นิพนธ์ต้นฉบับ   **Original Article**

Comparison of two Risk of Malignancy Indices in the Prediction of Ovarian Malignancy

การเปรียบเทียบการใช้ดัชนีความเสี่ยงในการทำนายมะเร็งรังไข่

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ABSTRACT

Objective: To evaluate the ability of two malignancy indices (RMI 1 and RMI 2) incorporating ultrasound finding, menopausal status and serum CA 125 level to discriminate between benign and malignant ovarian masses.

Materials and methods: Two risk of malignancy indices (RMI 1 and RMI 2) based on ultrasound finding, menopausal status and serum CA 125 level were used on, ninety-two patients admitted between October 2010 and September 2013 for the surgical excision of ovarian masses. To diagnose for ovarian malignancy sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of serum CA 125, RMI 1 and RMI 2 were compared.

Results: A total of 26 patients (28.3%) presented with malignant pathology while 66 (71.7%) with benign pathology. Prevalence of malignancy increased as age and ultrasound score increased. Both variables, age and ultrasound score, were statistically significant at 0.05 level. Additionally, more postmenopausal than premenopausal women suffered from malignant disease were statistically significant at 0.05 level. The results of serum CA 125 used to distinguish benign and malignant masses pre-operatively at a cut off level of 35 U/ml, with a sensitivity of 80.8%, a specificity of 39.4%, a PPV of 34.4%, and a NPV of 83.9%. In predicting of malignancy, based on ROC curve evaluation, the study found that RMI 2 at a cut off level of 100 resulted in a sensitivity of 80.8%, a specificity of 60.6%, a PPV of 44.7%, and a NPV of 88.9%.

Conclusion: RMI is a simple, easily applicable method for the primary evaluation of women with ovarian masses. RMI 2 was more reliable in discriminating between benign and malignant ovarian masses than RMI 1.

Keywords: RMI, Ovarian malignancy

บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาความสามารถของ RMI 1 และ RMI 2 ซึ่งเกิดจากการรวมผลอัลตร้าซาวด์สภาวะวัยทอง และระดับของ CA 125 ในการแยกก้อนของรังไข่ชนิดไม่ร้ายแรงกับมะเร็งรังไข่

วิธีการศึกษา: ศึกษาผู้ป่วยจำนวน 92 คนที่ได้รับการวางแผนให้นอนโรงพยาบาลเพื่อผ่าตัดเนื้องอกรังไข่ระหว่าง เดือนตุลาคม 2554 ถึง กันยายน 2556 โดยการรวบรวมข้อมูลผลอัลตร้าซาวด์สภาวะวัยทองและผลการตรวจ CA 125 จำแนกเป็น RMI 1 และ RMI 2 มีการหาความไว ความจำเพาะ คุณค่าในการทำนายผลบวก คุณค่าในการทำนายผลลบ ของ CA 125 RMI 1 และ RMI 2

ผลการศึกษา: ผู้ป่วย 26 คน (ร้อยละ 28.3) มีผลการตรวจทางพยาธิเป็นมะเร็งรังไข่ และ 66 คน (ร้อยละ 71.7) เป็นก้อนที่รังไข่ชนิดไม่ร้ายแรง อายุที่มากขึ้นและคะแนนจากผลอัลตร้าซาวด์ที่เพิ่มขึ้นมีความสัมพันธ์ต่อการเกิดมะเร็ง อย่างมีนัยสำคัญทางสถิติที่ระดับ 0.05 สภาวะหลังวัยหมดระดูมีความสัมพันธ์ต่อการเกิดมะเร็งอย่างมีนัยสำคัญทางสถิติ ที่ระดับ 0.05 เมื่อเทียบกับวัยก่อนหมดระดู จุดตัดที่เหมาะสมสำหรับ CA 125 อยู่ที่ 35 U/ml ได้ค่าความไวร้อยละ 80.8 ความจำเพาะร้อยละ 39.4 คุณค่าในการทำนายผลบวกร้อยละ 34.4 และคุณค่าในการทำนายผลลบร้อยละ 83.9. จุดตัดที่เหมาะสมของ RMI 2 อยู่ที่ 100 ได้ค่าความไวร้อยละ 80.8 ความจำเพาะร้อยละ 60.6 คุณค่าในการ ทำนายผลบวกร้อยละ 44.7 และคุณค่าในการทำนายผลลบร้อยละ 88.9.

