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Original Research Article

Comparison of risk of malignancy indices in the preoperative evaluation of adnexal masses

Hassan Mansour Hegaab[1], Hossam El Sokkary[1]*, Reham Abo Elwafa[2], Eman Salem Elzeity[1]

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Alexandria, Egypt
[2]Department of Clinical and Chemical Pathology, Faculty of Medicine, Alexandria University, Egypt

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***Correspondence:**
Dr. Hossam El Sokkary,
E-mail: hossamsokkary@hotmail.com

ABSTRACT

Background: An adnexal mass patient is a common cause of hospital admission. The differentiation between malignant and benign cases is an important step in the management of such patients. The risk of malignancy index (RMI) is a simple scoring system depend on ultrasound data, menopausal status and serum concentrations of CA-125 tumor marker and has a great value in differentiation between benign and malignant adnexal masses. 4 different types of risk of malignancy index are created. The objective of the study was to compare the diagnostic performance of the four malignancy risk indices in differentiating benign and malignant ovarian tumors.
Methods: This prospective study was performed on 60 patients with an adnexal mass confirmed on vaginal ultrasound.
Results: There was statistical significance difference between the 4 types of RMI in benign and malignant groups. RMI 1, RMI 2, and RMI 3 had nearly the same area under the ROC curve; however, at the cut-off of>58.41, RMI 3 was more sensitive and less specific than RMI 1 or RMI 2. The RMI 2 was the most specific in predicting malignancy in terms of area under the curve; however, there was no statistically significant difference in performance of RMI 2 and 4 in malignant group.
Conclusions: RMI 1, RMI 2, and RMI 3 had nearly the same area under the ROC curve; however, at the cut-off of >58.41, RMI 3 was more sensitive and less specific than RMI 1 or RMI 2, on the other hand the most specific was RMI 2 more than the other 3 RMIs.

Keywords: Adnexal masses, Risk of Malignancy indices, Ovarian cancer

INTRODUCTION

Ovarian cancer represents a major health problem, it ranks the second most common gynecologic cancer after endometrial cancer, the fifth most common cause of death due to malignancies in women and the leading cause of death among genital tract malignancies in developed countries.[1]

Malignant tumors should be managed in specialized centers for gynecologic oncologic surgery with multidisciplinary team, therefore, differentiation between benign cases from malignant adnexal masses cases is essential to get the optimal management by referral to these specialized centers. The absence of an accurate examinations for early identification of ovarian cancer is important cause of deaths from this disease. Symptomatology of ovarian cancer is unspecific and related to gastrointestinal tract as nausea, vomiting constipation or urinary symptoms as dysuria and frequency that's why most cases are diagnosed at a late stage.[2]

An adnexal mass patient is a common cause of hospital admission. The differentiation between malignant and benign cases is an important step in the management of

such patients. Up to 24% of ovarian masses in premenopausal women are malignant and up to 60% of ovarian masses in postmenopausal are malignant.[3]

Ultrasonographic examination of adnexal masses is a simple cost-effective method with good access to the ovaries. It provides an accurate assessment of size, can differentiate between cystic and solid lesions, monitor changes in · appearance, and assess vascular supply and flow. Limitation of ultrasonographic examination of adnexal masses is a dependency on operator and quality of machine used.[4]

Many scoring systems have been tested for the aim to differentiate between benign or malignant adnexal masses.[5]

The risk of malignancy index (RMI) is a simple scoring system depend on ultrasound data, menopausal status and serum concentrations of CA-125 tumor marker. The combination of this multiple parameters is more sensitive and specific than a single parameter.[6] The RMI can be applied in less specialized centers not only in specialized centers for gynecologic oncologic. The risk of malignancy index is an equation in which we multiply the ultrasound scores by the menopausal score and the absolute value of serum CA-125 tumor marker levels.[6]

Tingulstad et al modified (RMI-1) for the first time in 1996 (RMI-2) and for the second time in 1999 (RMI-3).[7] RMI cut level value of 200 has been proven to be the best for differentiation between benign and malignant adnexal masses, recently, a fourth RMI was developed by Mohammed et al which includes tumor size as an additional parameter.[8]

Aim of the work

The aim of the study is to compare the diagnostic performance of the 4 types of malignancy risk indices in differentiating benign and malignant ovarian tumors.

