RESEARCH COMMUNICATION

The Risk of Malignancy Index (RMI) in Diagnosis of Ovarian Malignancy

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Abstract

Objective : To evaluate the ability of two risk of malignancy indices (RMI) based on serum levels of CA 125, ultrasonographic score, and menopausal status to discriminate between benign and borderline or malignant ovarian tumor. Materials and Methods: A retrospective study was conducted in 209 women with pelvic masses admitted for laparotomy at Srinagarind Hospital, between January 2002 and December 2007. The sensitivity, specificity and positive predictive (PPV) and negative predictive (NPV) values of two RMI were calculated. Results: Using a cut-off level of 200 to indicate malignancy, the RMI 1 gave sensitivity of 70.6%, specificity of 83.9%, PPV of 75%, and NPV of 80.6%. The RMI 2 gave sensitivity of 80%, specificity of 78.2%, PPV of 71.6%, and NPV of 85.1%. The RMI 2 was significantly better in predicting malignancy than RMI 1. Conclusion: The RMI is able to discriminate between benign and borderline or malignant ovarian tumor.

Key Words: Risk of malignancy index - serum CA 125; Menopausal status- ultrasonographic score; ovarian tumou

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Introduction

In Thailand, ovarian cancer is the second most common cancer of the female genital tract with an annual incidence of 5.6 per 100,000 women, and a death rate of 2.6 per 100,000 women per year. Due to the often asymptomatic nature of the early stage of disease, many cases of ovarian cancer present in the advanced stage for which the 5-year survival rate remains low (Benjapibal et al., 2007). The quality of primary cytoreductive surgery is one of the most important prognostic factors. The extent of cytoreductive surgery is associated with the specific skills and experience of well-trained gynecologic oncologists. The discrimination between benign and malignant ovarian masses is thus important in selective referral of relevant patients to specialized cancer centers (Soegaard et al., 2003).

At the present, one clinical feature provides inadequate performance in discriminating benign and malignant ovarian tumor. For ultrasonographic techniques, the sensitivity and specificity in diagnosis of malignant condition were 62% and 73%, respectively (Morgante et al., 1999; Leelahakorn et al., 2005). Serum CA 125 is another promising tool. Elevation of serum CA 125 concentrations is documented in 85% of epithelial ovarian cancers (Benjapibal et al., 2007;Leelahakorn et al., 2005). At the cut-off level of 35 U/ml, the sensitivity was 83.1%; butthe specificity was only 39.3% (Benjapibal et al.,2007).

The risk of malignancy index (RMI) is a scoring system of the combination of various clinical features. It has been developed to improve diagnostic accuracy for ovarian malignancy. Jacob et al. (1990) originally developed the RMI based on ultrasonographic findings, menopausal status, and serum levels of CA 125. By using the RMI at a cut-off level of 200 to indicate malignancy, so called RMI 1, sensitivity and specificity were 85.4% and 96.9%, respectively (Jacobs et al., 1990). Tingulstad et al. (1996) then developed RMI 2. A direct comparison showed that RMI 2 was significantly better at predicting malignancy than RMI 1 (p value < 0.001). The RMI 2 gave sensitivity of 80%, specificity of 92% and positive predictive value (PPV) of 83% while RMI 1 gave sensitivity of 71%, specificity of 96%, and PPV of 89%.

In Thailand, Leelahakorn et al. (2005) studied the role of ultrasonographic score, CA 125, menopausal status, and one type of the RMI in discriminating benign from malignant ovarian tumors. For the RMI, the sensitivity, specificity, PPV, and negative predictive value (NPV) were 88.6%, 90.7%, 70.5%, and 97%, respectively. The ultrasonographic criteria used in this study were based on those set by Ferazzi et al. (1997). The focus was on the basic features of the ovarian mass itself such as the cystic wall, septation, vegetations, and echogenicity. As these features need a very particular and meticulous examination when comparing to the ultrasonographic criterias in the RMI which developed by Jacob et al. (1990) or Tingulstad et al. (1996). Therefore, the purpose was to evaluate the ability of the RMI 1 and RMI 2 in discriminating of pelvic masses at Srinagarind Hospital, a tertiary care hospital of Thailand.

