EVALUATE THE EFFECTIVENESS OF THE RISK MALIGNANCY INDEX (RMI) IN BOTH PREMENOPAUSAL & POSTMENOPAUSAL WOMEN WITH OVARIAN TUMOR

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ABSTRACT

Objective

To evaluate the effectiveness of a risk malignancy index (RMI) in both premenopausal and postmenopausal women with ovarian tumor.

Study design

Prospective observational study between October 2017 and October 2018.

Setting

Department of obstetrics and gynecology, Baghdad teaching hospital.

Patients and methods

Fifty-two women with ovarian mass enrolled in the study Preoperative serum CA125 level, ultrasound findings and menopausal status were recorded to calculate the risk malignancy index (RMI) accounting for each patient. Laparotomy done for each patient and histopathological result were recorded.

Results

From the Fifty-two women, 71.2% were premenopausal and 28.8% were postmenopausal, twenty-two women (42.3%) had malignant ovarian tumors and 65% of malignant cases were postmenopausal.

CA125 concentration was more significant among postmenopausal women than premenopausal (median 152IU/ml versus 32 IU/ml) respectively.

Risk malignancy index (RMI) score yielded better diagnostic performance for ovarian masses differentiation than individual parameter. The optimal RMI score to predict malignancy was at a cut-off value of 209 with a sensitivity of 72.7 % and a specificity of 100%. The ROC (receiver operating characteristic) curve for the RMI score was 0.97, which greater than the areas for U/S (0.94) and CA125 (0.84).

Conclusion

Risk malignancy index (RMI) is a simple diagnostic tool provides a quantitative assessment of risk of malignancy by incorporating serum CA125 levels, U/S findings and menopausal status (in both pre menopause and post menopause) performed individually in women with ovarian masses.

The main purpose of this study was the evaluation of the risk of malignancy index defined in a selected population with ovarian tumor.

It can be used to discriminate between benign and malignant ovarian tumors.

It is useful in referring patients with advanced tumors to a more complex health care unite, although it does not seem to show prognostic value.

This index is a simple score system which can be applied directly to clinical practice and might be of value in the preoperative assessment of the ovarian mass with only a few numbers of false negative cases.

Key word: ovarian tumors, benign and malignant ovarian tumors, Risk Malignancy index (RMI)

الخلاصة:

الهدف من الدراسة: لتقييم فعالية مؤشر خطورة الاصابة بورم المبيض في كل من النساء في سن الانجاب وبعد سن اليأس.

نوع الدراسة: دراسة انية لمدة سنة واحدة من تشرين الثاني 2017 ولغاية تشرين الثاني 2018.

مكان الدراسة: مستشفى بغداد التعليمي- مدينة الطب .

تصميم البحث :اثنان وخمسون(52 (امرأة مصابة بورم المبيض سجلت ضمن هذه الدراسة، تم قياس نسبة CA125في المصل لكل مريضه مع الفحص بجهاز الامواج الفوق الصوتية وتسجيل عمر المريضة، وتم حساب نسبة مؤشر خطورة الاصابة بسرطان المبيض لكل مريضة، وقد اخضعت جميع المريضات لعملية فتح البطن وارسلت الكتل والانسجة المرضية المستأصلة للفحص النسيجي للوصول الى التشخيص النهائي للمرض .النتائج من (52 (امرأة، 2,71 %من النساء كانوا قبل سن اليأس و 8,28 %كانو بعد سن اليأس،) 22)امرأة (3,42 (%يحملون اورام خبية، و65 %من هذه النسبة كانو بعد سن اليأس، نسبةال) CA125)كانت اكثر اهمية لدى النساء بد سن اليأس(متوسط 152 وحدة/مل للنساء بعد سن اليأس ، مقابل 52 وحدة/ مل للنساء قبل سن اليأس .(مؤشر خطرة الاصابة بسرطان المبيض) RMI) يسفر عن نتيجة افضل لتشخيص ورم المبيض .افضل نسبة لـ (RMI)كانت عندالحد (209)مع 7,72 %حساسية وخصوصية (100 %).

اكبر مساحة تحت منحني تشغيل خاصية الاستقبال (curve ROC)كانت لـ 97,0 RMIتليها مساحة الفحص لجهاز الامواج الفوق الصوتية (94,0 (ثم مساحة).84,0(CA125 حصيلة البحث مؤشر خطورة الاصابة بورم المبيض) RMI) هو سجل تشخيصي قادر على التمييز بين اورام المبيض الحميدة والخبيثة قبل اجراء اي تداخل جراحي، وهو يساعد على قياس نسبة الاورام الخبيثة باناس معينيين ويساعد على تحويل المرضى المصابين بسرطان المبيض في المراحل المتقدمه الى وحدة الاورام المتخصصة.

