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Risk of Malignancy Index (RMI) as Preoperative Diagnosis of Ovarian Mass

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ABSTRACT

Background: Pelvic masses are among most the common causes of patient admission into gynecology clinics and gynecologic oncology departments due to the risk of uterine or ovarian malignancies. Aims and Objectives: To estimate the risk of malignancy as an effective method for differentiation of malignant vs. benign masses in an attempt to achieve early pre-operative diagnosis. **Methods:** A total of 100 women in the age group of 20 to 80 years presenting with at least one persistent ovarian mass that was selected for surgical intervention, were included in the study. The risk of malignancy index was estimated by using a combination of serum CA125 level, menstrual status (M), and ultrasound findings (U), the latter being composed of five characteristics (cystic multilocular lesion, solid lesion, bilateralism, ascites, and metastasis). **Results:** Of 100 ovarian masses included in the study, 82 (82%) were benign and 18 (18%) were malignant. The mean value of preoperatively determined CA125 serum levels of the patients with benign cases was 28.91u/ml, and those with malignant cases was 561.90u/ml. 88.8% of malignant cases have true RM12 value of >200 RMI 2 at a cut off 200. **Conclusion:** RMI to be a valuable, reliable, and applicable method in the primary evaluation of patients with pelvic masses.

Keywords: CA125, Malignancy Index, Ovarian Mass, Premenopausal, Postmenopausal, Ultrasonography.

INTRODUCTION

The most prevalent type of pelvic masses is ovarian masses, which include cysts and tumors. The size of the mass, its mobility, consistency, shape, possible internal aqueous component, and associated pain are helpful features for diagnosis of the nature of the mass.[1]

Ovarian mass is the frequent cause of gynecological consultation and are often detected during imaging studies or exploratory surgery for acute abdomen. They occur across different age groups and could result from benign to malignant. Ovarian masses, however benign in 90% of cases, are the fourth most common gynecological causes for hospitalization. The differential diagnosis of ovarian mass varies from functional cysts to benign and malignant tumors.[2,3]

Up to 24% of ovarian tumors in premenopausal woman is malignant and upto 60% are malignant in postmenopausal women.' They have lowest 5-year survival rate (30-50%) among gynecological cancers. correct preoperative diagnosis is crucial and remains a challenging issue for gynecologists. On the other hand, identifying women with benign pathology is important in order to avoid unnecessary morbidity as well as unnecessary costs. Preoperative evaluation of ovarian mass is rather complicated process as the differentiation of benign and malignant mass is difficult. However, when evaluated individually the efficacy of ultrasound, demographics and biochemical values are incapable of distinguishing benign from malignant tumors.[4-6]

The rate of malignancy in pelvic masses of pre-menopausal women is approximately 24% while in post-menopausal women it increases to more than 60%, mostly from uterine or ovarian cancer. Unfortunately, most of these masses are asymptomatic or considered unimportant, leading to a delay in admission, difficulty of curative surgery, and ultimately decreased survival. In retrospective studies published during the past decade, the importance of estimating the risk of malignancy as an effective method for differentiation of malignant vs. benign masses was emphasized in an attempt to achieve early pre-operative diagnosis by using a combination of serum CA125 level, menstrual status (M), and ultrasound findings (U), the latter being composed

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of five characteristics (cystic multilocular lesion, solid lesion, bilateralism, ascites, and metastasis).[2,3]

The risk of malignancy index (RMI) was developed for referral of relevant patients to gynecologic oncologic centres. It has been suggested that decisions on how to manage women with an ovarian mass be taken on the basis of the Risk of Malignancy Index (RMI) by the Royal College of Obstetricians and Gynecologists (RCOG).[7,8]

MATERIALS & METHODS

This is a descriptive correlative study conducted in the Department of Obstetrics and Gynecology, Chalmeda Anand Rao Institute of Medical Sciences, Karimnagar, Telangana, India from October 2017 to November 2019. A total of 100 women were included in the study. The research protocols were ratified by the Ethics Committee at Chalmeda Anand Rao Institute of Medical Sciences and informed consent was obtained from all the subjects.

Inclusion Criteria:

Women in the age group of 20 to 80 years presenting with at least one persistent ovarian mass that was selected for surgical intervention were eligible for the study.

