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Comparative Analysis of Two Risk of Malignancy Indices (RMI) in the Accurate Detection of Pre-Operative Malignant/Benign Ovarian Masses

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ABSTRACT

Background: Any pelvic/ovarian mass, whether unilateral or bilateral, is one of the leading indications in OPD for sending a patient to gynecologists. However, these gynecological masses often are benign and may or may not require surgical excision. Almost 24% of pelvic tumors in women of reproductive age group are malignant and in Postmenopausal up to 60% are malignant.

Objective: The study was aimed at comparative analysis of accuracy of two different RMI indices (i.e. RMI- 2 & RMI-3) in the pre-operative detection of malignant ovarian masses in females of all ages.

Methods: This prospective study intended to include 75 women who got 1st admission to the Gynecology Department of Lady Willingdon Hospital for the evaluation and management of pelvic or ovarian masses. To differentiate between malignant and benign ovarian tumors, their sensitivity, specificity, Positive and Negative predictive values and the ability to diagnose accurately of two RMIs (RMI 2 and RMI 3) was ascertained.

Results: Study findings reveal no mathematically significant difference in the results of the two different Risk of Malignancy Indices (RMIs) when assessing for malignancy. Nevertheless, it is noteworthy that RMIs emerged as more reliable tools in detection compared to relying solely on blood CA-125 levels, if female is pre or post-menopausal, or certain ultrasound features and size of the tumor in isolation for identifying malignant ovarian masses.

Conclusion: It can be summed up that any of the two RMIs described in this study can be applied for evaluation of patients for appropriate therapy. This method of RMI is a simple basic technique and it can be used anywhere, in less-equipped gyne departments to help the doctor in the establishing the nature of cases for referral to an oncology department or hospital.

Keywords: *Pelvic mass, Ovarian CA, Risk of malignancy index (RMI), Benign Ovarian*

INTRODUCTION

Any pelvic/ovarian mass, whether unilateral or bilateral, is one of the leading indications in OPD for sending a patient to gynecologists. However, these gynecological masses often are benign and may or may not require surgical excision. Almost 24% of pelvic tumors in women of reproductive age group are malignant and in Postmenopausal up to 60% are malignant.[1-3] Using current available diagnostic modalities The pre-op decision of whether a mass is malignant or benign is always in doubt. Early Surgery may be planned only if malignant nature of an ovarian mass is proven. Factors like preponing surgery, extent of surgery and expertise of the oncological surgeon play an important part in prognosis of patient. A very effective method for the pre-op determination of a pelvic mass from benign to malignant will definitely lead to much more women receiving 1st step of treatment from a properly trained surgeon in no time.[4,5] Therefore more efficient and improved, specified methods for diagnosing accurately the ovarian cancers in no time are need of the hour.

Investigators from all around the world are using a variety of sonographic records and dimensions so as to precisely detect a malignancy, including the Doppler studies of masses.[6-12] Discussions include the relation between ovarian tumors and many other tumor markers.[13-16] Various prepositions are there to use cumulative methods for evaluating the cancer risk in a pelvic mass.[17,18] Beauty of this RMI is a simple multiplying system that uses the menopausal status, different sonographic findings, and multiplies them with blood concentration of specific tumor marker. This method, in turn, gives us much better outcome than keeping in view any single counting parameter.[18-23] The RMI can be applied in less privileged/ dedicated gyne or cancer centers. The (RMI) index comprises of three variables: the sonographic scores (*U*), the menopausal status of the lady represented as *M*, and the laboratory value of blood/serum CA-125:

RMI = $M \times U \times$ CA-125.

Now known as RMI 1, the original RMI was formulated by Jacobs et al[18] in late 1990s. tingulstad, [19] in 1996,

redesigned RMI 1 to create RMI 2, which he then modified again in 1999 to the RMI 3.[20, 24] These researchers included size of tumor to RMI and renamed it as RMI 4.

The main perspective this study was carried out was to evaluate and compare the ability of the two RMI (2 & 3) in distinguishing a benign from a malignant pelvic mass and thus establish which one of the two performs better and accurate.

