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CO-RELATION OF HISTOPATHOLOGICAL DIAGNOSIS WITH CONVENTIONAL RMI SCORING IN EVALUATION AND DIFFERENTIATION OF BENIGN FROM MALIGNANT ADNEXAL MASS

Dr Sachin Siddu[1], Dr Sadhana Bharati[2*], Dr Anita Gond[3], Dr Sunil Kumar[4]

[1]Assistant professor, department of obstetrics and gynaecology, MRAMC Ambedkar Nagar
[2*]Senior resident, department of obstetrics and gynaecology, MRAMC Ambedkar Nagar
[3]Assistant professor, department of obstetrics and gynaecology, MRAMC Ambedkar Nagar
[4]Senior resident, department of general surgery, BKASMC Chandauli

***Corresponding author:**Dr Sadhana Bharati
*Senior resident, department of obstetrics and gynaecology, MRAMC Ambedkar Nagar

ABSTRACT

BACKGROUND: To study the efficacy and reliability of RMI scoring in differentiating malignant from benign adnexal mass and its co-relation with histopathological diagnosis.

METHODS: This is hospital based observational study for a period of 1 year which included 133 patients of adnexal mass attending the OPD who required admission and operative intervention. All cases underwent clinical examination, ultrasonography and RMI scoring. Following surgery specimens were sent for histopathological examination and the reports were co-related with RMI scoring.

RESULTS: Out of the total of 133 patients, 33(24.8) patients had malignant adnexal mass, and 100(75.2%) patients had benign adnexal mass. The average RMI for benign and malignant mass was 66.89 and 1341.88 respectively and p value is <0. 001. Out of 33 malignant tumors, 5(15.15%) had RMI <200 and among 100 benign tumors, 95 had RMI<200. Out of 33 malignant tumors, only 28 (84.84) had RMI score >200 where out of 100 benign tumors only ,5 (5%) had RMI score >200. The sensitivity, specificity, positive and negative predictive value of RMI cut off score are 84%, 95%, 95% and 84%. The mean RMI in benign cases is 48.57 (±82.11), while in malignant cases, it is significantly higher at 999.75 (±2082.83). The t-value is -4.32 with a p-value of less than 0.001, indicating a highly significant difference. The benign group contained 8 (8.99%) persons with a menopause score of 0, whereas the malignant group had none. The benign group comprised 54 persons (60.67%) with a menopause score of 1, whereas the malignant group had 16 (37.21%). In the benign group, 27 (30.34%) had a score of 3, whereas 27 (62.79%) in the malignant group.

CONCLUSION: The present study demonstrated that RMI scoring is a reliable, effective and simple method in determining the risk of malignancy in adnexal mass in low resource settings. It can be used as a primary method in differentiating malignant adnexal mass from benign, can also be used as an index of referral to higher center from an institute with limited resources for further evaluation and management.

Keyword: Adnexal mass, Malignancy, Ultrasonography, Histopathology

1. Introduction

The ovary is a crucial organ because it is involved in the creation of offspring. Mesenchymal cells and sex cells, which are totipotent and multipotent, respectively, make up the ovary. Consequently, almost any type of tumor can develop when it turns neoplastic. [1]

Adnexal mass is commonly seen among both pre-menopausal and post-menopausal women.[2] In pre-menopausal women, the most common causes of adnexal mass are ectopic pregnancy, ovarian cysts, tumors, polycystic ovaries and abscess. Malignant adnexal mass are usually seen among postmenopausal women, though the majority of these women have benign pathologies. [3,4]

After cervical and uterine cancers, ovarian cancer is the third most common gynecologic malignancy in women.[5] Rate of ovarian cancer survival in the general population varies between 30 to 40% in the world.[6] Ovarian cancer has a 6.6/100,000 "age-standardized" incidence rate and a 3.9/100,000 mortality rate.[7] The incidence of ovarian cancer in India is reportedly the second highest worldwide. Menopausal women account for 90% of ovarian cancer cases, often between the ages of 55 and 64, suggesting that longer life expectancy may be contributing to the global rise in ovarian cancer rates.[8] Ovaries are least accessible female reproductive organs because of which there is delay in diagnosis of ovarian disorders including borderline tumors and ovarian malignancies.[9]