สรุป: RMI เป็นวิธีที่ทำได้ง่ายในการประเมินเนื้องอกรังไข่เบื้องต้นและ RMI 2 มีความน่าเชื่อถือต่อการแยกก้อน ที่รังไข่ชนิดไม่ร้ายแรงกับมะเร็งรังไข่ได้ดีกว่า RMI 1

คำสำคัญ: ดัชนีความเสี่ยง มะเร็งรังไข่

Introduction

Ovarian malignancy is the fifth most common cause of death from malignancy in women in the United States.[1] It is asymptomatic in the early stages, resulting in a delayed diagnostic.[2,3] Most women (90 percent) with ovarian tumors present symptoms with a median symptom duration of 4 months, greater awareness of symptoms by women and physicians is needed for the earlier detection of ovarian tumors.[4] Because the ovaries are located deep within the body, physical examination has not been effective in detecting localized disease. Consequently, alternative methods have been developed to improve detection; nonetheless, these are not conclusive. Ultrasonography is considered the primary imaging modality for confirmation of the ovarian origin of the mass and characterization of the nature of the mass as benign or malignant.[5] Available data suggest that serum CA 125 is the leading indicator in the majority of epithelial ovarian malignancies prior to clinical presentation.

In the past, Nakhonpathom Hospital has used ultrasonographic finding, menopausal status and serum CA 125 level separately to discriminate between benign ovarian masses and malignant ovarian masses.

Since 2010, Nakhonpathom Hospital introduced RMI as the primary method to evaluate between benign and malignant ovarian masses. The present study evaluates the ability of two malignancy

indices, (RMI 1 and RMI 2), incorporating ultrasonographic finding, menopausal status, and serum CA 125 level to discriminate between benign and malignant ovarian masses.

Materials and methods

The clinical data consist of 92 patients admitted between October 2010 and September 2013 for the surgical excision of ovarian masses at Nakhonpathom Hospital. Peripheral venous blood samples of serum CA 125 were drawn from each patient before surgery. And an ultrasound scan was performed as part of a routine preoperative assessment for each patient. The scans were performed via the abdominal route under the full bladder technique, using a 3-6 MHz transducer. A total ultrasound score (U-score) was calculated for each patient, scoring one point for each of the following characteristics; multilocular cyst, evidence of solid areas, bilateral lesions, presence of ascites, and evidence of metastases. Post-menopausal status was defined as one year or more of amenorrhea, or an age of 50 years or more if the woman had undergone a hysterectomy. All the other women were considered to be premenopausal status.

The RMI based on ultrasonographic findings, menopausal status, and serum CA 125 level was introduced by Jacobs et al[6] defining the risk of malignancy index (RMI) as the product of ultrasound score (U), menopausal status (M) and serum CA 125 level : RMI 1 = U x M x serum CA 125. The calculation was based on a simplified regression equation where total ultrasound score of 0 gave U = 0, score 1 U = 1, and score $\geq$ 2 U = 3; premenopausal status gave M = 1, postmenopausal M = 3. The serum level of

CA 125 was applied directly into the calculation. Tingulstad et al[7] defined RMI 2 = U x M x serum CA 125. The calculation was based on a simplified regression equation where total ultrasound score of 0 or 1 gave U = 1 and a score $\geq$ 2 gave U = 3; premenopausal status gave M = 1, postmenopausal M = 4. The serum level of CA 125 was applied directly into the calculation.

Statistical analysis was performed using the X^2 and Mann-Whitney U tests. McNemar's test was used when testing differences in performances between RMI 1 and RMI 2.

To diagnose ovarian malignancy, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of serum CA 125, RMI 1 and RMI 2 were compared. The histopathologic diagnosis was regarded as the definite outcome.

Results

From October 2010 to September 2013, out of a total of 92 patients, 66 (71.7%) had benign pathology and 26 (28.3%) had malignant pathology. Benign gynecological conditions included endometriosis (n = 39), mucinous cystadenoma (n = 8), serous cystadenoma (n = 5), mature cystic teratoma (n = 5), ovarian cyst (n = 4), benign sclerosing stromal tumor (n = 2), fibroma (n = 1), spindle cell tumor (n = 1), and struma ovarii (n = 1). The malignant tumors were serous carcinoma (n = 6), clear cell carcinoma (n = 6), mucinous carcinoma (n = 5), borderline mucinous cystadenocarcinoma (n = 3), micropapillary serous carcinoma (n = 1), mixed serous and endometrioid adenocarcinoma (n = 1), granulosa cell tumor (n = 1), endometrioid adenocar-