Patients

The study was carried out on 60 patients with an adnexal mass confirmed on vaginal ultrasound. They recruited from Gynecology clinic or cases referred to the Gynecology unit of El-Shatby Maternity university hospital. Patients were followed until biopsy tacking and divided into 2 groups benign and malignant according to histopathological examination, each group was 30 patients.

Inclusion criteria were premenopausal or post-menopausal Patients with adnexal masses. Unilocular masses should be followed up for 2 months at least and more than 5 cm to be included in the study to exclude functional ovarian cyst. Solid masses or multilocular masses of any size were included from the start. The cases should be selected so that 30 benign masses and 30 malignant masses were included. Regarding exclusion criteria included any adnexal mass with pregnancy, cases with history of prior neo adjuvant chemotherapy, and Patients refused consenting to participate in the study.

METHODS

The study design was observational prospective analytic cross-sectional study.

All cases of this study submitted to the following

Informed consent, thorough history taking, menopausal status estimation as post-menopausal status was defined as more than one year of amenorrhea or age older than 50 years in women who had undergone hysterectomy without salpingo opoherectomy, all other women were considered premenopausal. Complete clinical examination, preoperative laboratory evaluation of the serum CA 125 levels by enzyme linked fluroscent assay and transvaginal sonography (TVS) was performed in all patients using machine with 5-7.5 mHz vaginal probe.

The characteristic appearance of masses (bilaterality, multilocularity of the adnexal mass, solid areas, ascites, intra-abdominal metastatic lesions) was recorded carefully as these points are used to calculate ultrasound score. Tumor size (S) was measured by ultrasound for each patient and used to calculate size score in risk of malignancy index.[4]

RMI scoring is based on ultrasonographic features, menopausal status, CA 125 levels and size for RMI.[4]

Based on the data obtained, RMI 1, RMI 2, RMI 3, and RMI 4 was calculated for all patients together with the sensitivity, specificity, diagnostic accuracy and positive and negative predictive values of the 4 risk of malignancy index. Calculation of risk of malignancy index is by multiplying ultrasound score, menopausal score, CA125 serum level and size score for only risk of malignancy index.[4]

For RMI 1, ultrasound score is calculated as follows 0 for no point, 1 for 1 point and 3 for 2 or more points while menopausal score is calculated as follows 1 for premenopausal state and 3 for postmenopausal status.

For RMI 2 ultrasound score is calculated as follows 1 for 0 or 1 point and 4 for 2 or more points while menopausal score is calculated as follows 1 for premenopausal state and 4 for postmenopausal status.

For RMI 3 ultrasound score is calculated as follows 1 for 0 or 1 point and 3 for 2 or more points while menopausal score is calculated as follows 1 for premenopausal state and 3 for postmenopausal status.

RMI 4 ultrasound score is calculated as follows 1 for 0 or 1 point and 4 for 2 or more points while menopausal score

is calculated as follows 1 for premenopausal state and 4 for postmenopausal status in addition size score is calculated as follows 1 for mass in which greatest diameter is less than 7 cm and 2 for mass with greatest diameter equal or more than 7 cm. Based on the data obtained, the RMI 1, 2, 3 and 4 scores was calculated for all patients and statistical correlation between 4 types concerning sensitivity, specificity, positive predictive value and negative predictive value were done. All cases are subjected to biopsy taking and histopathological examination after surgical staging or cytoreduction in apparently malignant cases, laparotomy in apparently benign cases and computed tomography scan guided biopsy in unresectable malignant cases. The histopathologic diagnosis of the adnexal masses regarded as the definitive outcome. The 60 cases were grouped into 2 groups benign and malignant according to histopathological examination.

Sample size calculation

The following formula was used to calculate the required sample size in this study;

$$n = Z^2 P(1-P) \div d^2$$

Where n is the sample size, Z is the statistic corresponding to level of confidence, P is expected prevalence, and d is precision (corresponding to effect size). The level of confidence was 95%. By using this equation the sample size was 30 cases in each group (i.e. 60 cases in the two groups).

Statistical analysis

The Data was collected and entered into the personal computer. Statistical analysis was done using Statistical Package for Social Sciences (SPSS/version 24) software.

The statistical test used as follow

Arithmetic mean, standard deviation, for normally distributed data, comparison between two independent population were done using independent t-test. Chi square test was used to compare between categorized data. The level of significant was 0.05.