Cancer Antigen (CA125) is elevated in ovarian cancers and hence can be used as biomarker for diagnosis of the same. "Human Epididymis protein" (HE4) is another biomarker used for diagnosis.[10] Determination of Ovarian Cancer using these biomarkers is highly specific yet insensitive. An improved, more useful and more sensitive metric is the "Risk of Malignancy Index" (RMI). RMI is calculated using a simple regression equation that takes into account the "menopausal status" score (M), the "ultrasonographic" score (U), and the "absolute" value of blood CA-125. [11-13] The RMI's excellent sensitivity for ovarian cancer diagnosis holds up when tested on a new cohort of women and remained consistent with the original paper outlining its development. A more precise diagnosis of ovarian cancer may be made using the RMI, the research found as compared to using the individual criteria.[14] A recent study indicated that a higher RMI cut-off of 238 had a sensitivity of 89.5%, specificity of 96.2%, positive predictive value of 77.3%, and negative predictive value of 98.4% when used for screening.[15]

2. Methods

This observational study was conducted on patients with an adnexal mass admitted for surgical management IPD from July 2018 to June 2019 for a total period of 1 year in department of Obstetrics and gynaecology , B.R.D. Medical college Gorakhpur.

Inclusion criteria -All consenting women who have an ovarian mass on presentation were recruited in this study and they were recruited in cohort and was operated and got histopathology reporting done.

Exclusion criteria – Patients with abdominal mass managed conservatively, Ectopic Pregnancy and patient diagnosed with malignant mass who are already on treatment for malignancy.

Detailed history, presenting complaints and menstrual history were obtained. Complete general physical with gynecological examination were performed and provisional diagnosis was made. To evaluate the adnexal mass further and ultrasonography examination consisting of transabdominal and transvaginal ultrasound were done where sonographic findings regarding size of adnexal mass, laterality, locularity, solid elements, hemorrhage, presence of ascites and evidence of metastasis. Color doppler was added in suspicious cases of malignancy and doppler studies with pulsatility index (PI) and resistance index (RI) were assessed, ultrasound scoring was made. Standard laboratory tests consisting of complete haemogram, blood sugar level, liver function test, renal function test and Serum CA 125 are done in every case. Risk of malignancy index scoring is calculated for every case by using formula RMI= serum CA-125 x M x U. In RMI scoring, U

indicates ultrasound score, it is 0 if no abnormality,1 if one abnormality and 3 if there are more than two abnormality and M indicates menopausal score ,1 in pre-menopausal, 3 for Post-menopausal. Laparotomy or Laparoscopy was performed, and specimen was sent for histopathological examination and reports were correlated with RMI score.

Histopathological report was considered as the primary outcome parameter. Age group, parity, menstrual history, Risk Malignancy Index, etc., were considered as explanatory parameters. Mode of presentation, USG features, etc., were considered as study relevant variables. Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. The association between explanatory variables and categorical outcomes was assessed by cross tabulation and comparison of percentages. Odds ratio along with 95% CI is presented. The Chi square test was used to test statistical significance.

Histopathological report was considered as gold standard. Risk of malignancy index was considered as screening test. The sensitivity, specificity, predictive values and diagnostic accuracy of the screening test along with their 95% CI were presented.

P value <0.05 was considered statistically significant data was analysed by using coGuide software, V.1.01.[16]

3. Observation

A total of 133 patients of various age group who presented with an adnexal mass in Gynaecology OPD of BRD Medical college, Gorakhpur for prediction of benign or malignant nature of lesion by calculating the RMI Scores, and the verification of diagnosis was done by histopathological examination of the tissue obtained after laparotomy.