الكلمات المفتاحية: أورام المبيض ، أورام المبيض الحميدة والخبيثة ، مؤشر الورم الخبيث

Introduction

Ovarian tumor is the 4th most common cancer in women in the United King, and average annual incidence between 1990-2001 was 6663. [(1)]In the United States alone, where ovarian cancer is the fifth most common malignant condition among women, some 22,000 women will develop the disease annually, and of these more than 13,000 will die. [(2, 3, 4)] In Iraq, ovarian cancer forms 38% of all gynecological malignancies .it was the seventh most common cancer among females with the incidence of 0.8 per 100,000 women in 1996. [(5)]The

majority (65%) of patients are diagnosed with advanced cancer, when 1 year survival is 55% and 5-year survival is only 29%.median survival is 14 months. [6, 7, 8]Thus early detection of the disease should reduce the mortality from ovarian cancer. The diagnosis of ovarian cancer in practice is difficult to be made preoperatively,so many methods for preoperative diagnosis of ovarian cancer would be made before diagnostic laparotomy and patients with ovarian cancer had a benefit of thorough surgical staging by an experienced surgeon.

Ovarian tumor can occur at any age of a woman's life, mostly germ cell tumor in childhood, functional ovarian cysts in reproductive age group (up to 45 year) and becoming more malignant towards and after menopause [9].

Ovarian cancer is often in the late stage already when diagnosed. There's no screening test for ovarian cancer like pap smear test for cervical cancer.

Resent research has focused on two screening strategies: one using ultrasound alone, the other using the serum tumor marker CA125 for primary screening.

Nevertheless, screening for ovarian cancer is still experimental, and early detection is currently more a matter of chance than a consequence of a scientific strategy, partly because of the fact that there's no single identifiable cause or marker for this disease. [10] Over all, the data from prospective studies of screening for ovarian cancer in general population [11] suggest that sequential multimodal screening has superior specificity and positive predictive value compared with strategies based on transvaginal ultrasonography alone.

However, US as a first – line test may offer greater sensitivity for early stage disease.

Risk malignancy index (RMI)

It is a scoring system that combines sonographic finding, menopausal status (age) and serum CA125 levels to give estimate of the risk of malignancy in a woman with an ovarian mass. First described by Jacobs and colleagues [17, 18].

How to calculate the malignancy index (RMI)?

RMI = serum CA125 level x ultrasound score x menopausal score

Ultrasound score: up to 3; postmenopausal: 3; premenopausal: 1.

U/S score is calculated by giving one point if one of the following and three if two or more found in U/S scan of ovarian mass:

-Multilocular cyst.

-Solid area.

-Bilateral lesions.

-Metastasis.

-Ascites.

RMI is an effective method of triaging women into those who are at low risk, moderate or high risk of malignancy and who may be managed by a general gynecologist, or in a cancer unite or cancer center respectively.

Using CA-125 with a cut-off of 30 IU/ml also lacks specificity, as the marker can be raised in a different condition, in benign and malignant: Pregnancy, fibroids, menstruation, endometrial cancer, many non-ovarian malignancy, Endometriosis, pancreatitis, colitis, pericarditis, diverticulitis and SLE. [14, 15, 16, 17]

Aim of study

Evaluate usefulness of the risk malignancy index (RMI) in management of ovarian tumor in Iraq.

Patient and methods

This is a prospective observational study, carried out in Baghdad teaching hospital, department of obstetrics and gynecology from October 2017 to October 2018. The study was approved by Iraqi scientific board of obstetrics and gynecology. Fifty-two women with ovarian mass enrolled in the study. Preoperative serum CA125 level, ultrasound findings and menopausal status were recorded to calculate the risk malignancy index (RMI) accounting for each patient.Laparotomy was done for each of these fifty-two patients by a senior gynecologist and specimen was sent for histopathological examination and results of histopathology were recorded. Also the patients are divided into two groups according to menopausal status and type of ovarian mass into benign and malignant.

Results

Table 1: Frequency distribution of the study sample by age and malignancy typing for ovarian mass.