RESULTS

The patients age ranged from 19-77 years with a mean of 49.4±11.28 years, the pre-menopausal cases were 23 cases (38.3%), while the post-menopausal were 37 cases (61.7%). There was no statistical significance difference between the 2 studied groups regarding the menopausal status.

Table 1: Comparison between benign and malignant group regarding clinical, ultrasound score, pathological and laboratory data.

	Malignancy		Test	P value
	Benign (n=30)	Malignant (n=30)		
CA125			199.50	0.001*
Mean± SD.	28.99±23.80	422.2±93607		
Tumor size				
Range Mean±S.D.	2-22 9.25±6.25	3-25 11.01±7.11	0.89	0.425
<7cm	13 (43.3%)	13 (43.3%)		
≥7cm	17 (56.7%)	17 (56.7%)		
U/S score				
0	5 (16.7%)	0 (0.0%)		
1	19 (63.3%)	3 (10.0%)	31.0	0.0001*
≥2	6 (20.0%)	27 (90.0%)		
Laterality				
Unilateral	28 (93.3%)	21 (70.0%)		
Bilateral	2 (6.7%)	9 (30.0%)	5.45	0.0208*
Locularity				
Unilocular	10 (33.3%)	3 (10.0%)		
Multilocular	20 (66.7%)	27 (90.0%)	4.81	0.020*
Ascites				
Negative	29 (96.7%)	14 (46.7%)	18.46	0.001*
Positive	1 (3.3%)	16 (53.3%)		
Premenopausal cases(n=23)	12 (52.2%)	11(47.8%)	0.071	0.791
Post menopausal cases(n=37)	18 (48.6%)	19 (51.4%)	0.071	0.791

Table 2: Comparison between four types of RMI.

	RMI 1	RMI 2	RMI 3	RMI 4
Benign (n=30)				
mean± SD.	81.55±130.7	141.1±218.2	95.26±126.9	220.7±355.7
Median	32.75	50.65	42.90	87.90
Malignant(n=30)				
Mean ± SD.	2504.1±3992.5	4166.5±6475.6	2504.1±10956.0	6583.5±10956.0
Median	597.6	981.6	1558.8	1558.8
P	0.001*	0.0001*	0.0001*	0.001*

Fr: Friedman test, Sig. bet. periods was done using Post Hoe Test (Dunn's) * : statistically significant at p<0.05. P: p value for comparing between benign and malignant in the same RMI

Table 3: Agreement (sensitivity, specificity) for different types of RMI and CA125 to predict malignant cases.

	AUC	P	95%C.I	Cut off	Sensitivity	Specificity	PPV	NPV
RMI 1	0.877*	<0.001*	0.791-0.962	>70.8	80.0	70.0	72.7	77.8
RMI 2	0.851*	<0.001*	0.753-0.949	>157.2	80.0	76.67	77.4	79.3
RMI 3	0.850*	<0.001*	0.752-0.948	>58.41	83.33	60.0	67.6	78.3
RMI 4	0.826*	<0.001*	0.719-0.932	>180.4	73.33	63.33	667.0	70.4
CA125	0.778*	<0.001*	0.659-0.898	>30.3	66.67	56.67	60.6	63.0

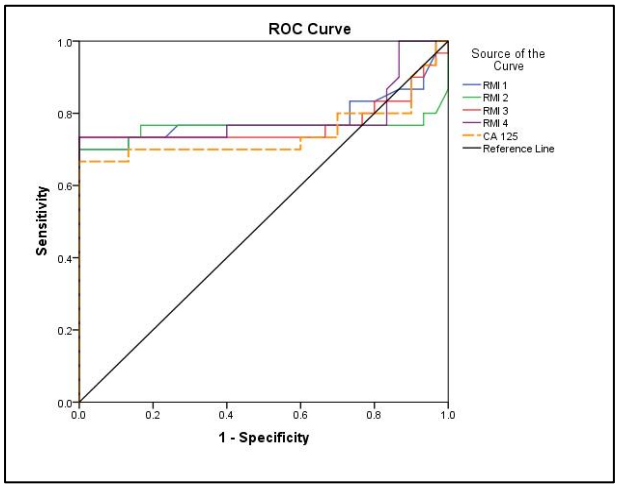

Figure 1: ROC curve to predict sensitivity and specificity of four types of RMI and CA-125. It showed that the most sensitive and negative predictive value of the 4 types of RMI was RMI3, while the most specific and positive predictive value was RMI2.