Table 1: Distribution of adnexal mass

Nature of tumor	Number	percentage
Malignant	33	24.8%
Benign	100	75.2%
Total	**133**	**100.0%**

Out of the total of 133 patients, 33(24.8) patients had malignant adnexal mass and 100(75.2%) patients had benign adnexal mass.

Table -2: Distribution of malignant mass based on histopathology

Histopathological type	Number	Percentage
1.Epithelial cell tumors	**24**	**72.72**
Serous cystadenocarcinoma	11	33.33
Mucinous cystadenocarcinoma	7	21.21
Endometrioid cystadenocarcinoma	3	9.09
Clear cell adenocarcinoma	3	9.09
2.Sex-cord stromal tumors	**9**	**27.27**
Immature teratoma	2	6.06
Endodermal sinus tumor	2	6.06
Dysgerminoma	3	9.09
Granulosa cell tumor	2	6.06
Total	**33**	**100**

Out of 33 malignant tumors in our study, majority (72.72%) were epithelial cell ovarian carcinoma. Out of this serous cystadenocarcinoma was the most common (33.33%) and clear cell carcinoma was the least common (9.09%). Sex cord stromal tumors were 9 in number, thus constitutated

27.27% of all the malignant mass ,among these dysgerminoma was the most common (9.09%) and granulosa cell tumor was the least common (6.06%).

Table -3:Distribution of benign mass based on histopathology

Histopathological type	Number	percentage
1.Non -Neoplastic	**27**	**27**
Endometrioma	9	9
Follicular cyst	11	11
Tubercular TO Mass	3	3
Corpus luteal cyst	4	4
Hydrosalphinx,TO-mass(non-tubercular)	5	5
2.Neoplastic	**73**	**73**
Serous cystadenoma	32	32
Mucinous cystadenoma	24	24
Fibroma	5	5
Thecoma	4	4
Dermoid tumor	8	8
Total	**100**	**100**

Out of the 100 benign mass, majority were of epithelial cell type 73%.Among these, serous cystadenoma was the most common 44% (32/73) followed by Mucinous cystadenoma 33% (24/73). Among the non-neoplastic tumors, follicular cyst is the most common.

Table4: Distribution of malignant and benign mass based on sonographic morphology

Sonographic morphology	Malignant(n=33)		Benign(n=100)		Total(n=133)	
	No	%	No	%	No	%
1.Multilocularity	22	66.6	48	48	70	52.6
2.Presence of ascites	18	54.5	29	29	47	35.3
3.Bilaterality	16	48.4	15	15	31	23.3
4.Presence of ascites	23	69.6	5	5	28	21
5.Evidence of metastasis	7	21.2	0	0	7	21.2

The sonographic feature which was most prevalent among the malignant group was the presence of ascites (69.6%), closely followed by the presence of multilocularity (66.6%). Multilocularity was also the most common sonography feature among the benign mass (48.%) . Evidence of metastasis was the most distinguishing sonography feature for malignancy, as this was found only among the malignant group (12.1% prevalence) and is never found in the benign mass. Solid areas and bilaterality were more commonly seen among the benign mass as compared to the malignant mass.

Table 5:Distribution of malignant and benign mass according to cut-off level of serum CA125

Serum CA125	Malignant(n=33)		Benign(n=100)		Total(n=133)	
	No.	%	No.	%	No.	%
>35 U/ml	25	75.75	33	33	58.75	43
<35 U/ml	8	24.24	67	67	75.24	56

Out of 33 malignant tumors, 25 (75.75%) had serum CA125 >35 U/ml, whereas out of the 100 benign tumors, only 33 (33%) had serum CA125 >35 U/ml ; these benign mass mainly belonged to the epithelial cell tumor group and inflammatory tubo-ovarian mass. Out of the 33 malignant tumors, only 8 (24.24%) had serum CA125 <35 U/ml. These included endodermal sinus tumor, dysgerminoma, granulosa cell tumor and immature teratoma**.**

