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Risk of Malignancy Index for a Diagnosis of Ovarian Malignancy

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ABSTRACT

Objective: To calculate the optimal cut-off point for the risk of malignancy index (RMI) in the diagnosis of ovarian malignancy.

Materials and methods: A retrospective study was conducted. We included women with adnexal masses who underwent elective surgery at Chonburi Hospital from January 2010 to December 2011. Data collected were age, menopausal status, serum CA 125, ultrasound findings, histopathology of masses, and stage of ovarian cancer. The RMI was obtained from multiplying the scores of menopausal status, serum CA 125, and ultrasonographic features. Primary outcome was the optimal value of RMI as well as its sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) to predict malignancy. Secondary outcomes were the association of each component of RMI and status of malignancy.

Results: One hundred and fifty-seven women met criteria; 61 cases (38%) were malignant and 96 (62%) were benign. We found the optimal RMI to predict malignancy was 257, with a sensitivity of 70.21%, specificity of 85.42%, PPV of 75.36% and NPV of 81.85%. Higher serum CA 125 levels and ultrasound findings (solid part and ascites) independently correlated with malignancy, while age and menopausal status gave poor correlation with diagnosis.

Conclusion: The optimal cut-off point of RMI to predict malignancy was 257. CA 125 and ultrasound features of solid area and ascites were independent factors determining malignancy.

Keywords: ovarian tumor, risk of malignancy index, serum CA 125, ultrasound score, menopausal status

Introduction

Among the gynecologic malignancies, ovarian cancer remains a challenge in diagnosis for most gynecologists. The nature of the disease, being mostly asymptomatic, leads to presentation at an advanced stage and low survival rate[1]. Cytoreductive surgery performed by a well-trained gynecologic oncologist undisputedly improves treatment outcomes[2,3]. However, not all patients with adnexal masses require such treatment, as malignancy accounts for only about 35%[4] of cases undergoing surgery. Therefore, pre-operative evaluation to determine the need to refer the patients to more specialized health care center should be as accurate as possible. This is to maximize

the chance that the patients can have an optimal treatment for their cancer and to minimize the cost of un necessary referring process.

Many tools have been created to increase the rate of accurate preoperative diagnosis or prediction of cancer. Jacobs et al[5] in 1990 proposed the risk of malignancy index (RMI) scoring system combining a serum CA 125 level, ultrasound findings and menopausal status. A cut-off point at 200 showed satisfactory sensitivity and specificity. Subsequent studies showed various results. Some studies[4, 6-8] validated the RMI at 200 as an optimal cut-off point for the diagnosis of malignant ovarian tumors, while other studies reported different values with better performance[9-13].

The primary outcome of this study was to evaluate an optimal cut-off point for the RMI in the diagnosis of ovarian masses, together with its sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), that is suitable for our hospital's population base. A secondary objective was to study the association between each clinical factor and status of malignancy.

Materials and methods

A retrospective study was conducted after approval from the ethical committee of Chonburi Hospital. Inclusion criteria were women underwent elective scheduled laparotomy at Chonburi Hospital (CBH)—a tertiary hospital—from January 2010 to December 2011. The women must have preoperative measurement of serum CA 125 from CBH laboratory and the presence of an ultrasound report made by CBH's gynecology division. Exclusion criteria were known cases of ovarian cancer, incomplete data and pregnancy. Data obtained from medical records were age, menopausal status, serum CA 125, ultrasound findings, histopathology of masses, and stage of ovarian cancer

Menopausal status (scoreM), ultrasound findings (scoreU) and serum CA 125 (CA 125) were used to calculate the RMI, in the same fashion as the original report[5].

RMI = scoreM x scoreU x CA 125

Premenopause and postmenopause status gave a score M of 1 and 3, respectively. For women with previous hysterectomy prior to menopause, age below 50 gave a score of 1 and age equal to or above 50 gave a score of 3. Abnormal ultrasound findings were defined as multiloculation, bilateral, ascites, solid part and evidence of metastasis. Score U was 0 for no abnormal findings, 1 for one finding and 3 for two or more findings. Absolute serum CA 125 in U/mL was directly used.