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Materials and Methods

We conducted a retrospective review of medical records of 209 women with pelvic masses admitted for laparotomy at Srinagarind Hospital, Department of Obstetrics and Gynecology, Faculty of Medicine, Khon Kaen University between January 2002 and December 2007. The study was approved by the Ethics Committee of Faculty of Medicine, Khon Kaen University. We included patients who met the following criterias; 1) age of 30 years or older 2) having adnexal mass diagnosed by an ultrasound evaluation by either a 3.75-MHz abdominal transducer or a 7.5-MHz transvaginal probe 3) having preoperative measurement of serum levels of CA 125 by using a radioimmunoassay (Elecsys, CA 125 II Roche, Indianapolis, USA) and 4) underwent laparotomy. The exclusion criterias were the patients with incomplete medical record or who already had histological diagnosis of malignant ovarian cancer.

The presence of multilocular cystic lesions, solid areas, bilateral lesions, ascites, and intra-abdominal metastases scored 1 point for each. A total ultrasonographic score (U) was calculated for each patient. Postmenopausal status (M) was defined as 1 year or more of amenorrhea. All other women were considered to be premenopausal. RMI 1 and RMI 2 were calculated for all patients together with the sensitivity, specificity and positive and negative predictive values of the two methods. We used cut-off level of at least 200 for indicating malignancy. The methods for RMI calculation were as follows:

1. RMI 1 (Jacobs et al.)(1990) = U _ M _ serum CA 125, where a total ultrasonographic score of 0 gave U = 0, a score of 1 gave U = 1 and a score of ≥ 2 gave U = 3; premenopausal status gave M = 1, postmenopausal status M = 3. The serum level of CA 125 was multiplied directly into the formula.
2. RMI 2 (Tingulstad et al.)(1996) = U _ M _ serum CA 125, where a total ultrasonographic score of 0 gave U = 0, a score of 1 gave U = 1 and a score of ≥ 2 gave U = 4; premenopausal status gave M = 1, postmenopausal status M = 4. The serum level of CA 125 was multiplied directly into the formula.

All statistical analyses were performed using the Statistical Package for the Social Sciences version 17 (SPSS Inc., Chicago, IL). The chi-square test was used to test differences in distribution of age, menopausal status and ultrasonographic score. The Mann-Whitney U test was applied when testing differences in distribution of CA 125. When applying logistic regression, interaction was tested at significance level of $p < 0.05$. McNemar's test was used to evaluate differences in performance of the two methods between RMI 1 and RMI 2. The sensitivity, specificity, positive predictive and negative predictive value with reference to the presence of a benign and borderline or malignant pelvic mass were calculated. Sensitivity was defined as the percentage of patients with borderline or malignant disease having a positive test result, specificity the percentage with benign disease having a negative test result, while the positive predictive value was defined as the percentage of patients with a positive test result having borderline or malignant disease.

Table 1. Age, Menopausal Status, Ultrasonographic Scores and Serum CA125 Levels with Reference to Pelvic Masses*

Variables	Benign	Borderline	Malignant	P value
Age (years)				
30-44	55 (44.4)	2 (18.2)	16 (34.9)	
45-54	36 (29)	6 (54.5)	22 (30.6)	< 0.002
≥55	33 (26.6)	3 (27.3)	36 (34.4)	
Menopausal status				
Premenopausal	86 (69.4)	6 (54.5)	29 (39.2)	< 0.000
Postmenopausal	38 (30.6)	5 (45.5)	45 (60.8)	
Ultrasonographic score				
0	37 (29.8)	0 (0)	2 (2.70)	
1	49 (39.5)	6 (54.5)	17 (23.0)	< 0.000
2-5	38 (30.6)	5 (45.5)	55 (74.3)	
CA 125 (U/mL)				
Mean	65.9	46.4	819	
Minimum	0.6	14.7	7.8	< 0.000
Maximum	995	218.9	5000	
Standard error	10.8	17.7	130.4	

*N (%) values

The negative predictive value was defined as the percentage of patients with a negative test result having benign disease. The histopathological diagnosis was considered as the gold standard for defining the outcomes. Tumors were classified according to World Health Organization definitions (1973).