	N	**%**
1.Age group (years)		
<30	8	15.4
30-39	17	32.7
40-49	12	23.1
50+	15	28.8
Total	**52**	**100**
Range (18-66)		
Mean +/- SD = 41.6+/-12.6		
2. Malignancy diagnosis for ovarian mass		

Benign	30	57.7
Malignant	22	42.3
Total	**52**	**100**

Note: The 95% confidence interval for the rate of malignancy among ovarian mass= 29-56.7%

Table 2: The difference in median serum CA125 concentration between malignant and benign ovarian mass stratified by menopausal status.

	Serum CA-125 concentration				
	Premenopausal		**Postmenopausal**		**P (Mann-Whitney) for difference between pre and post-menopausal**
Malignant disease	**Median**	**N**	**Median**	**N**	
Benign	24	23	18.7	7	**0.36[NS]**
Malignant	32	9	152	13	**0.51[NS]**
P (Mann-Whitney) for difference between malignant and benign	**<0.001**		**0.001**		

Table 3: The difference in median serum CA125 concentration and RMI score between malignant and benign ovarian mass.

	Malignant disease		
	Benign	**Malignant**	**P (Mann-Whitney)**
1. Serum CA-125			**<0.001**
Range	(9 - 216)	(12 - 369)	
Median	22	139	
Interquartile range	(16 - 40)	(31 - 215)	
N	30	22	
2. Risk of malignancy index (RMI)			**<0.001**
Range	(0 - 168.3)	(48 - 3078)	
Median	4.8	615	
Interquartile range	(0 - 44)	(105 - 1368)	
N	30	22	

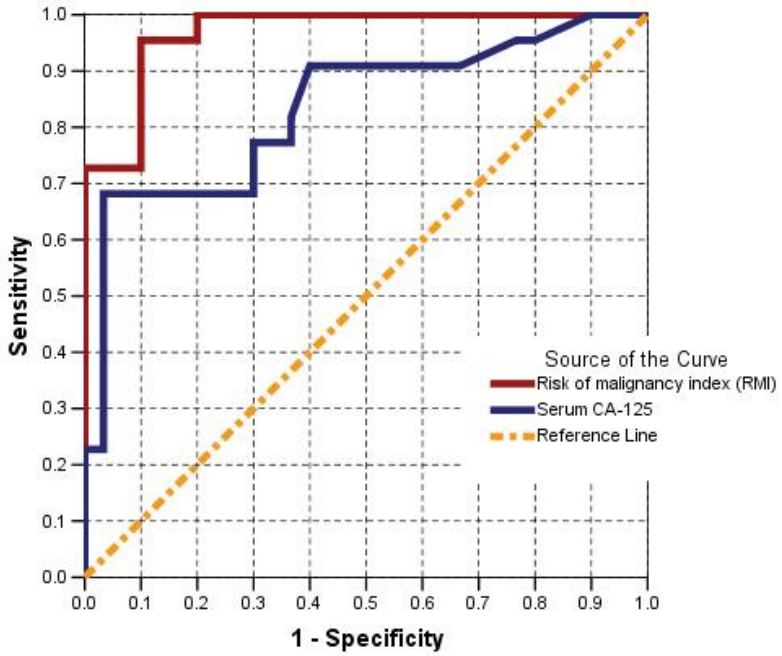

Figure 1: ROC curve showing the trade-off between sensitivity (rate of true positive) and 1-specificity (rate of false positive) for different cut-off values of selected variables when used as test to diagnose malignancy differentiating it from benign disease among subjects with ovarian mass.

Table 4: The ROC area for selected variables when used as tests to diagnose malignancy differentiating it from benign disease among subjects with ovarian mass.

	Area	**P**
Serum CA-125	0.835	<0.001
Risk of malignancy index (RMI)	0.962	<0.001

Table 5: The validity parameters for serum CA-125 and RMI score when used as tests to diagnose malignancy differentiating it from benign disease among subjects with ovarian mass.