Exclusion Criteria:

1. Pregnant women with ovarian masses,
2. Patients who are diagnosed with ovarian malignancy before and who are on treatment.

Data Collection:

At the time of registration, a standardized history was taken, including the patient's age and menopausal status, information on personal history of ovarian and breast cancer, number of first-degree relatives with ovarian or breast cancer, current hormonal therapy and previous gynecological surgery.

Preoperative menopausal status, ultrasound findings and serum CA-125 levels were noted. Postmenopausal status was defined as more than 1 year of amenorrhea or age older than 50 years in women who had undergone hysterectomy. All other women were considered premenopausal.

The ultrasound was performed transabdominally by a 7.5-MHz transducer (Philips HD11 machine).A standardized approach was used to carry out ultrasonography in all the women. A score was assigned for the presence of following ultrasound features suggestive of malignancy: Multilocularity, Solid areas, Bilateral lesions, Ascites and Intraabdominal metastases. A score of one was assigned for the presence of each ultrasound feature. A total ultrasound score (U) was thus calculated for each patient. In the event of multiple masses, the mass with the most complex used ultrasound morphology was collect information on tumor characteristics for statistical analysis. When masses with similar morphology were observed the larger of the two masses or the one most easily visible by ultrasonography was included.

Serum samples were collected peripheral venous blood samples of 5ml were drawn preoperatively from each patient observing universal precautions. The blood was centrifuged at 3000 rpm for 10 minutes. CA125 was assayed in the serum by electrochemiluminescence immunoassay using a commercial kit by Global diagnostics.

Data Analysis:

Data was analyzed by Pearson's Chi square test. The x-test was used to test differences in distribution of age, menopausal status, ultrasound score. All statistical analyses were done using Statistical Package for Socla Sciences (SPSS) 17.0.

The histopathological diagnosis was considered as the gold standard for defining the outcomes. Tumors were classified as benign, borderline or invasive. Surgery was performed by laparoscopy or laparotomy according to the surgeon's judgment, and the subsequent tissue examination was performed at the Department of Pathology, Chalmeda Anand Rao Institute Of Medical Sciences. In case of a borderline or invasive tumour, surgical stage was recorded according to the criteria recommended by the International Federal of Gynecology and Obstetrics (FIGO).

RESULTS

Of 100 ovarian masses included in the study, 82 (82%) were benign and 18 (18%) were malignant [Table 1 & Figure 1].

Table 1: Nature of Ovarian masses

Nature of Ovarian Mass	Number of Cases	Percentage of Cases
Benign	82	82%
Malignant	18	18%

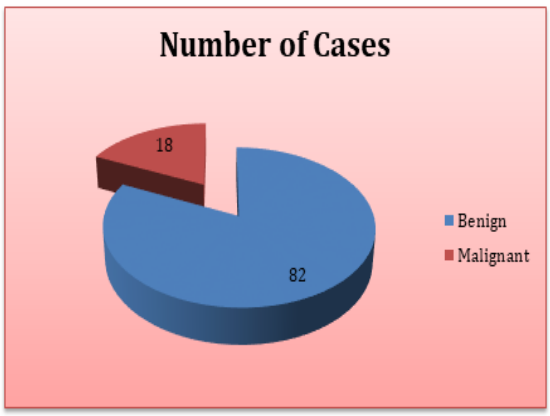

Figure 1: Nature of Ovarian masses

The mean age of the patients with benign lesions was 37.16 years, those with malignant masses was 56.6 years. Of 100 cases, 73 were premenopausal and 27 postmenopausal. 11 out of 18 malignant cases were seen in postmenopausal group. The mean value of preoperatively determined CA125 serum levels of the patients with benign cases was 28.91u/ml, and those with malignant cases was 561.90u/ml. Multilocular cysts were seen in 77.78% of malignant ovarian tumour in comparison to 47.56% of benign tumours. 72.3% of the malignant ovarian were found to have solid areas in contrast to only 23.2% of benign tumours. Only 4 of the 18 malignant masses was bilateral, among benign lesions 11 were bilateral. Ascites was present in 44.5% of malignant tumour but it was absent in benign tumour. 3 out of 18 malignant cases had distinct metastasis, none in benign cases. Total ultrasound score is calculated, score >2 is seen in 61.1% of malignant cases and 19.52 % of benign cases [Table 2].

