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Assessment of the Value of a Modified Risk of Malignancy Index (RMI) in Preoperative Discrimination Between Benign and Malignant Ovarian Masses

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Abstract

Objectives: To assess the diagnostic accuracy of different risk of malignancy index (RMI) scores and to evaluate the role of a modified RMI (RMI 5) in pre-operative discrimination between benign and malignant ovarian masses.

Study Design: Prospective observational study.

Patients and methods: Women with a suspicious ovarian mass scheduled for laparotomy or laparoscopy were potentially eligible for inclusion in the current study. Trans-abdominal and trans-vaginal ultrasound with Doppler assessment of the adnexal masses was done. Calculation of the RMI 1, RMI2, RMI 3, RMI 4, and RMI5 was done. We compared RMI to histopathological outcome. In the current study, a new RMI score was created by adding Doppler blood flow of the ovarian mass to the calculation of the previous RMI1.

Results: One hundred and fifty women with ovarian masses were included in the current study. Ninety six women (64%) had benign ovarian masses while, malignant ovarian masses were found in 54 women (36%). Comparison between benign and malignant ovarian masses regarding to the risk of malignancy indices revealed that that there was a statistically significant difference between the two groups regarding to the risk of malignancy indices with P-value<0.001. Receiver operator characteristic curve analysis of the 5 RMI indices shows that the best method for prediction of malignant ovarian tumor was RMI 1. Also there was no statistically significant difference between the five methods in prediction of malignant ovarian tumors. RMI5 with cut off value of 250 is reliable tool at a tertiary center to discriminate between ovarian cancer and benign ovarian masses with a sensitivity of 90.38% and specificity of 93.88%. There was statistically significant difference between the different stages of ovarian cancer and RMI 5 with (P<0.05).

Conclusion: The RMI 1 is the gold standard for preoperative discrimination between benign and malignant ovarian masses. Adding Doppler flow to the parameters of RMI 1 (RMI 5) increased specificity of RMI 1 in detecting malignant ovarian masses.

Keywords: Risk of malignancy index (RMI); Ovarian malignancy; Gynecology

Introduction

Patients with malignant tumors should be evaluated by gynecologic oncologist as the quality of cytoreduction surgery and surgical staging/lymph node dissection are critical prognostic parameters in ovarian malignancy [1]. Before ultrasound was routinely feasible, the finding of a pelvic mass or a palpable ovary in a postmenopausal patient was contemplated to be an indication for surgery [2]. However, the large numbers of ovarian cysts now being ascertained by ultrasound and the low risk of malignancy of many of these cysts recommends non-surgical management [3]. The finding of an ovarian mass raises questions about the most suitable management and the place where this management is to be implemented [2]. The risk of malignancy index (RMI) is a simple scoring system depends on menopausal status, ultrasound findings, and the serum CA125 level. This score has given significantly superior results than the use of a single parameter [2]. Jacobs et al. in 1990 originally established the RMI, which they have assigned, RMI 1 [4]. Tingulstad et al. developed their variant of the RMI in 1996 and it is known as RMI 2 [5]. Furthermore, Tingulstad et al. in 1999 modified the RMI 2 and was termed RMI 3 [5]. The RMI 3 was adjusted by Yamamoto et al. to RMI 4 [6]. In the current study a modified RMI was created by adding Doppler blood flow to the parameters of ultrasound criteria and this scoring system was termed RMI 5. Doppler evaluation of adnexal masses was initially recommended as means of decreasing the false positive rates of ultrasound for ovarian cancer [7]. The role of color Doppler ultrasound in differentiating adnexal masses has been suggested in various published studies reporting diagnostic accuracies of about 90% [8]. Malignant tumors characteristically contain dilated saccular and randomly dispersed vessels [9]. 92.59% of malignant tumors showed RI less than 0.6 in contrast to only 9.49% of benign tumors [8].The aim of the current study was to assess the diagnostic accuracy of different RMI scores and evaluate the role of a modified RMI (RMI 5) in pre-operative discrimination between benign and malignant ovarian masses.