Positive if ≥ cut-off value	**Sensitivity**	**Specificity**	**Accuracy**	**PPV at pretest propability =40%**	**PPV at pretest propability =40%**
Serum CA-125					
≥11 ***(Highest sensitivity)***	100.0	10.0	48.1	42.6	100.0

Positive if ≥ cut-off value	Sensitivity	Specificity	Accuracy	PPV at pretest propability =40%	PPV at pretest propability =40%
≥56 ***(Typical)***	68.2	96.7	84.6	93.2	96.5
≥220.5 ***(Highest specificity)***	22.7	100.0	67.3	100.0	92.1
Risk of malignancy index (RMI)					
≥46 ***(Highest sensitivity)***	100.0	80.0	88.5	76.9	100.0
≥71 ***(Typical)***	95.5	90.0	92.3	86.4	99.4
≥209 ***(Highest specificity)***	72.7	100.0	88.5	100.0	97.1

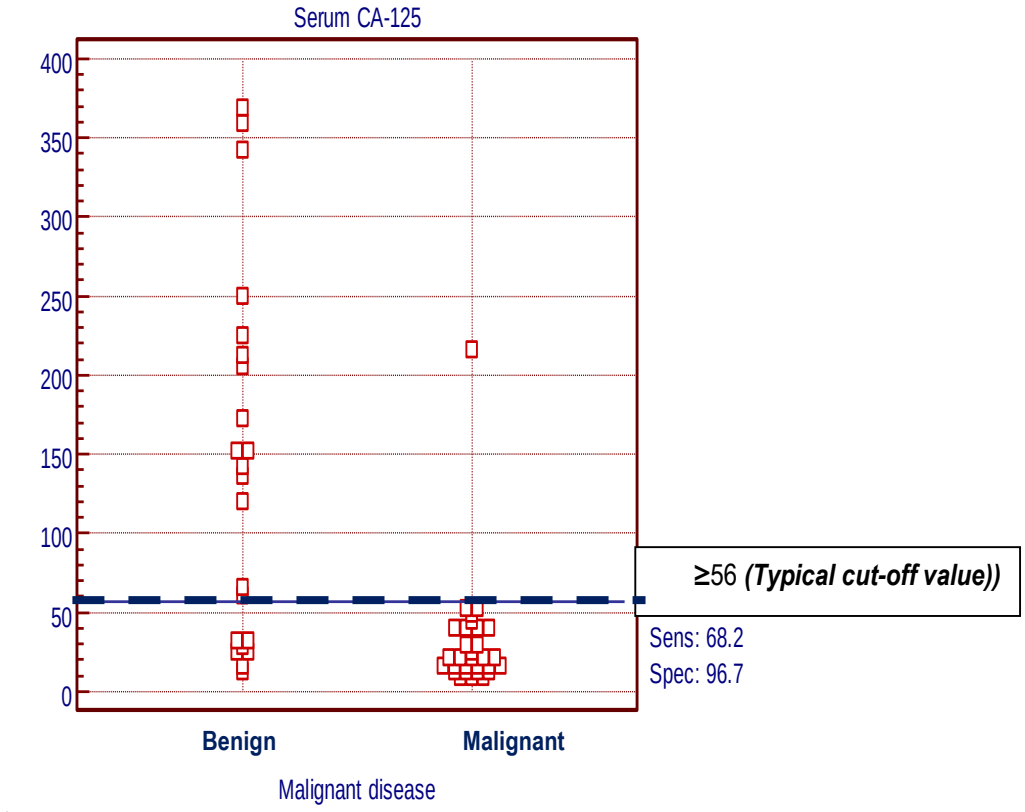

Figure 1: Dot diagram showing the distribution of malignant and benign ovarian mass cases in relation to the typical cut-off value of serum CA125 values.