All ultrasonography was performed with GE Voluson V730 pro (GE Healthcare, Thailand) by gynecologic staff and residents under staff supervision with either transabdominal or transvaginal probe, or both. Preoperative serum CA 125 from CBH laboratory was measured with ARCHITECT i2000SR machine (Abbott, Thailand). Pathologic diagnosis was considered the gold standard for diagnosis.

Primary outcomes were the RMI cut-off point and its sensitivity, specificity, positive predictive value, and negative predictive value. Secondary outcomes were the association of each clinical factor and status of malignancy. Ultrasound findings of multiloculation, bilaterality, ascites, solid part and evidence of metastasis were entered into the logistic regression analytic equation separately from other factors.

Statistical analysis

MedCalc® version 12.7.2 (MedCalc Software, Mariakerke, Belgium) was used to analyze the data. Receiver operating characteristic (ROC) curve was used to calculate the optimal cut-off point for the RMI. *T*-test, Mann-Whitney U test or Kruskal Wallis test was used to compare difference of continuous data depending on their distribution. For categorical data, Fisher's exact or x^2 was applied. The number of samples required was calculated by The TDR Diagnostics Evaluation Expert Panel 2008 equation14 (expecting sensitivity of 85% and prevalence of malignancy in women with adnexal masses at 35%[4]) to be 136 cases at least. $P < 0.05$ was considered statistically significant. Logistic regression analysis was performed to identify independent factors predicting malignancy.

Results

One hundred and fifty-seven patients met criteria. Prevalence of malignancy was 38% (N=61) with a distribution of pathologic cell type and stage of disease as shown in table 1. Benign tumors or lesions were found in 62% (N=96).

Table 1. Distribution of histopathology diagnosis and stage.

Malignant cases	**61**	**%**
Serous cystadenocarcinoma	19	(31.2)
Endometrioid carcinoma	11	(18.0)
Mucinous cystadenocarcinoma	9	(14.8)
Clear cell carcinoma	6	(9.8)
Granulosa cell carcinoma	5	(8.2)
Metastatic adenocarcinoma	2	(3.3)
Undifferentiated carcinoma	2	(3.3)
Immature teratoma	1	(1.6)
Borderline tumor	6	(9.8)
Stage of Caner		
Stage I	22	(36.1
Stage II	4	(6.5)
Stage III	33	(54.1)
Stage IV	2	(3.3)
Benign cases	96	%
Endometrioma	35	(36.6)
Serous cystadenoma	8	(8.4)
Mucinous cystadenoma	19	(19.9)
Mature cystic teratoma	14	(14.6)
Leiomyoma	4	(4.2)
Partubal cyst	4	(4.2)
Benign cyst	3	(3.1)
Others*	9	(9.0)

*Others: Müllerian cyst, brenner tumor, hydrosalpynx, fibrothecoma, spindle cell tumor, enteric cyst, lymphoma, tubo-ovarian abscess, tuberculosis peritoneum

Table 2 shows association between each clinical finding and status of malignancy. There were no significant differences in age and menopausal status between benign and malignancy groups. Ultrasound findings of solid part and ascites were significantly more commonly found in malignant tumors. Although bilaterality was found more frequently in the malignant group, the difference was not statistically significant different. Ultrasound score and median serum CA 125 were significantly higher in malignant tumors than those of benign lesions ($p<0.0001$). The RMI also showed statistically significant difference between benign and malignant tumors, with a median value of 73.5 and 519, respectively.

Table 2. Demographic data and clinical findings.

	Benign (N=96)		Malignant (N=61)		p	test
Age	**44.4**	**(±11.1)**	**46.6**	**(±14.0)**	**0.3112**	**t-test**
Menopausal status	n	(%)	n	(%)		
- Pre-menopause	67	(69.7)	35	(57.3)	0.1563	x^2
- Post-Menopause	29	(30.3)	26	(42.7)		
Ultrasound findings						
- Multiloculation	47	(48.9)	24	(39.3)	0.2536	Fisher's exact
- Bilateral	24	(25.0)	19	(31.1)	0.4637	Fisher's exact
- Solid	41	(42.7)	47	(77.0)	<0.0001	Fisher's exact
- Ascites	10	(10.4)	27	(44.2)	<0.0001	Fisher's exact
- Metastasis	0	(0)	1	(1.6)	0.3850	Fisher's exact
Ultrasound score						
0	6	(6.3)	0	(0)	<0.0001	Kruskal Wallis
1	63	(65.6)	19	(31.3)		
3	27	(28.1)	42	(68.7)		
CA 125 U/mL (median)	37.4	(3.7-660)	165	(11-9871)	<0.0001	Mann-Whitney
RMI (median)	73.5	(0-1524)	519	(14.4-88839)	0.0004	Mann-Whitney
Mean ± SD, Median (Range)						