Table 1 shows that there was statistically significant difference between two studied group regarding CA125, U/S score, laterality, locularity, and ascites (p<0.05) while there was no statistically significant difference regarding tumor size (p>0.05).

Table 2 shows that there was statistically significant difference between different types of RMIs in both benign and malignant group, the higher significant difference was found in RMI3 and RMI 2, while both RMI 1 and 4 show a significant difference but less than RMI3 and 2.

Table 3 and figure 1 showed that different types of RMI had a significant predictive power in the differentiation of benign and malignant patients (p<0.05). The cut off value of different RMI from 1 to 4 were >70.8, >157.2, >58.41 and >180.4 respectively, while the cut off value of CA125 was >30.3. figure 1 shows ROC curve which demonstrates that the most sensitive and negative predictive value of all the 4 types of RMI was the RMI 3, while the most specific and positive predictive value was RMI 2.

DISCUSSION

In the present study, there was statistical significance increase in malignant group more than benign group regarding the ultrasound score of four types of risk malignancy indices.

The most important sonographic feature for diagnosis of malignancy was presence of ascites, bilaterality and complex solid areas that were evident in 94.l%, 81.8% and 80% of cases respectively; multilocularity is not constant feature for ovarian malignancy as it was evident in only 57.4% of cases.

The most sensitive and negative predictive value RMI was RMI3, while the most specific and positive predictive value was RMI2.

In agreement with the present study, Ali et al study in which 85.7% of women with ovarian malignancy had ultrasound scores more than 1, while only 6.5% of benign cases had ultrasound scores more than 1.9.

There was no statistical significant difference in malignant group more than benign group according to size of the tumor and the present study found that 56.7% of malignant cases had tumor size greater 7 cm. But the same time, 56.7% of the benign cases also had tumor size greater than 7 cm.

Therefore, tumor size greater than 7 cm could not be used to identify malignant ovarian masses.

In the study by van den Akker et al, which found that tumor size was useless for diagnosis of malignant ovarian masses because 60% of benign cases had the tumor size greater than 7 cm. also Ali et al study found that 85.7% of malignant cases had tumor size greater than 7 cm. But at the same time, nearly half of the benign cases (55.8%) also had tumor size greater than 7 cm.[10]

Regarding tumor marker CA125 in the studied group, CA125 showed statistical significant increase in malignant group more than benign group according to CA125 in the present study.

In agreement with the present study, Yamamoto et a1, found the mean serum level of CA125 was significantly higher among women with malignant ovarian masses compared with women with benign ovarian masses. With a mean of 1379.8 U/mL in suspected malignant group and a median of 285.3 U/mL, while in benign group its mean was 39.7 U/mL and its median was 18.8 U/mL.[11]

In the present study, four types of RMIs showed statistical significance with CA125 and ultrasound score, but menopausal status and tumor size show no significant difference.

In disagreement with the present study, Park et found that RMIs showed statistical significance with menopausal status (p=0.001) and tumor size (p=0.03), but not with CA125 ultrasound score (p>0.05}.[12]

In Park et al study, 43.4 % of patients with malignant ovarian tumors were post-menopausal compared to 24.7 % of patients with benign ovarian tumors. Also 85.0% of malignant cases had tumor size greater than 7 cm while 48.4% of the benign cases had tumor size greater than 7 cm.[12]

Manjunath et al study the difference between RMI 1, RMI 2, and RMI 3 with each other and established that there was no significant difference among these three directories in benign-malignancy prediction. This may be due to using different cutoff value which confirms the high specificity of all three risks of malignancy indices at an optimal cutoff of level of 200. The specificities of RMI 1, RMI 2, and RMI 3 were 91, 82, and 91 % respectively. Also, the reason may be that Manjunath et al had a higher percentage of ovarian cancer patients in the premenopausal age group (51 % vs36.7% in the present study).[13]

Also, Akturk et al found that there is no statistically significant difference in the performance of four types of malignancy risk indices in discriminating malignancy.[6] This may be due to using different cutoff value or low percentage of malignant cases in his study which include only 20% of cases with malignant ovarian tumors.

In the present study, The RMI 1 at cutoff: >70.8 yielded the sensitivity of 80.0%, specificity of 70.0% (AUC: 0.877, CI: 0.791 - 0.962), PPV 72.7% and NPV 77.8%.