Table 2: Characteristics of Ovarian masses

Characteristic of Ovarian Mass	Benign	Malignant
Age	37.16 years	56.6 years
Mean CA125 serum level	28.91u/ml	561.90u/ml
Multilocular cysts	47.56%	77.78%
Solid Areas	23.2%	72.3%
% of Bilateral cases	13.41%	22.22%
Presence of Ascites	Absent	44.5% cases
Total ultrasound score of <2	80.48% cases	38.9% cases
Total ultrasound score of >2	19.52 % cases	61.1% cases
RMI <200	91.4 % cases	11.1 % cases
RMI >200	8.5 % cases	88.8 % cases

Table 3: Mean RMI in all cases

Histopathology	No. Of Cases	Incidence (%)	Mean RMI
Serous cystadenocarcinoma	12	5	1457.54
Mucinous cystadenocarcinoma	5	27.7	2088.08
Dysgerminoma	1	0.5	38.8
Simple cyst	16	19.5	41
Endometriosis	9	10.9	83.47
Functional cyst	11	13.4	27.98
Haemorrhagic cyst	3	3.6	21.36
Serous cystadenoma	27	32	62.1
Mucinous cystadenoma	9	10.9	154.48
Dermoid cyst	6	7.3	50.48
Granulosa cell tumour	1	1.02	5

Table 4: Diagnostic efficacy of RMI 2 scoring system

Statistical Parameter	Percentage
Sensitivity	88.8%
Specificity	91.4%
Positive predictive value	69.5%
Negative predictive value	97.4%

In total 7 cases were false positive (RMI >200, benign) and 2 cases were false negative (RMI <200, Malignant). Among the false positive ovarian cystadenomas accounted 42.8%, simple cysts for 14.3%, dermoid cyst for 14.3%, endometriosis for 28.6%.the false negative cases were primarily stage 1 invasive carcinoma and dysgerminoma having RMI <200 [Table 3 & 4].

DISCUSSION

Pelvic masses are one of the most common reasons for the patient's referral to gynecologic oncology centres. The rate of malignancy in pelvic masses of premenopausal age group is approximately 24% and while in postmenopausal women it increases to more than 60%. Unfortunately most of these masses are asymptomatic or considered unimportant leading to delay in admission, difficulty in curative surgeries and ultimately decreased survival. 2/3rd of ovarian cancers are detected after metastasis or at stages 3 and 4 where the survival rate is very low. RMI is a straight forward algorithm that is simple to apply in clinical practice. It uses inexpensive tests that are commonly available and easily reproducible. It is the simple scoring system which can be used in daily clinical practice by all gynecologists in detecting malignant ovarian tumors. It is also reliable and convenient method for preoperative differentiation and early referral to gynecologist.[9-11]

Guidelines from the Royal College of Obstetricians and Gynecologists (RCOG) in the UK suggest using the RMI to categorise women with an ovarian mass into three groups. For tumours classified as low risk, the proposed management is expectant management or laparoscopic surgery by a generalist in a gynecology unit. If at moderate risk, laparoscopic surgery in a cancer unit by a surgeon with a special interest is suggested. If at high risk, referral of the woman to a cancer centre for a full staging procedure by a subspecialist gynecological oncologist is advised.[8-12]

Formula for RMI 1, 2 and 3: U x M x CA125.

Formula for RMI 4: U x M x CA125 x S.

CA125 levels are taken as serum values applied directly as u/ml.

Ultrasonography is widely accepted as best imaging method for evaluation of ovarian pathology. In this present study 61.1 % of the malignant masses had an ultrasound score of 22 compared to only 19.5 % of the benign lesions. The sensitivity of ultrasound in present study is 61.1% which is similar to Aziz etal.4 Univariate analysis of the individual ultrasound parameters showed that presence of solid areas and ascites were highly suggestive of malignancy CA 125 level is widely accepted as a useful biomarker for estimating the risk of ovarian malignancy.