METHODS

The clinical records of 75 women admitted to LWH between June 1, 2020 and January 31, 2021 who presented with an undiagnosed ovarian mass selected for laparotomy/laparoscopy were obtained. Women fulfilling inclusion and exclusion criteria were included in study. Detailed history including age, menopausal status, parity etc were taken. Clinical examination done in detail. Any risk factor was carefully considered. Consent form for being included in study was signed by women and care taker. Permission of study was taken from (i) Ethical Committee (ii) IRB

Inclusion Criteria include women with an ovarian mass clinically of any size, women of any age, woman that has not gone through any surgical intervention before, Post-menopausal status is defined as an amenorrhea of >1year, or woman age >50years or woman has undergone hysterectomy.

Exclusion Criteria include women having tumour with other conditions like Endometrioses, fibroids, pregnancy, PID, women not fit for a major surgery due to kidney or heart disease or pelvic surgery history. Any morbid condition, intra-operatively any mass other than ovary was found.

Serum CA-125 levels measured pre-operatively, ultrasonography findings made in detail covering all 5 diagnostic points, and menopausal status of women were noted. An expert Sonologist would do the TVS ultrasound transvaginal on every candidate by a 7.5-MHz transducer (Siemens). A simple abdominal scan would also be needed if a mass was larger. Each of the following ultrasound features was assigned a number to multiply to RMI scoring, thus suggestive of malignancy:

Ultrasound Findings (U)	total points attainable: 5
Multi-locular cysts	points gained: 1
Existence of ascites	points gained: 1
Lesions of bilateral nature	points gained: 1
Evidence of metastases	points gained: 1
Evidence of solid areas	points added: 1

U=0 would give an ultrasound score of 0 whereas
U=1 is considered for an ultrasound score of 1. However
U=3 will stand for an ultrasound score of 2-5

Preoperatively, peripheral vein blood samples were obtained from these women, and blood CA-125 levels were determined using (ECLIA) radioimmunoassay method specs in compliance with the manufacturing company's instructions. A level >200IU/ml in pre M and >25IU/ml in menopoaused women was considered high and at risk.

Menopausal status was given numbers as per RMI-2 and RMI-3 calculations.

Based on the above collected data, RMI 2 and RMI 3 were assessed for all patients. The following formulas were used to determine the specificity, sensitivity, NPV (i.e. Negative Predictive Value), PPV (Positive Predictive Value) and diagnostic accuracy for both methods:

1. RMI 2 (By Tingulstad in 1996):
    - Formula: M × U × CA-125
    - U (sonographic score): 1 if total score is 0 or 1, 4 if score is ≥2
    - M (menopausal status): 1 for premenopausal, 4 for postmenopausal
    - CA-125: Serum level used for multiplication [19].
2. RMI 3 (By Tingulstad in 1999):
    - Formula: M × U × CA-125
    - U (sonographic score): 1 if total score is 0 or 1, 3 if score is ≥2
    - M(menopausal status): 1 for pre-menopausal, 3 for post-menopausal
    - CA-125 value, directly put in the formula [20].

The gold standard for definitive outcomes was considered to be the histopathological findings of the removed pelvic masses and the subsequent pathology lab diagnosis. Borderline tumors were not included in the study, and the International Federation of Gynecology and Obstetrics (FIGO) classification was used to stage any positively identified tumor in the women under study.[21]

All calculations were obtained using SPSS version 15.0. The chi-square test was used to see the differences in the age distribution, menopausal status, and ultrasonography score. The Mann-Whitney U-test was used to test any differences in serum CA-125 distribution in women diagnosed with pelvic masses.

The sensitivity of the RMI is defined as the %age of patients with malignant disease and a positive RMI result, while specificity is said to be patient %age with benign disease and getting a negative RMI result. PPV is patient's percentage with a positive test result having malignant disease, and the NPV is the percentage of patients with a negative test result having benign disease.