Materials and Methods

The current prospective observational was conduct at Ain Shams University Maternity. The Ethics Committee of Ain Shams University approved the study protocol. Informed consent was obtained from all participants after the nature of the procedures had been fully explained. Women with a suspicious ovarian mass scheduled for laparotomy or laparoscopy were potentially eligible for inclusion in the current study. All women were subjected to full history taking, general, abdominal aand local examinations. Trans-abdominal and trans-vaginal ultrasound with Doppler assessment of the ovarian masses was done using trans-abdominal 5 MHz and trans-vaginal 7.5 MHz probes, respectively (Medison, Sonoace X6, Korea). All ultrasound scans were performed by one sonographer who was blinded to the clinical history of the patients.

Serum CA125 levels were estimated pre operatively. Calculation of the RMI 1, RMI2, RMI 3, RMI 4, and RMI5 was done. We compared RMIs to histopathological outcome.

RMI 1=U x M x CA125. A total ultrasound score of 0 yielded U=0, a score of 1 yielded U=1, and a score of ≥2 yielded U=3. Premenopausal status yielded M=1 and postmenopausal status yielded M=3. The serum level of CA125 was multiplied directly to the formula [4]. RMI 2=U x M x CA125. A total ultrasound score of 0 or 1 yielded U=1, and a score of ≥2 yielded U=4. Premenopausal status yielded M=1 and postmenopausal status yielded M=4. The serum level of CA125 was applied directly to the calculation [5].

RMI 3=U x M x CA125. A total ultrasound score of 0 or 1 yielded U=1, and a score of ≥2 yielded U =3.Premenopausal status yielded M=1 and postmenopausal status yielded M=3.The serum CA125 level was applied directly to the calculation [5]. RMI 4=UxMxSxCA125. Where a total ultrasound score of 0 or 1 yielded U=1, and a score of ≥2 yielded U=4. Premenopausal status yielded M=1 and postmenopausal status yielded M=4. A tumor size (single greatest diameter) of <7 cm yielded S=1, and ≥7 cm yielded S=2. The serum level of CA125 was applied directly to the calculation [6].

In the current study, a new RMI was created by adding Doppler blood flow of the ovarian mass to the calculation of the previous RMI. RMI 5=CA125xUxMxD. Serum level of CA125 >30 U/ml was considered abnormal. Ultrasound findings (U) were scored with one point for each of the following: Multi-locular cyst, evidence of solid areas, evidence of metastases, presence of ascites, bilateral Lesions. U=0 (ultrasound score of 0), U=1 (ultrasound score of 1), U=2 (ultrasound score of 2–5). Menopausal status (M) was scored as follows: Postmenopausal status is graded M=3. Premenopausal status is graded M=1. Post menopausal status was assigned if the woman had more than one year of amenorrhea or was over 50 years of age if she had undergone hysterectomy. Doppler blood flow (D) of the ovarian mass was scored as follows: High blood flow is graded D=2. Low blood flow is graded D=1 [2].

Sample Size Justification

Data from a recent relevant study showed that among the included 253 women, 40(15.8%) had malignant lesion. The sensitivity of an RMI >200 in prediction of ovarian malignancy in the same study was 80%. Calculation of these values to produce the least statistically-acceptable figure produced a minimal sample size of 128 cases [6]. Therefore, 150 women with ovarian mass planned for laparoscopy or laparotomy was included in this study.

Statistical Methods

Statistical analysis was performed using Microsoft Excel version 2010 and Statistical Package for Social Sciences (SPSSR) for Windows® version 15.0. Continuous data presented as mean and standard deviation (if parametric). Dichotomous or categorical data presented as number and percentage. Difference between two independent groups estimated using independent student's t-test (for parametric continuous variables), Mann-Whitney's U-test (for non-parametric continuous variables) and Chi-squared test (for categorical variables).Receiver operator characteristics (ROC) curve constructed to assess the predictability of RMI for ovarian malignancy. Validity of this predictability expressed in terms of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Significance level is set at 0.05.