Table 6: Distribution of adnexal mass based on cut of RMI score

RMI cut of score	Malignant(n=33)		Benign(n=100)		Total (133)	
	No	%	No	%	No	%
<200	5	15.15	95	95	100	75.18
>200	28	84.84	5	5	33	24.82

Malignant and benign tumors were divided taking a cut-off level of RMI Score 200 out of 33 malignant tumors 5(15.15%) had RMI <200 where out of 100 benign tumors only 95 had RMI<200.Out of 33 malignant tumors, only 28 (84.84) had RMI score >200 where out of 100 benign tumors only 5 (5%) had RMI score >200. The sensitivity, specificity, positive and negative predictive value of RMI cut off score are 84%, 95%, 95% and 84%.

Table 7: Average values of the RMI scoring

Variable	Malignant	Benign	P value
RMI Value	1341.88±2362.02	66.89±95.82	<0.001

The average RMI for benign and malignant mass was 66.89 and 1341.88 respectively and p value is <0.001.

Table 8: Association of mean RMI and CA-125 in between Benign and Malignant

	Benign		Malignant		t	p-Value
	Mean	±SD	Mean	±SD		
RMI	48.57	82.11	999.75	2082.83	-4.32	<0.001

The table presents a comparison of the Risk of Malignancy Index (RMI) and CA-125 levels between benign and malignant cases. The mean RMI in benign cases is 48.57 (±82.11), while in malignant cases, it is significantly higher at 999.75 (±2082.83). The t-value is -4.32 with a p-value of less than 0.001, indicating a highly significant difference.

Table 9:

Test Result variable(s)	Area under curve	Std.Error[a]	Asymptomatic Sig.[b]	Asymptomatic 95% Confidence interval	
				Lower Bound	Upper bound
CA -125	0.838	0.065	0.000	0.711	0.964
Menopause	0.555	0.080	0.490	0.398	0.712
RMI Score	0.841	0.068	0.000	0.708	0.973
USG	0.498	0.080	0.981	0.342	0.654
Solid areas	0.383	0.079	0.141	0.227	0.538
Multi-locularity	0.439	0.078	0.442	0.286	0.592
Bilaterality	0.347	0.081	0.054	0.188	0.505
Ascites	0.188	0.069	0.00	0.052	0.324
Metastasis	0.294	0.084	0.010	0.130	0.458

Serum CA 125 had an area of 0.838, SE of 0.065 and Asymptomatic 95% CI of 0.711 to 0. 964.Thus in the present study, CA 125 was found to be relevant predictor of malignancy. Menopausal status had a area of 0.555, SE of 0.080 and Asymptomatic 95% CI of 0.398 to 0. 712.Thus, menopausal status was a poor predictor of malignancy if used alone.RMI had the greatest area of 0.841,SE of 0.068 and Asymptomatic 95% CI of 0.708 to 0.973.Although ,statistically significant differences were recorded between malignant and benign groups in the ultrasound score variable as a whole, the individual parameters of ultrasonography did not appear to be good

predictor of malignancy when used individually. The area under the curve for solid areas was 0.383, multilocularity was 0.349, bilaterality was 0.347, ascites was 0.188 and metastasis was 0.294.
The test result variables serum has at least one tie between the positive actual state group and negative actual state group. Statistics may be biased because of
a. Under the non-parametric assumption
b. Null hypothesis: true area=0.5

Table 10: Association of frequency of different menopausal score between Benign and Malignant

		Benign		Malignant		Chi Sq.	p-Value
		n	%	n	%		
MENOPAUSAL SCORE	0	8	8.99	0	0.00	14.34	<0.001
	1	54	60.67	16	37.21		
	2	0	0.00	0	0.00		
	3	27	30.34	27	62.79		

The benign group contained 8 (8.99%) persons with a menopause score of 0, whereas the malignant group had none. The benign group comprised 54 persons (60.67%) with a menopause score of 1, whereas the malignant group had 16 (37.21%). No one in either group scored 2. In the benign group, 27 (30.34%) had a score of 3, whereas 27 (62.79%) in the malignant group did. Researchers found a substantial link between menopausal scores and the chance of a disease developing malignant (chi-square test: 14.34, p-value <0.001).