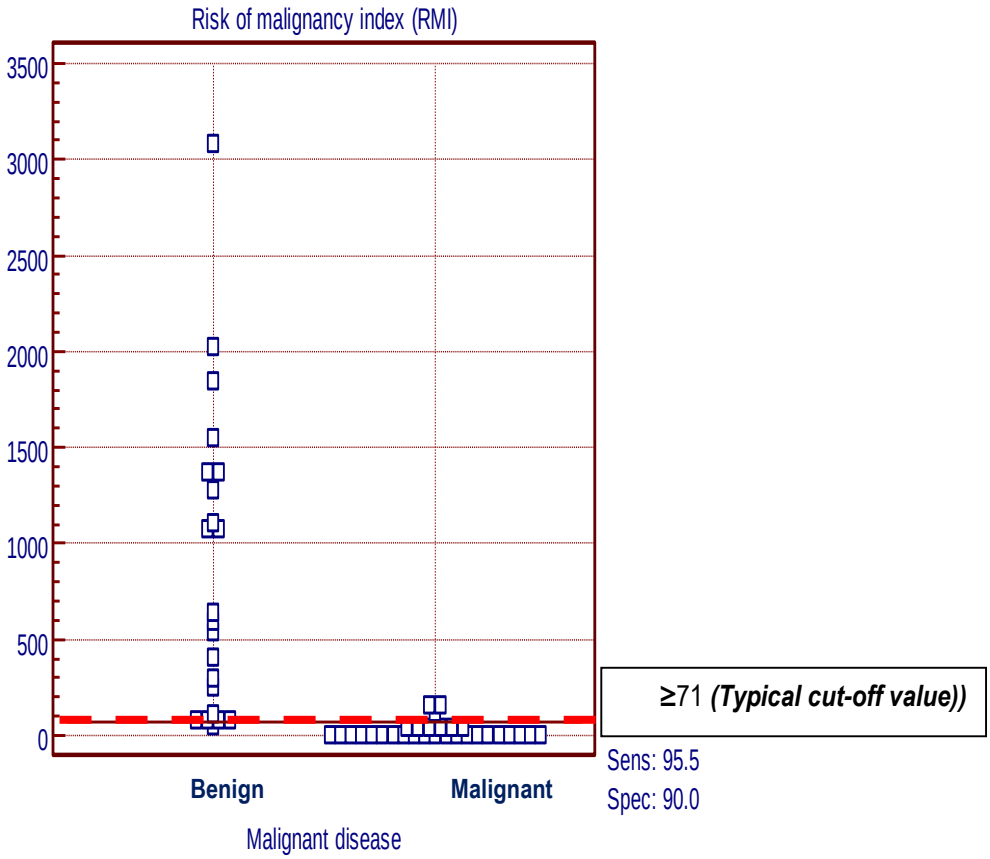

Figure 2: Dot diagram showing the distribution of malignant and benign ovarian mass cases in relation to the typical cut-off value of RMI scores.

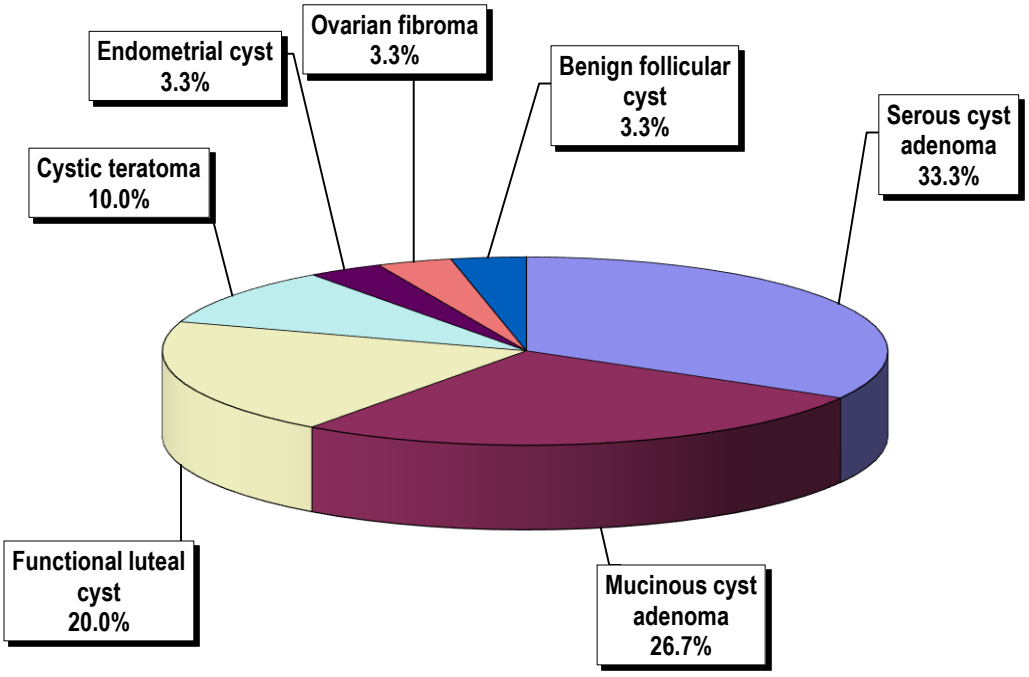

Figure 3: Pie chart showing the relative frequency of different pathological types of benign ovarian mass.