Results

One hundred and fifty women with ovarian masses were included in the current study. Ninety six women (64%) had benign ovarian masses while, malignant ovarian masses were found in 54 women (36%). In the current study, the most common benign ovarian pathology was the dermoid cyst (29.17%) followed by the endometriotic cyst (20.83%). In the current study, the most common malignant ovarian pathology in the current study was serous cyst adenocarcinoma (31.48%), followed by the mucinous cyst adenocarcinomas (20.37%), metastatic carcinoma (14.81%), anaplastic proliferative serous tumour (11.11%), papillary serous carcinoma (9.26%), Sertoli cell carcinoma (7.41%) and endometrioid adenocarcinomas (5.56%). The most prevalent malignant stages were stage 1b (16.7%), 2b (16.7%), 4(16.7%), followed by 1a (14.8%), 2a (7.4%), 2c (7.4%), 3c (7.4%), 1c (5.6%), 3a (3.7%) and 3b (3.7%). For all include women, the means of RMI1, RMI2, RMI3, RMI4 and RMI5 were 226.47 ± 380.34, 522.12 ± 985.29, 322.41 ± 568.86, 801.63 ± 1598.26 and 512.38 ± 944.86, respectively. Comparison between benign and malignant ovarian masses regarding to the risk of malignancy indices revealed that that there was a statistically significant difference between the two groups regarding to all the RMI indices with P-value<0.001 (Table 1). ROC curve analysis of the 5 RMI indices shows that the best method for prediction of malignant tumor was RMI 1 (Table 2 and Figure 1).

	Benign masses	Malignant masses	P value¥
RMI1	53.54 ± 71.47	533.91 ± 497.05	0
RMI2	98.59 ± 173.91	1275.07 ± 1331.34	0
RMI3	71.05 ± 108.21	769.28 ± 755.55	0
RMI4	158.23 ± 338.57	1945.46 ± 2212.02	0
RMI5	80.99 ± 132.07	1279.32 ± 1241.85	0
€Values are expressed as mean ± standard deviation ¥Analysis using Mann-Whitney test			

Table 1: Comparison between benign and malignant ovarian masses regarding to the risk of malignancy indices (RMIs)€.

Also the table shows that there was no statistically significant difference between the five methods in prediction of malignant tumors. RMI5 with cut off value of 250 is reliable tool at a tertiary center to discriminate between ovarian cancer and benign pelvic

masses with a sensitivity of 90.38% and specificity of 93.88%. There was statistically significant difference between the different stages of ovarian cancer and RMI 5 with (P<0.05).

	Cut-off value	AUC	Sensitivity	Specificity	PPV	NPV
RMI 1	>205	0.934	87.04%	83.33%	74.60%	92.00%
RMI 2	>189	0.915	83.33%	87.50%	78.90%	90.30%
RMI 3	>211	0.918	81.48%	87.50%	78.60%	89.40%
RMI 4	>315	0.907	79.63%	90.62%	82.70%	88.80%
RMI 5	>220	0.911	81.50%	92.70%	86.30%	89.90%
P value			0.648			

ROC: Receiver operator characteristic curve; AUC: Area under the curve; PPV: Positive predictive value; NPV: Negative predictive value

Table 2: Comparison between ROC curves for the risk of malignancy indices (RMIs) in prediction of malignant tumors.

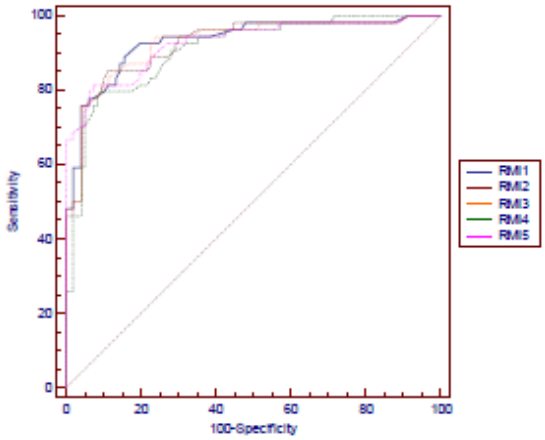

Figure 1: Receiver operator characteristic (ROC) curves for the risk of malignancy indices (RMIs) in prediction of malignant tumors.