4. Discussion

1.Out of the total of 133 patients, 33(24.8) patients had malignant adnexal mass and 100(75.2%) patients had benign adnexal mass.

2.Out of 33 malignant tumors in our study, majority (72.72%) were epithelial cell ovarian carcinoma. Out of this serous cystadenocarcinoma was the most common (33.33%) and clear cell carcinoma was the least common (9.09%). Sex cord stromal tumors were 9 in number, thus constituted 27.27% of all the malignant mass ,among these dysgerminoma was the most common (9.09%) and granulosa cell tumor was the least common (6.06%).
A study conducted by Rai Ret al came to conclusion that female with age more than 50 years, post-menopausal status, and high RMI were significantly associated with malignant epithelial ovarian tumors but BMI, parity and the OCP did not show significant association.[17]

3.Out of the 100 benign mass, majority were of epithelial cell type 73%. Among these, serous cystadenoma was the most common 44% (32/73) followed by Mucinous cystadenoma 33% (24/73). Among the non-neoplastic tumors, follicular cyst is the most common.
Another study conducted by Rai Ret al came to conclusion that adnexal masses are an important cause of morbidity and mortality. The most commonly encountered adnexal mass were benign and arose from the ovary. Germ cell tumors and serous cystadenocarcinoma being the most common malignant and benign ovarian tumor respectively. Benign adnexal mass were most common in younger women. However, patients with malignancy were seen old females and mostly postmenopausal. Fifteen percent of all adnexal mass were malignant and most of them presented in the advanced stages.[17]

4.The sonographic feature which was most prevalent among the malignant group was the presence of ascites (69.6%), closely followed by the presence of multilocularity (66.6%). Multilocularity was also the most common sonography feature among the benign mass (48.%) . Evidence of metastasis was the most distinguishing sonography feature for malignancy, as this was found only among the

malignant group (12.1% prevalence) and is never found in the benign mass. Solid areas and bilaterality were more commonly seen among the benign mass as compared to the malignant mass.
5.Out of 33 malignant tumors, 25 (75.75%) had serum CA125 >35 U/ml, whereas out of the 100 benign tumors , only 33 (33%) had serum CA125 >35 U/ml ; these benign mass mainly belonged to the epithelial cell tumor group and inflammatory tubo-ovarian mass. Out of the 33 malignant tumors, only 8 (24.24%) had serum CA125 <35 U/ml. These included endodermal sinus tumor , dysgerminoma, granulosa cell tumor and immature teratoma**.**
Khoiwal K et al. conducted a study and concluded that with respect to adnexal mass, both CA-125 and RMI scoring are important diagnostic tools. RMI scoring has better efficacy than CA-125 in predicting malignancy in adnexal mass. RMI scoring improves the prognosis of patient with ovarian malignancy and it provides the general gynecologist an idea regarding the treatment options and an further option to refer patient with suspected malignancy to oncologist.[18]

6.Malignant and benign tumors were divided taking a cut-off level of RMI Score 200 out of 33 malignant tumors 5(15.15%) had RMI <200 where out of 100 benign tumors only 95 had RMI<200.Out of 33 malignant tumors, only 28 (84.84) had RMI score >200 where out of 100 benign tumors only 5 (5%) had RMI score >200. The sensitivity , specificity, positive and negative predictive value of RMI cut off score are 84%, 95%, 95% and 84%.
One more study conducted by Dora SK et al are in a view that there is no universal screening method for differentiation between benign and malignant adnexal mass as of now. So many researchers have tried for earliest diagnosis of malignant ovarian tumors by various investigations. These may be earliest clinical features, tumor markers, imaging studies, cytology but no method yet is a definite method for screening of cancer ovary, In conclusion, the present study demonstrated that in the absence of a definite biomarker, Risk of Malignancy Index (RMI 3) was a better estimate in diagnosing adnexal masses with high risk of malignancy and subsequently guiding the patients to gynecological oncology centers for suitable and effective management compared with individual parameters of Ultrasound score, CA-125 or menopausal score and a cut-off point of 236 shows a very high sensitivity, specificity , positive predictive value , negative predictive value and diagnostic accuracy were respectively 72.5%,98.2%,98.1%,74.7% and 84.13% for discriminating malignant and benign pelvic masses. Simplicity and applicability of the method in the primary evaluation of patients with pelvic masses makes it a good option in daily clinical practice in non-specialized gynecologic departments. Besides in a low resource setting where sophisticated radiological and biochemical test may not be available at all places where RMI can be used as a investigations for the triage of patient with adnexal mass and referral to a higher center.[19]