Results

There were 209 women included in the study. Table 1 shows patients' characteristics. Mean age (+SD) was 50.0±11.8 years. The 121 cases (57.9%) were premenopausal. The median preoperative serum CA 125 value was 90.8 U/mL and ranged from 0.6 to 5000 U/mL. The most common ultrasonographic score was 2-5 (46.9%). For the histological examination, 74 of 209 patients (35.4%) had malignant, 11 (5.3%) had borderline disease, and 124 (59.3%) had benign disease. The distribution of histological diagnoses is shown in Table 2.

Univariate analysis showed that there were statistically significant differences between the benign, borderline, and malignant group in the following factors, i.e. age, menopausal status, ultrasound score, and serum levels of CA 125 (Table 1).

The results of evaluation by RMI 1 and RMI 2 are summarized in Table 3. By using a cut-off level of 200 U/mL to indicate malignancy, the RMI 1 gave sensitivity of 70.6%, specificity of 83.9%, positive predictive value of 75%, and negative predictive value of 80.6%. The RMI 2 gave a sensitivity of 80%, specificity of 78.2%, positive predictive value of 71.6%, and negative predictive value of 85.1% (Table 4).

Table 5 shows the rate of false positive and false negative. In total, at cut-off level of 200 the false positive cases in cancer detection of RMI 1 and RMI 2 were reported in 20 and 27 cases, respectively. The false negative cases were 25 in RMI 1 and 17 cases in RMI 2. Among the false-positive cases, mucinous cystadenomas and dermoid cysts were the most commonly accounted

Table 2. Distribution of Diagnoses in the 209 Women with Pelvic Masses

Diagnosis	N	(%)
Benign cases	124	(100)
Endometrioma	28	(22.6)
Serous cystadenoma	10	(8.1)
Mucinous cystadenoma	33	(26.6)
Dermoid cyst	23	(18.5)
Leiomyoma	15	(12.1)
Follicular cyst	4	(3.2)
Corpus luteum cyst	1	(0.8)
Tuberculosis	3	(2.4)
Tubo-ovarian abscess	2	(1.6)
Adenomyosis	1	(0.8)
Parovarian cyst	2	(1.6)
Chronic ectopic	1	(0.8)
Salpingitis	1	(0.8)
Borderline cases	11	(100)
Serous borderline tumor	1	(9.1)
Mucinous borderline tumor	10	(90.9)
Malignant cases	74	(100)
Serous cystadenocarcinoma	26	(35.1)
Mucinous cystadenocarcinoma	8	(10.8)
Serous-mucinous cystadenocarc	1	(1.4)
Clear cell carcinoma	8	(10.8)
Endometrioid carcinoma	10	(13.5)
Granulosa cell carcinoma	3	(4.1)
Mixed carcinoma	1	(1.4)
Immature teratoma	1	(1.4)
SCCA arising from mature teratoma	2	(2.7)
Metastatic adenocarcinoma	13	(17.6)
Hodgkin lymphoma	1	(1.4)

Table 3. Results of Evaluation by RMI

RMI 1	Benign	Borderline	Malignant
< 200	104	10	15
≥ 200	20	1	59
RMI 2	Benign	Borderline	Malignant
< 200	97	7	10
≥ 200	27	4	64

diseases. The false-negative cases were mainly borderline ovarian tumors up to 41.1%.

Discussion

For this study, the RMI 2 provided better diagnostic accuracy than the RMI 1 does. At the cut-off level of 200, RMI 1 and 2 gave the sensitivity of 70.6% and 80%, respectively, and the specificity of 83.9% and 78.2%, respectively. These findings are important for the clinical applicability of the RMI as a tool for referral of patients with ovarian cancer to gynecological cancer centers.

The prevalence of malignancy in the present study (35%) is similar to those in previous studies (Jacobs et al., 1990;Tingulstad et al., 1996;Davies et al., 1993;Ulusoy et al., 2007). In our study the prevalence was 35% while the others ranged from 29-35%. In the present study the sensitivity of both RMI 1 and RMI 2 to predict malignant was lower than those reported by the previous studies (Leelahakorn et al., 2005;Jacobs et al., 1990;Obeidat et al., 2004). One possible explanation is that the relatively higher rate of early stage (stage I) and borderline ovarian tumor found in this study. In Jacob's study (1990), the prevalence of stage I was 26% while the prevalence was 36% in our study. In addition, the differences in the study population as well as the setting may attribute to the differing diagnostic performance.