We found RMI of 257 would yield the optimal diagnostic function, with an area under curve (AUC) of 0.839 giving a sensitivity of 70.21% (95% CI 55.1-82.7), specificity of 85.42% (95% CI 76.7-91.8), PPV 75.36% and NPV 81.85%. (Fig. 1.)

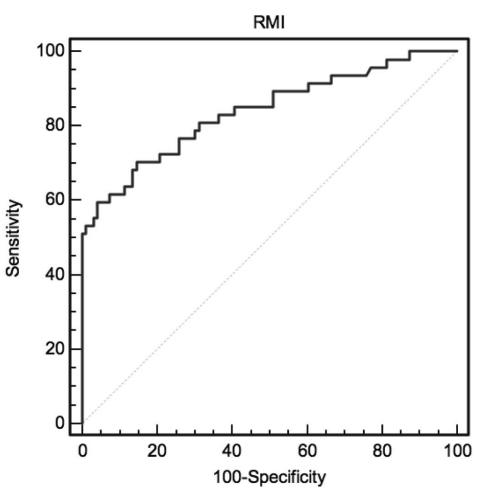

Fig. 1. The receiver operating characteristic curve of the risk of malignancy index. RMI of 257 yielded the maximal area under curve with sensitivity of 70.21% and specificity of 85.42%.

Applying the cut-off point of RMI at 257 resulted in a false negative diagnosis in 18 out of 61 cases (29%): 5 mucinous carcinomas, 3 clear cell carcinomas, 3 borderline tumors, 2 endometrioid carcinomas, 2 granulosa cell carcinomas, 2 undifferentiated carcinomas and 1 immature teratoma. Of these 18 cases, all were early stage cancer. All advanced staged ovarian cancer cases were correctly diagnosed with their RMI higher than 257. False positive diagnosis was found in 15 cases (15.6%). The most common of which was endometriosis (8 cases). The others were infection (TOA or TB peritoneum), lymphoma, mature cystic teratoma, spindle cell carcinoma and serous cystadenoma.

Ultrasound findings of solid part and ascites, serum CA 125, and ultrasound score were identified as significant in determining the diagnosis from multivariable logistic regression analysis (Table 4).

Table 4. Multivariate logistic regression analysis.

	OR	95% CI	p
Ultrasound score	1.91	1.2-2.8	0.0013
Ultrasound finding			
- Solid	5.78	2.35-14.26	0.0001
- Ascites	6.35	2.59-15.56	0.0001
CA 125	1.00	0.95-1.05	0.0037

Discussion

Our optimal cut-off point for the RMI was 257 giving a sensitivity of 70.21%, specificity of 85.42%, PPV of 75.36% and NPV of 81.85%. Independent factors predicting of malignancy were ultrasound findings of solid part and ascites, serum CA 125 and ultrasound score. Age, menopausal status, ultrasound findings of bilaterality or metastasis or multiloculation showed no statistically significant association. Various cut-off points of RMI reported by previous studies[9-13] ranged from 120 to 250 because the different in calculation methods and prevalence of malignancy and benign cases found.

Using our cut-off point, the false negative diagnosis for mucinous carcinoma was over 50%. This is consistent with the fact that mucinous carcinomas usually do not produce CA 125 especially in early disease. However, when the cancers were in advanced stage, even the mucinous tumors, might have caused peritoneal reaction with rising of CA 125 high enough to raise the RMI value that no case of advanced mucinous cancer were missed from the RMI of 257. Interestingly, all serous carcinoma cases, which accounted for the most cell types found, were correctly diagnosed even with early stage disease. Ultimately, high stage carcinomas correlated with higher accuracy in diagnosis, regardless of histologic cell type. No advanced stage cases were missed in our report.