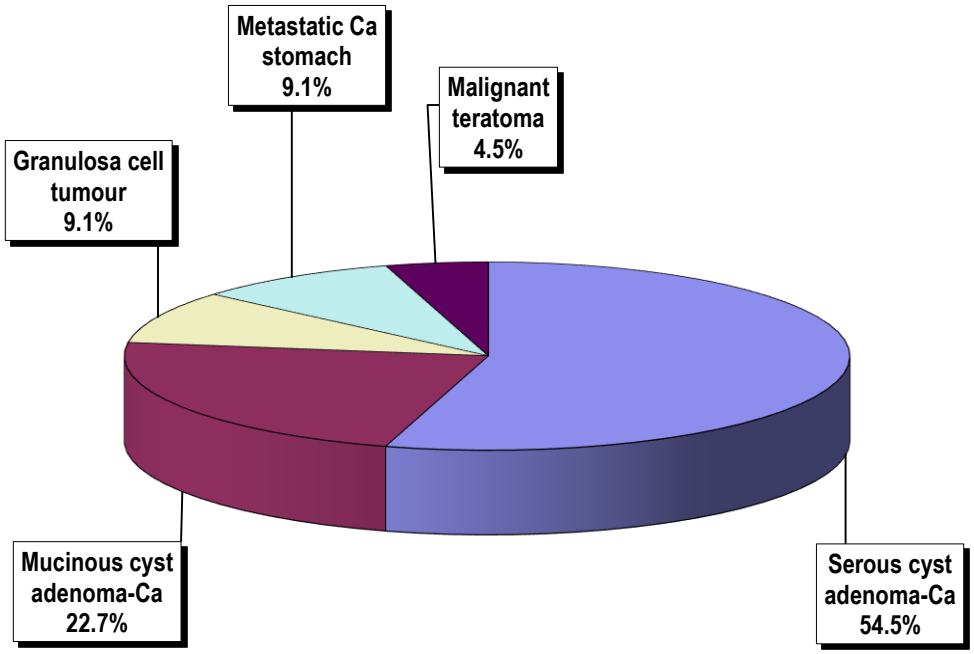

Figure 4: Pie chart showing the relative frequency of different pathological types of malignant ovarian mass.

Table 6: The risk of malignant ovarian mass by selected independent (explanatory) variables.

	Malignant disease						
	Benign		**Malignant**		**Total**		
	N	**%**	**N**	**%**	**N**	**%**	**P**
1. Age group (years)							**0.07[NS]**
<30	5	62.5	3	37.5	8	100	
30-49	20	69	9	31	29	100	
50+	5	33.3	10	66.7	15	100	
2. Menopausal status							**0.009**
Premenopausal	23	71.9	9	28.1	32	100	
Postmenopausal	7	35	13	65	20	100	
3. U/S score							**<0.001**
0	15	100	0	0	15	100	
1	10	83.3	2	16.7	12	100	
≥2	5	20	20	80	25	100	
4. Serum CA-125-categories							**<0.001**
Lowest tertile (<22)	14	87.5	2	12.5	16	100	
Intermediate tertile (22-51.9)	13	72.2	5	27.8	18	100	
Highest tertile (52+)	3	16.7	15	83.3	18	100	
5. Protocol for triaging women according to RMI score							**<0.001**
Low risk (<25)	19	100	0	0	19	100	
Moderate risk (25-250)	11	61.1	7	38.9	18	100	
High risk (>250)	0	0	15	100	15	100	

Table 7: The validity parameters for selected variables when used as tests to diagnose malignancy differentiating it from benign disease among subjects with ovarian mass.

Positive if ≥ cut-off value	Sensitivity	Specificity	Accuracy	PPV at pretest probability =40%	NPV at pretest probability =50%
1. Postmenopausal (compared to premenopausal)	59.1	76.7	69.3	62.8	94.4
2. U/S score					
≥ score 1	100.0	50.0	71.2	57.1	100.0
≥ score 2	90.9	83.3	86.5	78.4	98.8
3. Serum CA-125-categories					
≥ Intermediate/Highest tertile (≥22)	90.9	46.7	65.4	53.2	97.9
≥ Highest tertile(≥52)	68.2	90.0	80.8	82.0	96.2
4. Protocol for triaging women according to RMI score					
≥ Moderate/High risk (RMI≥25+)	100.0	63.3	78.8	64.5	100.0
≥ High risk (RMI>250)	68.2	100.0	86.5	100.0	96.6

