Original Article

EVALUATION OF RISK OF MALIGNANCY INDICES 1, 2, AND 3 IN PRE-OPERATIVE ASSESSMENT OF THE OVARIAN MASSES

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Abstract

Background: One of the common reasons, patients consult the gynecologist, is pelvic mass/adnexal mass. About 60% of ovarian tumors are malignant in post-menopausal women. Management of patients with adnexal masses primarily depends upon the nature of the mass, whether benign or malignant. In the pre-operative primary evaluation of ovarian/pelvic masses, different methods have been investigated. One of the most common methods that have been introduced is a risk of malignancy index(RMI) and its variants like RMI 1, RMI 2, RMI 3, and RMI 4. The efficacy of these indices has been compared based on their results. This study was conducted to evaluate the diagnostic role of RMI 1, 2, and 3, to assess the patients with ovarian masses before operation.

Objective: Evaluate the diagnostic role of risk of Malignancy Index 1, 2, and 3, in the primary Assessment of Patients with ovarian masses.

Methods: Study Design: observational Prospective study. Setting: At Fauji-Foundation Hospital Rawalpindi Pakistan. Duration: The Study was conducted for two years. One hundred and forty-one patients admitted for surgical exploration of ovarian mass were included in this study. Pre-operative ultrasound of ovarian mass, menopausal status, and serum biomarker CA125 were carried out for the patients. RMI 1, RMI 2, and RMI 3 for patients were calculated by applying the formula (RMI=U X M X serum biomarker CA125). Post-operative histopathology of resected ovarian mass was done in all the cases to confirm the diagnosis.

Results: Positive Predictive Value, Negative Predictive, Sensitivity, and Specificity were calculated for three RMIs. RMI 2 had higher Sensitivity than RMI 1 and 3. Receiver operating characteristic(ROC) curve was drawn for RMI1, 2, and 3. The area under the curve for RMI 2 is higher (0.812) than for RMI 1 and 3 (0.748).

Conclusion: RMI 2 showed better sensitivity than other indices. Test with a high specificity could increase the burden on resources by increased referral and more surgical removal of benign masses by a gynecological oncologist. This can be reduced by selecting a test with high sensitivity. So RMI 2 with high sensitivity can be selected out of other indices for prospective trials.

Keywords: Risk of Malignancy Index (RMI), Receiver Operating Characteristics (ROC), Biomarker Cancer Antigen 125 (CA125), Ovarian masses, oncological surgeries.

Introduction

Ovarian cancer is called a silent killer and has the highest mortality as compared to other cancers of the female reproductive system. Globally, 1.2 million females suffered from ovarian cancer merely in the year 2015 causing 160,000 deaths [1, 2]. One of the common reasons that patients consult a gynecologist, is pelvic mass/adnexal mass. Management of patients with adnexal masses primarily depends upon the nature of the mass, whether benign or malignant. An assessment tool that can preoperatively identify probable malignant masses can help to decide the first-line treatment for women with masses. Nowadays it looks workable method to subjectively identify ovarian tumors by an expert sonographer in combination with the use of serum markers preoperatively Mathematical predictive algorithms because of their simplicity are very effective and useful for those sonographers who have less expertise [3, 4]. Available pre-operative assessment tools including Pelvic assessment, tumor biomarkers like CA125, and radiological investigations, are not adequately sensitive or specific in their individual capacity. Different types of combined pre-operative assessment tools have been reported and studied in the literature to find out some better diagnostic tools [5-7]. Among them, the RMI is a commonly used method, which is based upon the female menopause standing or a tumor biomarker serum CA125 and mass features seen on ultrasonology [8]. This is a method in which scoring is done to select patients for initial tumor surgery at an oncology center. It can accurately differentiate malignant pelvic tumors from benign ones [6, 7, 9]. This simple tool with good sensitivity and specificity has been advised in the Guidelines of the Royal College of Obstetricians and Gynaecologists (U.K.) [10]. Jacobs et al for the first time introduced it and named as RMI 1. Then later on Tingulstad et al introduced RMI 2 and in 1999 after modification, they introduced RMI 3. Some researchers found no difference among all three RMIs' efficacy that may be considered statistically important [11], although few claimed RMI 1 more useful as compared to the other two [12]. This study was conducted to assess the diagnostic value of all three RMIs in the initial assessment of ovarian tumor patients,

Methodology

It was a prospective study carried out at Fauji Foundation Hospital Rawalpindi Pakistan. We obtained ethical approval from the ethical review board of Fauji foundation university medical college/hospital with IRB number FF/FUMC/215-79/phy/20.