Table 1 Distribution of age, menopausal status, ultrasound score and serum CA 125 levels in 92 patients with benign (n = 66) or malignant (n = 26)

Variables	Benign		Malignant		P	test
	(n = 66)	(%)	(n = 26)	(%)		
Age						
< 30	18	(27.3)	0	(0)	.000	X^2 = 32.797*
30-44	33	(50.0)	4	(15.4)		
45-54	9	(13.6)	8	(30.8)		
> 54	6	(9.1)	14	(53.8)		
Menopausal status						
Premenopausal	58	(87.9)	8	(30.8)	.000	X^2 = 30.006*
Postmenopausal	8	(12.1)	18	(69.2)		
Ultrasound score						
0	27	(40.9)	1	(3.8)	.001	X^2 = 16.829*
1	31	(47.0)	14	(53.9)		
2-5	8	(12.1)	11	(42.3)		
CA 125 (U/ml)						
Mean	108.97		1024.73		.000	U = 419.000*
Median	47.25		300			
Minimum	5		19			
Maximum	1193		9535			
Standard error	20.851		397.316			
1^0 quartile	23.78		53			
3^0 quartile	125.38		1038.83			

* statistically significant at 0.05 level

cinoma (n = 1), undifferentiated carcinoma (n = 1), and metastatic adenocarcinoma (n = 1). The distribution of benign and malignant pathology by age, menopausal status, ultrasound score and serum CA 125 is described in Table 1.

The sensitivity, specificity, positive predictive value and negative predictive value of the serum CA 125 to predict malignancy are reported in Table 2.

The performance of RMI 1 and RMI 2 at different cut off levels are shown in Table 3. The RMI 2 was significantly better at predicting malignancy than RMI 1 (McNemar's test $p < 0.01$).

The performance of CA 125, RMI 1 and RMI 2 are shown in the receiver-operator curves (Fig.1).

Table 2 Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of serum CA 125 in the diagnosis of malignant ovarian masses (percentages).

	sensitivity	specificity	PPV	NPV
CA 125 (U/ml)				
10	100.0	3.0	28.9	100.0
20	96.2	16.7	31.3	91.7
35	80.8	39.4	34.4	83.9
50	76.9	53.0	39.2	85.4
80	69.2	65.2	43.9	84.3
120	61.5	74.2	48.5	83.1

Table 3 Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), at different cut off levels, of RMI 1 and RMI 2 (percentages).

Cut off	sensitivity		specificity		PPV		NPV	
	RMI 1	RMI 2	RMI 1	RMI 2	RMI 1	RMI 2	RMI 1	RMI 2
25	92.6	100.0	52.3	19.7	44.6	32.9	94.4	100.0
50	88.9	96.2	61.5	37.9	49.0	37.9	93.0	96.2
75	74.1	92.3	66.2	50.0	47.6	42.1	86.0	94.3
100	69.2	80.8	72.7	60.6	50.0	44.7	85.7	88.9
150	65.4	69.2	81.8	71.2	58.6	48.7	85.7	85.5
200	61.5	69.2	87.9	80.3	66.7	58.1	85.3	86.9
250	61.5	69.2	90.9	86.4	72.7	66.7	85.7	87.7
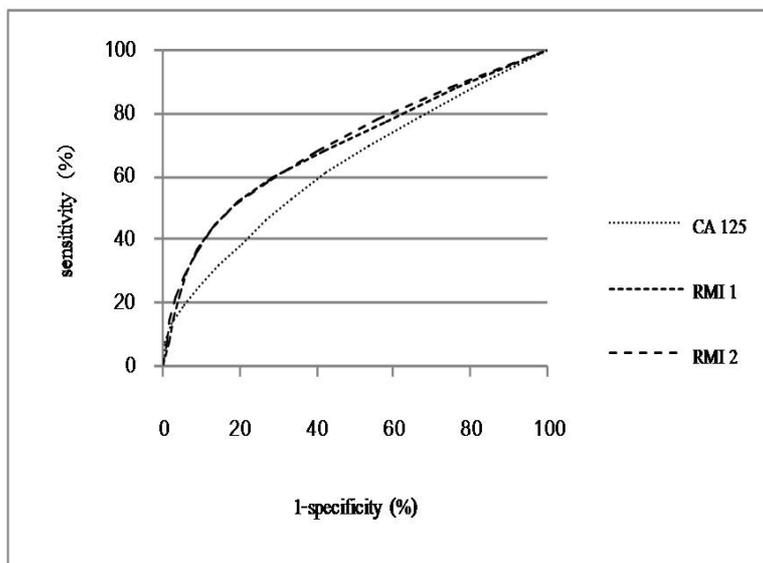
Area under the ROC curve of RMI 2 = .703, Area under the ROC curve of RMI 1 = .693, Area under the ROC curve of CA 125 = .633

Fig 1 Receiver-operator characteristic curve showing the relation between specificity and sensitivity for CA 125, RMI 1 and RMI 2.