In agreement with Terzic et al who found that The RMI at cutoff point of 107.4 had a sensitivity of 80.0% and a specificity of 70.3%.[14]

Terzic et al described a cutoff level of 200, with a sensitivity of 85% and a specificity of 97%.[14] However, most studies evaluate a range of cutoff levels varying between 25 to 200 and according to Geomini et al study When 200 was used as cutoff level, pooled estimate for sensitivity was 78% and for specificity was of 87%. At a cutoff level of 50, the pooled estimate sensitivity was 91% and for specificity was of 74%.[15]

In the present study the RMI 2 at cut off >157.2 yielded the sensitivity 80.0% and specificity of 76.67% (AUC: 0.851, CI: 0.753 - 0.949), PPV of 77.4% and NPV of 79.3%.

In agreement with the present study, Geomini et al set the cut-off value at 200, the pooled estimate of sensitivity was 79% and specificity was 81%.[15]

The RMI 3 at cut off: >58.41 had a sensitivity 83.33% and specificity of 60.0% (AUC: 0.850, CI: 0.752 - 0.948), PPV of67.6% and NPV of78.3% in the current study.

In agreement with the present study Ertas et al who found sensitivity of RMI 3 In postmenopausal women 84% at cutoff 200.[16]

The present study showed that RMI 4 at cut off of 180.4 had a sensitivity 73.33% and specificity of 63.33% (AUC: 0.826, CI: 0.719-0.932), PPV of66.7% and NPV of 70.4%.

The most sensitive and negative predictive value in the 4 types of RMIs was RMI3, while the most specific and positive predictive value was of RMI2.

The sensitivity of RMI 4 in the present study was similar to Yamamoto et al study that evaluated RMI 4 performance in discriminating ovarian masses. (56) in which RMI 4 had a sensitivity of 75%, specificity of 97.3%, PPV of 85.7%, NPV of 94.8 %.[11]

In a study by Clarke et al with a cut-off of 120, establish that RMI 1 a had a sensitivity of 72% and a specificity of 87%; RMI 2 had a sensitivity of 76% and a specificity of 81 %; RMI 3 had a sensitivity of 74% and a specificity of 84%.[17]

RMI 1, RMI 2, and RMI 3 had nearly the same area under the ROC curve; however, at the cut-off level of >58.41, RMI 3 was more sensitive and less specific than RMI 1 or RMI 2.

However, the RMI 2 was the most specific in predicting malignancy in terms of area under the curves; however, there was no statistically significant difference in performance of RMI 2 and 4 in malignant group.

In agreement with the present study, Yamamoto et al in which a direct comparison of the 4 indices showed that RMI 2 was significantly better at predicting malignancy than RMI 1 and 3 (p=0.04). There was no statistically significant difference in performance of RMI 2 and 4 using cut- off values of 200 for RMIs 1, 2, and 3 and cut-off value of 450 for RMI 4, The sensitivity of RMIs l, 2, 3, and 4 were 73.0%, 81.1 %, 73.0%, and 77.0%, respectively. The specificity of RMIs 1, 2, 3, and 4 were 93.7%, 89.6%, 93.7%, and 92.3%, respectively.10 In disagreement with the present study, Ertas et al found the RMI 1 was the most reliable in predicting malignancy in terms of area under the curves. This may be due to using different cutoff value 200 for RMI 1, 2, 3 and 336 for RMI 4; The RMI 1, 2, 3 and 4 yielded sensitivities of 76.1, 79.1, 76.l and 76.1 and specificities of 91.5, 89.1, 90.6, and 88.6 respectively.[16]

The main weakness in the present study was the limited number of cases so authors recommend to increase the cases number so cutoff value, specificity, sensitivity, positive and negative predictive value of the different RMI indices can be calculated more precisely.

CONCLUSION

In conclusion, the current study has proved that the 4 types RMIs are a valuable, dependable, and appropriate scoring system in the primary evaluation of females with adnexal masses and a usable method in referral of relevant patients to specialized centers of gynecologic oncologic. RMI 1, RMI 2, and RMI 3 had nearly the same area under the ROC curve; however, at the cut-off of >58.41, RMI 3 was more sensitive and less specific than RMI 1 or RMI 2, on the other hand RMI 2 was more specific than the other 3 RMIs.

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