One forty-one patients having ovarian masses scheduled for surgical intervention were inducted in the study after explanation and their written consent from the gynecology outdoor patient clinic at Fauji foundation hospital Rawalpindi Pakistan . Patients having functional cysts of <5 cm, signs evident of metastasis like peritoneal, hepatic or lung metastasis, already diagnosed ovarian malignancy cases receiving treatment like chemotherapy, masses that has arisen from gastrointestinal or urinary tract were not included in the study.

From all study participants, full history information was gathered, and general, as well as gynecological examination, was performed. For the calculation of serum CA125, we collected 5 ml of venous blood from all participants and send them to the bio-chemistry lab of Fauji foundation hospital. Women's status of menopause was also noted. The definition of menopause was taken as women having amenorrhea of one or more than one year or a hysterectomy was done. Then for these patients transabdominal or transvaginal ultrasound was carried out. The 3.5 MHz transducers were used for transabdominal scans and the 7.5 MHz transducers were used for transvaginal scans. The adnexal masses were studied for the following sonographic features: solid areas, bilaterality, multilocularity, metastases, and ascites.

We calculated RMI1, 2, and 3 by using the definitions by jacobs and S.Tingulated, who introduced RMI1, 2, and 3 for the first time [13, 14, 15].

	Menopausal status	**Ultrasound score**
RMI1	Premenopausal ⇨ M=1	Without any feature ⇨ U=0

	Post-menopausal ⇨ M=3	One feature ⇨ U=1 More than 2 features ⇨ U=3
RMI2	Premenopausal ⇨ M=1 Post-menopausal ⇨ M=4	<1 feature ⇨ U=1 >2 feature ⇨ U=4
RMI3	Premenopausal ⇨ M=1 Post-menopausal ⇨ M=3	<1 feature ⇨ U=1 >2 feature ⇨ U=3

CT scan and RMI were performed on the patients with inconclusive ultrasound findings. Specimens of the adnexal tumors were sent for histopathology to the department of Pathology, Fauji Foundation Hospital, Rawalpindi, Pakistan. A Definite diagnosis for every patient was made after the histopathology report results.

Data for RMI1, 2, and 3 were analyzed separately. Sensitivity, specificity, positive like hood ratio, and negative like-hood ratio, and accuracy were calculated. The diagnostic accuracy of RMI1, 2, and 3 were determined by ROC curves, conventionally prepared by plotting sensitivity against specificity.

Results

Histopathology of the surgical specimen revealed 107 benign masses (75.9%) and 34 malignant (24.1%). The mean age of the participants enrolled having benign and malignant masses was 39.41 ±12.21 years and 46.35 ±17.18 years respectively. Regarding histological subtypes, as shown in table1, out of benign masses, benign ovarian cysts were highest followed by endometrioma and mature teratoma. Regarding malignant masses, serous cystadenocarcinoma has the highest percentage followed by mucinous cystadenocarcinoma.

Table 1: Histological subtypes of ovarian masses

Benign tumors			**Malignant tumors**		
Subtype	**Number (107)**	**Percentage %**	**Subtype**	**Number (32)**	**Percentage %**
Serous cystadenoma	8	7.47	Serous cystadenocarcinoma	12	37.5
Mucinous cystadenoma	6	5.60	Mucinous cystadenocarcinoma	5	15.6
Mature teratoma	22	20.56	Endometroid adenocarcinoma	2	6.25
Endometrioma	25	23.36	Sarcomatous tumor	3	9.3
Benign ovarian cysts	30	28.03	Immature teratoma	2	6.25
Endometrioid tumor	3	2.80	Granulosa cell tumor	4	12.5