Discussion

Ovarian masses cause diagnostic and management problems for gynecologists, as the pre-operative diagnosis of benign or malignant ovarian masses has not been completely solved. However, various diagnostic procedures have been utilized with various levels of success to determine the presence of malignant ovarian masses. These include the physical examination of patients, ultrasonography and tumor markers such as serum CA 125, which are used individually or are combined to form a risk malignancy index (RMI). The study successfully analyzed two RMI that incorporated the aforementioned methods.

In the study, patients under 30 years of age all were diagnosed with benign ovarian pathology.

However, malignant ovarian masses were found in the additional age groups. Malignancy prevalence was statistically significant as the group's age increased, and as the ultrasound score increased. Additionally and significantly more postmenopausal than premenopausal patients suffered from malignant disease. The mean serum level of CA 125 was significantly higher among patients with malignant ovarian masses (mean serum CA 125 1024.73 U/ml, range 19-9535 U/ml) when compared with patients suffering from benign ovarian masses (mean serum CA 125 108.97 U/ml, range 5- 1193 U/ml). Postmenopausal patients with ultrasonographic finding was single ovarian cyst had benign pathology (ovarian cyst (n = 1), serous cystadenoma (n = 2), struma ovarii (n = 1) and fibroma (n = 1) and no malignancy

pathology.

The results of serum CA 125 used to distinguish benign and malignant masses pre-operatively at a cut off level of 35 U/ml, with a sensitivity of 80.8%, a specificity of 39.4%, a PPV of 34.4%, and a NPV of 83.9% were similar to a study conducted by Benjapibal[8] Of these, two patients with ovarian malignancies presented with CA 125 < 35 U/ml (granulosa cell tumor and mucinous carcinoma). Thirty-seven patients with benign ovarian masses presented levels of CA 125 >35 U/ml. The finding was not surprising as CA 125 levels could rise during conditions such as pelvic infections, ovarian cysts and endometriosis.[9] The cut-off level of 35 U/ml resulted as a suitable method to differentiate malignancy pre-operatively, nonetheless it was different from the results of Ulusoy S et al[10] who found that a cut-off level of 80 U/ml was appropriate to differentiate malignancy.

In predicting of malignancy, based on ROC curve evaluation, the study found that RMI 2 at a cut off level of 100 resulted in a sensitivity of 80.8%, a specificity of 60.6%, a PPV of 44.7% and a NPV of 88.9% which was inconsistent with the results of other studies.[6,10] The RMI 1 developed by Jacobs et al[6] found a cut off level of 200 U/ml with a sensitivity of 85.4% and a specificity of 96.9%. Ulusoy S et al found cut off level of 153 had a sensitivity of 76.4%, a specificity of 77.9%, a PPV 65.9% and a NPV 86.46%. An RMI 2 was more reliable in discriminating between benign and malignant ovarian masses, similar with studies from Tingulstad et al[7] and Morgante G et al[9], who found RMI 2 was more reliable than RMI 1. This study had a cut off level lower than other studies,[7,9] due to a low ultrasound score from a transabdominal ultrasonography, which could improve the ultrasound score if using a transvaginal ultrasound. Five patients with ovarian malignancies presented with a RMI 2 < 100 (clear cell carcinoma (n = 2), mucinous carcinoma (n = 2), granulosa cell tumor (n = 1). Twenty six patients with benign ovarian masses presented with RMI 2 > 100.

The combination of ultrasonographic findings, menopausal status, and serum CA 125 in the RMI 2 to discriminate between benign and malignant ovarian masses was more predicting than using RMI 1 or serum CA 125 alone.

Conclusion

RMI is a simple, easily applicable method in the primary evaluation of women with ovarian masses. RMI 2 is more reliable in discriminating between benign and malignant ovarian masses than RMI 1. RMI used in clinical practice can improve early detection of ovarian cancer and the prognosis of ovarian cancer patients.

Acknowledgement

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