Discussion

Due to the usual asymptomatic nature of the early stage ovarian cancer, many patients of ovarian cancer presented in the advanced stage for which the 5-year survival rate remains low [10]. The preoperative assessment of whether a mass is malignant cannot always be concluded with current diagnostic modalities. The diagnostic performance of demographics, ultrasound, and biochemical markers are insufficient for clinical application [1]. The development of a mathematical formula using a logistic model, including menopausal status, the serum level of a glycoprotein called CA 125 and ultrasound findings in a score system, has been authenticated in the literature in the form of different malignancy indices. This method has been developed to increase diagnostic accuracy for ovarian malignancy [8]. In the current study, at the cut-off level of 205, RMI I gave the sensitivity of 92.4% and, and the specificity of 83.33%. In agreement with the present study, at a cut-off point of 200, other investigators found that RMI 1 gave a sensitivity of 93% and a specificity of 91% [4]. Yet, other study reported lower results as RMI 1 gave sensitivity of 70.6%, specificity of 83.9%, at a cut off value of 200 [11]. Clarke et al. concluded that using a threshold (cut-off) value of 120, RMI 1 had a sensitivity of 72% and a specificity of 87% [1]. In the current study RMI 2 at a cut off value 189 gave sensitivity of 83 .33 % and specificity of 87.5 %. Moolthiya et al. found nearly similar results at a cut off value of 200, RMI 2 gave sensitivity of 80%, specificity of 78.2% and they denoted that RMI2 provided better diagnostic accuracy than the RMI 1 does.

In the current study RMI 3 at a cut off value 211 had sensitivity of 81.48% and specificity of 87.5%. The results of Yamamoto et al. were the nearest to the current study, as they concluded that at cut off value of 200, RMI3 had sensitivity of 82.6% and specificity of 84.6% [6].The current study depicted that at a cut off level of 315 RMI 4 gave the sensitivity of 79.63% and specificity of 92.7%. Yamamoto et al. at a higher cut off level of 450 reported a better sensitivity of 86.8%, whereas a specificity of 91.0% was comparable to the current results. To summarize, the current study shows that the most accurate diagnostic preoperative method which could differentiate benign from malignant ovarian masses is RMI 1 with sensitivity 92.4% and specificity of 83.3%.This is consistent with RCOG guidelines which considered RMI 1 the gold standard for preoperative discrimination between benign and malignant ovarian masses [3]. However, this disagrees with other investigators who concluded that RMI2 provided better diagnostic accuracy than the RMI 1 does [1,11]. Yamamoto et al authenticated that the RMI 4 at a cutoff level of 450 was significantly predicting malignancy better than RMI 1, RMI 2, and RMI 3 at a cutoff level of 200. The RMI 4 at a cutoff level of 450 had a sensitivity of 86.8%, a specificity of 91.0%, which could be attributed to the high cut off value (450).

The prevalence of malignancy in the current study is higher than that in the general population. This could be attributed to the fact that, our institution is a tertiary center. However, the prevalence of malignancy in the present study (35%) was similar to those in previous studies ranging from 29-35% [4,5]. The current study depicted that adding Doppler flow to the parameters of ultrasound increased sensitivity of RMI 5 in detecting malignant ovarian masses which agrees with others who suggested that ultrasound supplemented with Doppler and other findings according to a specific scoring system can facilitate the preoperative classification of complex benign ovarian lesions [12]. Also, the current study confirmed that the higher the RMI 5, the higher the suspected surgical stage of the ovarian cancer. This can be very helpful as regarding referral for a tertiary gynecology center for neo-adjuvant chemotherapy. However, this point still needs further verification by future studies due to lack of sufficient literature covering this point. As regarding age, most studies have evaluated patients with age above 30; however the present study included patients above 18 which gave the study a point of strength. Finally, despite the fact ultrasound reports were of good quality lack of standardization of ultrasound reports was a significant limitation for this study.

Conclusion

The RMI 1 is the gold standard for preoperative discrimination between benign and malignant ovarian masses. Adding Doppler flow to the parameters of RMI 1 (RMI 5) increased specificity of RMI 1 in detecting malignant ovarian masses.

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