RESULTS

The Research, which involved a histopathological examination of specimens collected surgically from 75 patients, the results revealed that 57 individuals (76%) had a benign condition, while 18 patients (24%) were diagnosed with malignant disease (Table 1). The classification based on histopathology of all cases, along with the staging of malignant cases, is detailed in Table 1. Additionally, the confirmed findings of benign & malignant cases based on sonography scoring, age, menopaused or not and the size of tumor based findings is presented in Table 2.

In the univariate analysis, a notable linear trend was observed for an increase in malignant transformation in correlation with rising ultrasound scores, as well as in both pre- and postmenopausal patients. While there is a tendency for the malignancy risk to increase with age, it did not touch statistical significance (p=0.051).

Table 1: *Classification (Histopathological) and Staging of All the Malignant Cases*

Sr. No.	Diagnosis	Pre-Menopause N = 56 N (%)	Post-Menopausal N = 19 N (%)	Total N = 75 N (%)
1.	Malignant = 18(24%) Epithelial Tumors Mucinous Clear cell	 3 (5.4) 2 (3.6)	 4 (21.1) 3 (15.7)	12 (16.0)
2.	Serous Cystadenocarcinoma		3 (15.8)	3 (4.0)
3.	Dysgerminomas	2 (3.6)	1 (5.8)	3 (4.0)
4.	Benign = 57 (76%) Simple Ovarian Cyst	15 (26.5)	2 (10.5)	17 (22.7)
5.	Adenofibroma	17 (30.4)	3 (15.8)	20 (26.7)
6.	Adenoma	6 (10.7)	1 (5.8)	7 (9.4)
7.	Dermoid Cyst	4 (7.2)	1 (5.8)	5 (6.7)
8.	Pyometra	3 (5.4)	1 (5.8)	4 (5.3)
9.	Tuberculous Cyst	4 (7.2)	-	4 (5.3)
	Total	56 (100)	19 (100)	75 (100)

The observations made in the study under consideration show no statistical or major difference in the effectiveness of the two RMIs used in diagnosing malignant from non-malignant masses

RMI-2 and RMI-3 had an accuracy of 88.5% and 90.4% respectively

It was also observed that both the risk of malignancy indices (RMI) are more reliable in detecting malignancy than the menopausal status, Or the blood CA-125 levels, Or the ultrasonography features Or the tumor size alone.

Receiver Operating Curves (ROC) showed RMI to be superior in diagnosing malignant cases more accurately than any of the parameters alone.

Table 2: *Distribution of the Benign Vs Malignant Cases Taking Age of Patients, Pre or Post- Menopaused Status, Serum CA-125 Levels and Ultrasonography Scoring*

Sr. No.	Variable	Benign N = 57 (%)	Malignant N= 18 (%)	P value
1.	Age			
	>30	20(35)	2(11.1)	>0.01
	30-35	7 (12)	3(16.7)	<0.05
	36-40	7 (12)	3(16.7)	<0.05
	41-46	11(19)	3(16.7)	<0.05
	>46	12 (21)	7(38.9)	>0.05
2.	Menopausal Status			
	Premenopause	47(82.5)	7(38.8)	>0.05
	Postmenopause	10(17.5)	11(61.3)	<0.05
3.	Imaging Score			
	0	8(14)	3(16.7)	>0.05
	1	21(36.5)	8(44.4)	<0.05
	2-5	26(49.1)	7(38.9)	<0.05
4.	Serum CA-125			
	level	95.3	164.3	-
	Mean	19	20	-
	Minimum	278	339	-
	Maximum			

Table 3: *Comparison Between RMI-2 & RMI-3 Tools in Diagnosing Accurately the Ovarian Pelvic Masses.*