The major limitation of CA125 is that it may be high in benign diseases, Such as endometriosis, ovarian cysts, and pelvic inflammatory disease. We found higher level of serum CA125 among women with endometriosis when compared to women with other benign tumors (70.26 U/ml versus 26.98 U/ml). This is similar to study by Yamamoto et al6 where mean serum level of CA125 significantly higher in those with endometriosis when compared to other benign tumors (85.4 U/ml versus 32.8 U/ml).

The present study has demonstrated the usefulness of the RMI in pre-referral evaluation of patients with demonstrated pelvic masses. It confirmed the ability of RMI 2 to discriminate correctly between malignant and benign pelvic masses, and confirmed the high specificity of the RMI at the optimal cut-off point of 200.The median values of the calculated RMI for benign and malignant cases were 24.9 (2-272) and 1460.85 (9.7-4446.4) respectively. There was a significant difference between the two groups ($p < 0.001$). The index (RMI 1) developed by Jacobs et al,[11] for distinguishing benign and malignant masses pre-operatively at a cut off level of 200 had a sensitivity of 85.4% and a specificity of 96.9%.

Yorito Yamamoto et al6 found that the optimum identification of malignant pathology with RMI 2 with cut off 200 showed sensitivity of 81.1 % and specificity of 89.6%. A lower specificity would lead to an undue number of referrals of benign cases, which is unacceptable for the referring hospital and unmanageable for the special centres. On the other hand, this will aid in selection of cases for a conservative nonsurgical approach, for example, ultrasound guided aspiration of clear cysts or those which can be managed by a general gynecologist.

Van Den Akker et al,[8] performed a study on 548 patients, with a mean age of 52 for those with benign lesion and 62 for those with malignant masses. This study involved 415 benign mass (76%), 80 malignant mass (24%), and 53 borderline malignancies (10%). The most common benign and malignant masses were mucinous cysadenoma and serous cystadenocarcinoma, respectively. They calculated one RMI with a cutoff point of 200, at which the sensitivity, specificity, PPV, and NPV were 81%, 85%, 48%, and 96%, respectively.[8]

Manjunath et al. study was done on 152 patients with pelvic masses (mean age for benign masses was 45 and for malignant ones it was 49). Of these masses, 38.8% (n=62) proved to be benign (the most common was cysadenoma) and 61.2% (n=93) proved to be malignant (the most common being serous cysadenocarcinoma). Three RMI were checked without considerable difference in calculated parameters and in all RMIs the best cutoff point was at 20.0.12

Ideally, preoperative evaluation should be able to identify all cases of malignant tumors of the ovary. Our results have demonstrated the limitations of RMI 2 in identifying patients with stage I invasive disease. The low level of CA 125 and the low ultrasonographic score along with the premenopausal status of the women, are likely to explain the false negative results.

28.5% of false positive results are endometriosis because of high CA 125 levels leading to high RMI score. The positive predictive value of RMI 2 was 69.5% which is almost similar to previous study by Watcharda et al9. The sensitivity of RMI is almost similar to other studies when compared to Obeidat et al and Jacobs et al.[10,11]

However, RMI uses ultrasonography imaging, which is subject to interpreter variability between and within centres, as well as variation between patient populations. The demerits of this study included the small sample size, late stage of diagnosis of malignancy and possible interobserver variability among sonographers.

It is important to address that both prevalence of ovarian malignancy and ultrasonographic skills have an impact on diagnostic performance. Therefore, the results of this study, which conducted at the tertiary care hospital, may not represent for primary or secondary care hospitals.

CONCLUSION

From the present study 88.8% of malignant cases have true RM12 value of >200 RMI 2 at a cut off 200 to differentiate between benign and malignant ovarian tumors had a sensitivity of 88.8% and specificity of 91.4%. Univariate analysis of the individual parameters showed that ultrasound Score of 22 and serum CA125 at cut off level of 35 U/ml were highly significant in predicting malignancy. Ultrasound score was associated with the sensitivity and specificity of 61.1% and 80.4% respectively.

The present study has demonstrated the RMI to be a valuable, reliable, and applicable method in the primary evaluation of patients with pelvic masses. Because of the simplicity of the method it can be used in daily clinical practice in nonspecialized gynecologic departments and by all gynecologists for differentiating benign from malignant ovarian masses. Hence RMI is very useful in preoperative evaluation of ovarian mass even in rural population.

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