Endometriosis constituted the majority of false positive cases in the benign group. Endometriosis was associated with rise in serum CA 125, especially with severe disease[15]. Even with a low ultrasound score and premenopausal score of 1, the RMI for these endometriosis cases were still higher than 257 due to the high levels of serum CA 125, which was found to be 660 U/mL in one case from our report.

Though RMI might not play a role as a screening test for ovarian cancer, the low sensitivity for diagnosis of a disease with high impact on mortality still raised our concern. Our main consideration for using the RMI was not to decide whether patients should undergo surgery, but whether it should be performed by a gynecologic oncologist. Considering that all cases had indication for surgery regardless of RMI, and a definite diagnosis would be made by histology report, then further management for initially unidentified ovarian

cancers would eventually be achieved. However, a diagnostic tool with high sensitivity is still needed. Until the risk of ovarian malignancy algorithm (ROMA) becomes widely available at lower cost, RMI is a simple method that can be used as a guide for the general gynecologist deciding on referrals and in pre-operative preparation for both doctors and patients. Further studies in patients with adnexal masses who do not yet have established indications for surgery would provide further insight into the role as a screening tool for ovarian cancer of the RMI, or even ROMA.

Conclusion

The optimal cut-off point of RMI to predict malignancy was 257. CA 125 and ultrasound features of solid area and ascites were independent factors determining malignancy.

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จุดตัดที่เหมาะสมของค่าดัชนีความเสี่ยงของการเป็นมะเร็ง ในการแยกวินิจฉัยเนื้องอกรังไข่

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วัตถุประสงค์ *: เพื่อหาจุดตัดที่เหมาะสมของค่าดัชนีความเสี่ยงของการเป็นมะเร็ง ในการแยกวินิจฉัยเนื้องอกรังไข่*

วัสดุและวิธีการ *: ศึกษาจากเวชระเบียนของผู้ป่วยที่ได้รับการวินิจฉัยว่ามีเนื้องอกรังไข่ที่ต้องได้รับการผ่าตัดของโรงพยาบาลชลบุรี ตั้งแต่เดือนมกราคม 2553 ถึง ธันวาคม 2554 โดยบันทึกข้อมูลสภาวะประจำเดือน, ค่า CA 125 ในซีรั่ม และผลการตรวจคลื่นเสียงความถี่สูง เพื่อให้ได้ค่าดัชนีความเสี่ยงของการเป็นมะเร็ง และนำค่านี้มาคำนวณหาจุดตัดที่เหมาะสมในการใช้วินิจฉัยแยกโรค พร้อมทั้งวิเคราะห์ความถดถอยแบบโลจีสติกเพื่อหาตัวแปรอิสระที่บ่งชี้ความเป็นมะเร็ง*

ผลการศึกษา *: ในผู้ป่วย 157 รายที่เข้าได้กับงานวิจัย มีจำนวนมะเร็ง 61 ราย เนื้องอกอื่นๆ 96 ราย จุดตัดที่เหมาะสมในการใช้ค่าดัชนีความเสี่ยงของการเป็นมะเร็งเท่ากับ 257 โดยมีความไว 70.21% ความจำเพาะ 85.42% ค่าพยากรณ์บวก 75.36% และค่าพยากรณ์ลบ 81.85% ตัวแปรอิสระที่บ่งชี้ถึงความเป็นมะเร็งได้แก่ ค่า CA 125 ในซีรั่ม, และการตรวจคลื่นความถี่สูงพบส่วนเนื้อตันหรือน้ำในโพรงเยื่อบุช่องท้อง*

สรุป *: จุดตัดที่เหมาะสมของค่าดัชนีความเสี่ยงของการเป็นมะเร็งในการแยกวินิจฉัยเนื้องอกของรังไข่คือ 257*

คำสำคัญ *: มะเร็งรังไข่, Risk of malignancy index, serum CA 125, Ultrasound score, วัยหมดประจำเดือน*