	RMI-2	RMI-3
Sensitivity	77.7	79.1
Specificity	80.7	76.6
Accuracy	88.5	90.4

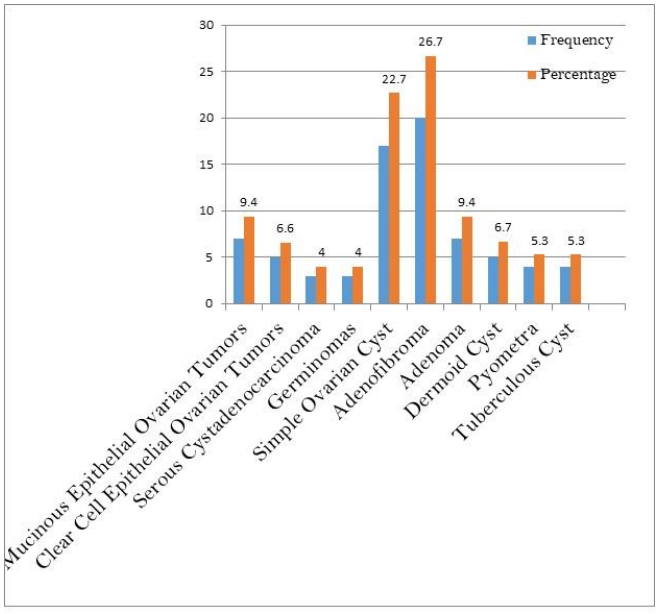

Figure 1: *Frequency and Percentage of Various Malignant/ Non Malignant Conditions of Pelvic Organs*

DISCUSSION:

Efforts have been made to identify a reliable, cost-effective, desktop-accessible tool for the pre-operative differentiation of benign from malignant transforming ovarian masses. The introduction of Malignancy Risk Indices (RMIs) in recent postgraduate medical studies aims to apply this practical predictive tool in clinical practice, contingent on achieving meaningful statistical significance (i.e. a p-value). Originating from the work of Jacobs et al[18], this method has been subject to experimenttation and validation in subsequent patient groups, confirming its superiority and accuracy in diagnosing CA over individual parameters.[22]

The study's analysis of the patient cohort indicates no statistically major or significant difference in the patient evaluation by the two distinct malignancy risk indices, RMI 2 and RMI 3, in distinguishing malignancy in pelvic masses. Earlier studies had suggested the greater reliability of RMI 2 in discerning between benign and malignant tumors.[19,23] Tingulstad[19] refined their RMI in 1996, designating it as RMI 2. Comparative analyses with RMI-1 demonstrated a significant superiority of RMI 2 at a cutoff value of multiples of 200. Consistently, across cut-off values ranging from 80 to 250, RMI 2 outperformed RMI 1 (p=0.0001). Further refinement by Tingulstad[20] introduced RMI 3, with sensitivity and specificity of 77.7% & 80.7%, respectively, at a cutoff level of 200.

In 2001, Manjunath et al[25] conducted a comparative study affirming no statistical distinction between RMI 2 & RMI 3 in discriminating benign from malignant pelvic masses. Results indicated a sensitivity of 85%, revealing a specificity of 87%, positive predictive value (PPV) of 60%, negative predictive value (NPV) of 95%, and 86% accuracy, comparable to Yamamoto et al.'s[24] findings. Importantly, the diagnostic performances of the other three indices differed from Yamamoto's results.

Malignancy Risk Index (RMI) emerges as a straightforward, highly accurate scoring system, positioning it as a promising tool in clinical practice. It is recommended as the primary test for preoperative evaluations of patients with adnexal masses. Subsequently, either RMI 2 or RMI 3 can be employed to precisely select cases for precise & direct therapy. The high specificity of RMI suggests its significant potential in

i- selecting cases for watchful waiting/ management (RMI <25)

ii- laproscopic/endoscopic excision for benign cases,(RMI<25)

iii- only aspiration of cyst under ultrasonography guidance

iv- laparoscopic cyst removal, with conservative management alone often proving sufficient. (RMI >25 <250)

CONCLUSION

However a women showing a high RMI score of more than 250 indicating the ovarian mass to be malignant, can be referred to tertiary care hospitals for a multidisciplinary approach. If the Ovarian Cancers can be diagnosed at stage I or II chances of survival of patient are increased by 85-90%.this leads to a decreased Mortality Rate by 50%. Thus this single RMI tool can help in saving time and direct triage of benign from malignant cases that Is of a great value for saving Human lives.

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AUTHORS' CONTRIBUTION:

SS: Conceived, designed and manuscript writing, analysis and data interpretation, final approval of manuscript.

MS: Helped in data collection and manuscript writing.

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