7.The average RMI for benign and malignant mass was 66.89 and 1341.88 respectively and p value is <0.001.

8.The table presents a comparison of the Risk of Malignancy Index (RMI) levels between benign and malignant cases. The mean RMI in benign cases is 48.57 (±82.11), while in malignant cases, it is significantly higher at 999.75 (±2082.83). The t-value is -4.32 with a p-value of less than 0.001, indicating a highly significant difference
A study conducted by Javdekar et al concluded that RMI is a reliable tool in differentiating benign from malignant adnexal mass. It is simple, easy to use and cost effective. However it's predictive accuracy was less for mucinous when compared to serous epithelial ovarian cancers. The study is limited by its small sample size.[20]
Another study conducted by Rai Ret al came to conclusion that RMI and histopathology findings are in positive correlation. Therefore, it can be concluded that RMI can be used for pre-operative evaluation of adnexal mass. The sensitivity of our preoperative evaluation through RMI can be improved along with the of new scoring models like IOTA rules and by integrating color Doppler study with gray-scale ultrasound.[18]

One more study conducted by Christopher A and concluded that risk of malignant index ,it is a reliable, cheap, readily available and cost-effective method in preoperative discrimination of benign from malignant adnexal mass. It is also helpful in triaging patients to different treatment groups.[21]

9.Serum CA 125 had an area of 0.838, SE of 0.065 and Asymptomatic 95% CI of 0.711 to 0.964.Thus in the present study , CA 125 was found to be relevant predictor of malignancy. Menopausal status had a area of 0.555, SE of 0.080 and Asymptomatic 95% CI of 0.398 to 0.712.Thus, menopausal status was a poor predictor of malignancy if used alone.RMI had the greatest area of 0.841,SE of 0.068 and Asymptomatic 95% CI of 0.708 to 0.973.Although ,statistically significant differences were recorded between malignant and benign groups in the ultrasound score variable as a whole, the individual parameters of ultrasonography did not appear to be good predictor of malignancy when used individually. The area under the curve for solid areas was 0.383 , multilocularity was 0.349, bilaterality was 0.347 , ascites was 0.188 and metastasis was 0.294.

10.The benign group contained 8 (8.99%) persons with a menopause score of 0, whereas the malignant group had none. The benign group comprised 54 persons (60.67%) with a menopause score of 1, whereas the malignant group had 16 (37.21%). No one in either group scored 2. In the benign group, 27 (30.34%) had a score of 3, whereas 27 (62.79%) in the malignant group did. Researchers found a substantial link between menopausal scores and the chance of a disease developing malignant (chi-square test: 14.34, p-value <0.001).

5. Conclusion

The present study demonstrated that RMI scoring is a reliable ,effective and simple method in determining the risk of malignancy in adnexal mass in low resource settings. It can be used as primary method in differentiating malignant adnexal mass from benign, can also be used as an index of referral to higher center for further evaluation and management.

7.Limitation

As this was a single center, hospital based study and it does not represent an entire population and as our sample size was relatively small, our results may have less statistical power and it is difficult to draw a definite conclusion.

8.Source of funding

None

9.Conflict of interest

The author declared no conflict of interest

10.Ethical approval

All procedures followed were in accordance with the institutional ethics committee for human research,

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