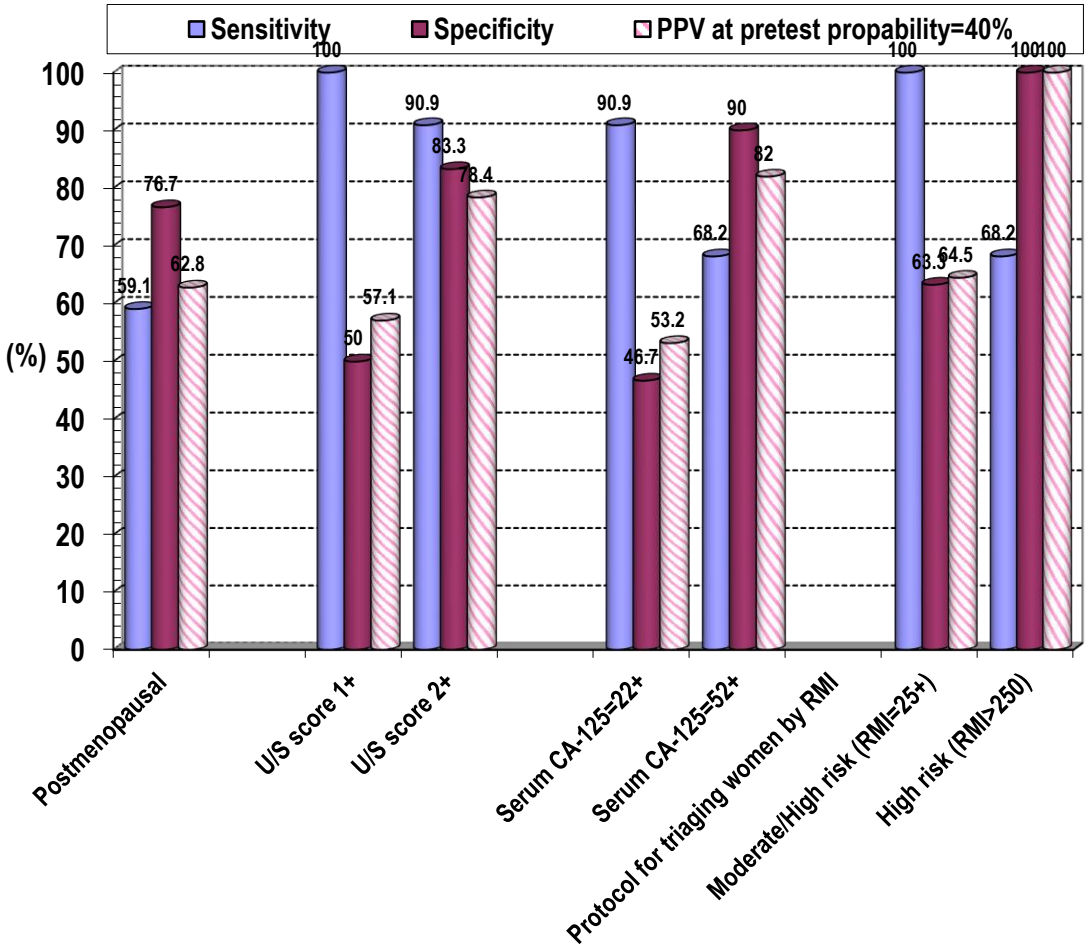

Figure 5: Bar chart comparing the validity parameters for the protocol for triaging women by RMI and its 3 component indices when used to predict malignancy among females with ovarian mass.

Study design

Cross sectional analytic study

Discussion

In our study, the age group ranged between 18-66 year and 71.2% of the patients were premenopausal and 28.8% were postmenopausal, benign cases constitute for 57.7% and malignant cases were 42.3%.

65% (13 of 20) of postmenopausal women had malignant pathology, this goes with what Morgante et al found in a study done at 1999 on 124 patients with pelvic mass that malignant pathology in 17 of 31 (58%) of the cases was at more than 55 year of age (24), so it should be taken seriously in those patient present with postmenopausal pelvic mass.

In this study, most of the cases were of epithelial type (as it is the commonest type of ovarian tumor), benign cases constitute for 60 %(18 of 30) and malignant epithelial tumors constitute for 77.2 %(17 of 22), serous type was the more common 33.3% and 54.5% for benign and malignant cases respectively.

CA125 level shows a variation in median (use median and not mean becauseCA125 level was non normally distributed non-normally distributed as shown by Semirnov-Kolmogorov test between pre and postmenopausal women and benign and malignant cases but it more significant in postmenopausal women (152ulml for malignancy and 18.7ulml for benign).