Fibroma	3	2.80	Dysgerminoma	1	3.1
Fibrothecoma	2	1.86	Ovarian yolk sac tumor	1	3.1
Paraovarian cyst	2	1.86	Fallopian tube adenocarcinoma	1	3.1
Tubo-ovarian abscess	3	2.80	Peritoneal carcinoma	1	3.1
Para-tubal cyst	3	2.80			

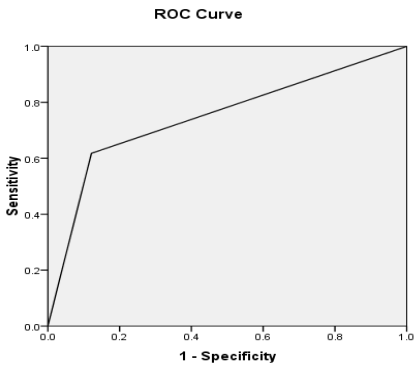
To assess the performance of RMI1, 2, and 3, sensitivity, specificity, Positive Predictive Value, Negative Predictive value, and accuracy were calculated at a cut-off value of 200 as shown in Table 2. Results show that RMI 2 has higher Sensitivity (76%) positive predictive value (63%), negative predictive value (92%), and accuracy (84%) than RMI 1 and 3respectively (62%,88%, 62%,88%,82%) but specify is slightly low (86%) than RMI 1, and 3(88%).

Table 2: Performance of RMI 1,2, and 3

	RMI – 1	**RMI - 2**	**RMI – 3**
Accuracy	82	84	82
Sensitivity	62	76	62
Specificity	88	86	88
Positive Predictive Value	62	63	62
Negative Predictive Value	88	92	88

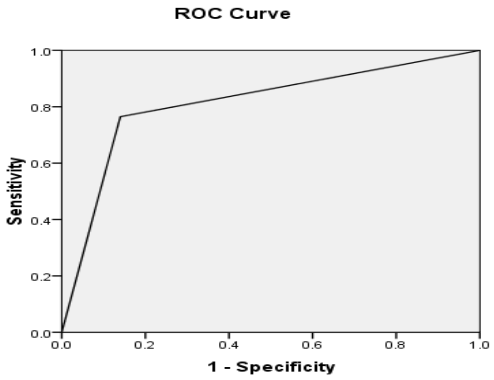
By plotting specificity against sensitivity, ROC curve was drawn for RMI1, 2, and 3 separately, shown in figs 1, 2, and 3. The area under the curve for RMI 2 is higher (0.812) than the area under the curve for RMI 1 and 3 (0.748) showing better performance of RMI2 than 1 and 3

Fig 1: ROC curve for RMI 1



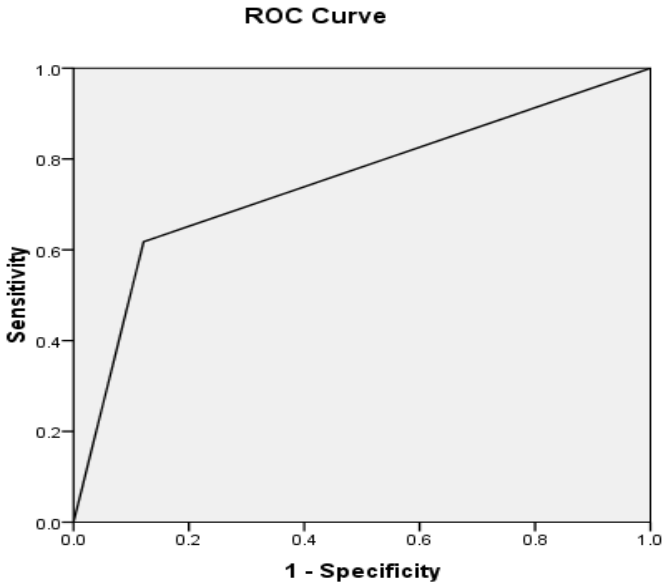
*Area under the curve 0.748

Fig2: ROC curve for RMI 2



* Area under the curve 0.812

Fig3: ROC curve for RMI 3



*Area under the curve 0.748

Discussion:

