Tingulstad et al. 1996 [8] found a sensitivity of 71%,80% and specificity of 96%,92% for RMI 1 and RMI 2 respectively at a cut-off level of 200. Zinatossadat and colleagues (2011) [31] study shows RMI at the optimal cut-off point of 265 with a sensitivity of 91.3%, a specificity of 96.2% and a PPV of 77.7% and an NPV of 98.7%. It was found to be comparable to our study.

The area under the curve as obtained by ROC analysis in this study for RMI in predicting the accurate diagnosis of malignant adnexal mass was 0.984 with 95% confidence interval (0.934, 0.998). The best cut-off for that RMI was found to be 450 with a sensitivity of 100% and specificity of 100% (Figure 2). In another study done by Geomini and colleagues (2009),[29] different models including various morphological scoring system of RMI 1, RMI 2 were compared in predicting malignancy of ovarian mass. They concluded the Risk of Malignancy Index should be the prediction model of choice in the preoperative assessment of the adnexal mass. Most studies reported an increased diagnostic accuracy and performance with an RMI cut-off of 200[32] similar to the findings of this study. Finally, according to the data published in the article depicting a registry of ovarian cancer in Kolkata,[33] a minimum sample size of (n=100) per study arm could have a greater statistical significance in establishing the effectiveness of RMI -3 score.

Limitations

There are certain limitations in this study which needs to be addressed. Firstly, the sample size of this study was small which definitely might have an impact the statistical analysis. Secondly, the short duration of the study i.e. 1 year and patient follow-up data did not form a part of this study. Thirdly, the study population included does not represent all social classes. Fourthly, this was not a multicentric study and any variation in the result from different institute cannot be analyzed from a single study centre.

CONCLUSION

RMI score can be a reliable tool in differentiating benign from malignant adnexal masses due to its simplicity, easy to apply and cost effectiveness thereby helping in identifying those patients who will require staging laparotomy. It can be effectively used by the general gynecologists at different level mainly practicing at the peripheral centers and transfer the doubtful patients to oncological centers so that those with ovarian masses with low RMI score can be treated by first line therapy with minimal aggressive procedures and thus improves their chances of survival.

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