In 1997, Ferazzi et al. reported that, based on the ultrasonographic morphology of ovarian cystic wall, septation, vegetation and echogenicity in determination of malignancy of ovarian tumors, the accuracy, sensitivity, specificity, PPV, and NPV were of 72%, 87%, 67%, 41% and 95%, respectively (Ferrazzi et al., 1997). The findings demonstrated the better results than those in other pervious ultrasonography scoring systems (Sassone et al., 1991;Granberg et al., 1990). This may partly explain by the differences in level of training and experience of ultrasonologists in each study. The diagnostic sensitivity and specificity for ovarian malignancy in Leelahakorn's study (2005), in which ultrasonographic scoring system developed by Ferazzi et al (1997) was used, were relative higher than those in our study. However, the ultrasonographic criterias used in this RMI need more specific training skill than the criteria used in our study. Our study used ultrasonographic scoring described by Jacob et al.(1990). These features are relatively simple.

Table 5. Numbers of False Positive and False Negative Cases

	RMI 1(n)	RMI 2 (n)
False positive	(n=20)	(n=27)
Dermoid cyst	4	6
Mucinous cystadenoma	4	6
Endometrioma	3	4
Tuberculosis	3	3
Serous cystadenoma	1	2
Leiomyoma	1	2
Corpus luteum cyst	1	1
Tubo-ovarian abscess	1	1
Adenomyosis	1	1
Chronic ectopic	1	1
False negative	(n=25)	(n=17)
Borderline tumor	10	7
Serous cystadenocarcinoma	5	2
Clear cell carcinoma	3	3
Granulosa cell carcinoma	2	2
Metastatic adenocarcinoma	2	1
Mucinous cystadenocarcinoma	2	0
Endometrioid carcinoma	1	1
Immature teratoma	1	1

Table 4. The Diagnostic Performance of RMI1 and RMI 2 Using a Cut-off Level of 200 to Indicate Malignancy*

	Sensitivity (95% CI)	Specificity (95% CI)	Positive PV (95% CI)	Negative PV (95% CI)
RMI 1	70.6 (59.7-80.0)	83.9 (76.2-89.9)	75.0 (64.1-84.0)	80.6 (72.7-87.0)
RMI 2	80.0 (69.9- 87.9)	78.2 (69.9-85.1)	71.6 (61.4-80.4)	85.1 (77.2-91.1)

*Data presented as percentages; PV, predictive value

Therefore, to select the type of RMI for discriminating benign and malignant ovarian tumor, both diagnostic performance and training skill of ultrasonologists should be taken into account.

In our study, the majority of histological diagnoses in the false negative cases were mucinous borderline ovarian tumors and early stage (stage I) of serous malignant tumors while the majority of false positive cases were dermoid cysts and mucinous cystadenomas. The low level of CA 125 and the low ultrasonographic score are likely to explain the false negative. Solid parts found in dermoid cysts and multilocular cystic lesions found in mucinous cystadenomas may attribute to the false positive. For endometriomas and tuberculosis, elevation of CA 125 level due to peritoneal irritation is likely to produce a high RMI score.

According to Thai gynecologic cancer society guideline, there is a suggestion to use the RMI developed by Jacobs et al (1990) as a diagnostic tool to aid in selecting a patient with ovarian tumor for referral to cancer centers for primary surgery. This study is the first in evaluating the diagnostic accuracy of these RMI. It is important to address that both prevalence of ovarian malignancy and ultrasonographic skills have an impact on diagnostic performance. Therefore, the results of this study, which conducted at the tertiary care hospital, may not represent for primary or secondary care hospitals; such that, a study to determine diagnostic performance of these RMI in primary or secondary care hospital is warranted before the RMI would be recommended in these hospitals.

The RMI is a simple method that can be used by general gynecologists to aid in selecting a patient for referral to cancer centers for primary surgery. For clinical application at this time, if we use the RMI 2 at cut-off level 200 to screen for a case to refer to gynecology oncologist, 80 of 100 borderline or malignant ovarian cases would have positive screening and then would be referred for appropriate management. The 20 of 100 borderline or malignant ovarian cases would have the negative results and then would be explored by general gynecologist. Development of a new simplified RMI would be of advantage to increase sensitivity and reduce the false negative rate.

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