Ovarian tumor patients report usually in the last stage of the disease because the early-stage disease is usually asymptomatic and with nonspecific symptoms. Available diagnostic tools in their individual capacity are not capable of differentiating preoperatively between the malignant and benign masses [4]. RMI is a good tool that helps to enhance investigative precision in the pre-operative evaluation and helps decision-making for the most appropriate treatment by the appropriate surgeon [12]. Different forms of risks of malignancy indices are formulated and used in the literature for this purpose [16]. The mean age of the participants enrolled having benign masses was 39.41 years with a standard deviation of 12.21 years and the mean age of the patients with malignant masses was 46.35 years with a standard deviation of years which is comparable to the mean age in another study by Qiu L. reporting that average age of patients with malignant tumor was 46.58±9.80 years, and in those with benign pathology, it was 37.11±12.20 years [17]. In a study by Al-Asadi, mean age of the patients with benign tumors was 36.9 ± 10.7 and 58.4 ± 8.4 for patients with malignant tumors [18]. In our study, 75.9% of patients were having benign ovarian masses, while 25.1% of patients had malignant masses. Dora, S.K. et al reported a higher percentage of malignant tumors 54.76% (69/126) as compared to benign tumors which is 45.24% [19]. Qiu L reported in his study 69 (45.7%) had a malignant disease and 82 (54.3%) had benign pathology [17]. In our study RMI 2 has higher Sensitivity (76%) positive predictive value (63%), negative predictive value (92%), and accuracy (84%) than RMI 1 and 3 respectively (62%,88%, 62%,88%,82%) but specify is low (86%) than RMI 1, and 3(88%). Kulkarni KA et al [20], reported sensitivity of RMI 4 and RMI 2 79% and 82% while for these both methods' specificity values were 81% and 78% respectively. He concluded in his study RMI 4 was a quality method with balanced sensitivity and specificity. Relative to the other indices, RMI 2 was more sensitive but to a very limited extent and was less specific as compared to RMI 4. In a study by Yamamoto Y et al [21] mentioned values of the sensitivity were 73%, 81.1%, 73%, and 77% for RMI 1, RMI 2, RMI 3, and RMI 4 respectively while mentioned values of specificity for above indices were 93.7%, 8.6%, 93.%, and 92.3% respectively. He concluded that RMI 2 is statistically good at predicting malignant tumors than RMIs 1 and 3 but the RMI 2 and 4 are the same in this regard. In our study, RMI 2 was also found better at predicting malignancy with an accuracy of 84 for RMI 2 and 82 for RMI 1 and 3 (table 2). Further confirmed by plotting ROC curve for all the three indices (fig 1, 2 3) Area under the curve for RMI 2 is high (0.82) as compared to RMI 1 and 2 (0.74) showing better performance of RMI 2. while Ozun Ozbay Pelin et al [22] in his study statistically found the performances of RMI 1 and 4 equally good. Shuang Zhang et al. [12] concluded in their study that RMI 1 was the best-performed method for differentiating borderline ovarian tumors from benign. Hayam FM et al [23], analyzed the receiver operator characteristic curve of 5 RMIs and observed the RMI 1 as the best predictor of malignant ovarian tumors. These results are exactly in line with the RCOG guidelines which consider RMI 1 as a gold standard for differentiating between benign and malignant tumors before surgical procedure. As we know that RMI and IOTA SR are extensively applied tools to feature the ovarian masses but nowadays for this sake a large number of other tools like IOTA-LR2 and the ADNEX-model are available. It increases more than ever the necessity to examine the accuracy of such tools [24].

Conclusion:

RMI 2 showed better sensitivity than other indices. Test with a high specificity could increase the burden on resources by increased referral and more surgical removal of benign masses by a gynecological oncologist. This can be reduced by selecting a test with high sensitivity. So RMI 2 with high sensitivity can be selected out of other indices for prospective trials.

Limitation:

There is limited data available particularly from Pakistan about gynecological Oncology.

The sample size must be increased to get better results.

Suggestions:

Gynecological oncology is an evolving field of medicine. It needs more research and evidence to improve it further.

Conflict of interest:

There is no conflict of interest.

Financial disclosure:

None

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