This indicate the importance of CA125 level in post-menopausal women, with high suspicion of malignancy, but in premenopausal women it may be elevated in some benign conditions as menstruation, fibroid, endometriosis, pregnancy and hemorrhagic ovarian cysts etc, all these conditions are infrequent in postmenopausal women.

In our study the cutoff value of CA125 was at a level of >= 56u|ml, which had a sensitivity of 68.2% and a specificity of 96.7% at this cut-off value the false negative rate is 31.8% (missing a possible malignant case).

This agrees with a study done in Egypt for 140 women with adnexal masses at 2002 where the CA125 cut-off value was 55u/ml with a sensitivity of 96.6% and specificity of 96.7%.19

Patsner et al, found an elevated levels of serum CA125 >= 35U/L had a sensitivity of 72% and a specificity of 78%.20

In our study, US scores used are 1, 2 and 3 according to the morphology of ovarian mass, bilateral lesions, presence of ascites and metastases, the sensitivities for US scores 1, 2 and 3 were 100%, 90.9%and 63.6% and specificities were 50%, 83.3% and 100% respectively. The false positive cases from U/S scores had similar characteristics of solid tumor such as dermoid cyst or other cystic tumors with hyperechoic content leading to high US scores. These conditions should be aware of when evaluating the ovarian tumors.

This compared with other studies using U/S to diagnose malignancy in adnexal masses which include:

Herman et al, a study of 304 women, 50 women were having malignant pathology and U/S had a sensitivity and specificity of 82% and 94% respectively .[21]

Finkler et al, a study of 106 women, 37 women were having malignant pathology and U/S had a sensitivity and specificity of 62% and 95% respectively.[22]

The study of CA125 in coupling with U/S findings had a better predictor of malignancy than an elevated serum CA125 alone and will lower the numbers of false positive results. Menopausal status was added to the two tests of CA125 and U/S score has also been studied to calculate the risk of malignancy (RMI).

There are three documented risk of malignancy indices. In our study, we use the index which used by Oram et al, who uses a cut-off point of 250 for RMI with a sensitivity of 70% and specificity of 90%.[23]

In this study, the median RMI score for benign ovarian masses was 4.8 while for malignant cases was 615, which is statistically significant in differentiation between benign and malignant ovarian tumors. In our study, the typical cut-off value was at a level of >=71 which had a sensitivity of 95.5%, the specificity was 90% with accuracy rate of 92.3% but the positive predictive value was 86.4%, the highest specificity (100%) was present at a cut-off value of >=209 with 72.7% sensitivity and 88.5% accuracy with positive predictive value (PPV) of 100%, which will establish the diagnosis of malignancy with 100% confidence in a clinical situation.

If we use the cut-off value of >=209 ,The false negative rate was 27.3% which may be due to 2 cases of mucinous cystadenocarcinoma, 2 metastatic CA stomach and 2 granulosa cell tumors. If we use a protocol for triaging women with ovarian masses according to RMI score, the risk of malignancy will increase with increase the cut-off value of RMI, the low risk group (<25) had no risk for malignancy, while the moderate risk (25-250) and high risk (>250) had 38.9% and 100% risks of having malignancy respectively, so the high risk group had 100%of having malignant ovarian tumor with.

This goes with the protocol for triaging women using RMI by Oram et al,where the low risk group had <3% risk of having malignancy and moderate and high risk groups having 20% and 75% respectively.[52]

If we suspect to use the protocol for triaging women according to the cut-off value of RMI used by Jacob (>200), so the moderate risk group (25-200) having 35.3% risk of having malignancy and100% risk for high risk group (>200).

On the basis of our analysis, we are use of RMI score as a preoperative test for prediction of malignancy which alerts the physician to suspect malignancy with propels counseling of the patients, better preoperative preparation and early referral to a specialized center.

Conclusion

1. Risk malignancy index (RMI) is a simple diagnostic tool provides a quantitative assessment of risk of malignancy by incorporating serum CA125 levels, U/S findings and menopausal status (in both premenopause and postmenopause) performed individually in women with ovarian masses.

2. It is useful in referring patients with advanced tumors to a more complex health care unite, although it does not seem to show prognostic value.

3. This index is a simple score system which can be applied directly to clinical practice and might be of value in the preoperative assessment of the ovarian mass.

Recommendations

We recommended to be introduced into clinical practice in Iraq to facilitate the selection of patients for primary surgery at a Gynecologic oncology unite.

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