RESEARCH ARTICLE

Should Cut-Off Values of the Risk of Malignancy Index be Changed for Evaluation of Adnexal Masses in Asian and Pacific Populations?

Ali Yavuzcan[1]*, Mete Caglar[1], Emre Ozgu[2], Yusuf Ustun[1], Serdar Dilbaz[1], Ismail Ozdemir[3], Elif Yildiz[1], Tayfun Gungor[2], Selahattin Kumru[1]

Abstract

Background: The risk of malignancy index (RMI) for the evaluation of adnexal masses is a sensitive tool in certain populations. The best cut off value for RMI 1, 2 and 3 is 200. The cut off value of RMI-4 to differentiate benign from malignant lesions is 450. Our aim was to evaluate the efficiency of four different malignancy indexes (RMI1-4) in a homogeneous population. Materials and Methods: We evaluated a total of 153 non-pregnant women with adnexal masses who did not have a history of malignancy and who were above 18 years of age. Results: A cut-off value of 250 for RMI-1 provided 95.9% inter-observer agreement, yielding 95.9% specificity, 93.5% negative predictive value, 75.0% sensitivity and 82.8% positive predictive value. A cut-off value of 250 for RMI-1 showed high performance in preoperative diagnosis of invasive malignant lesions than cut-off value of 200 in our population. A cut-off value of 350 for RMI-2 provided 94.5% inter-observed agreement, yielding 94.2% specificity, 93.4% negative predictive value, 75.0% sensitivity and 77.4% positive predictive value. RMI-2 showed the higher performance when the cut-off value was set at 350 in our population. A cut-off value of 250 provided 95.2% inter-observer agreement, yielding 95.0% specificity, 93.2% negative predictive value, 75.0% sensitivity, and 88.0% positive predictive value. RMI-3 showed the highest performance to diagnose malignant adnexal masses when the cut-off value was set at 250. In our study, RMI-4 showed similar statistical performance when the cut-off value was set at 400 [(Kappa: 0.684/p=0.000), yielding 93.8% inter-observer agreement, 93.4% specificity, 93.4% negative predictive value, 75.0% sensitivity, and 75.0% negative predictive value]. Conclusions: We showed successful utilization of RMIs in preoperative differentiation of benign from malignant masses. Many studies conducted in Asian and Pacific countries have reported different cut-off values as was the case in our study. We think that it is difficult to determine universally accepted cut-off values for RMIs for common use around the globe.

Keywords: Adnexal mass - ovarian cancer - risk of malignancy index

Asian Pac J Cancer Prev, **14 (9)**, 5455-5459

Introduction

It is of particular importance to establish accurate preoperative diagnosis for adnexal masses. Reliable recognition of benign masses would reduce the number of redundant surgeries for asymptomatic benign lesions. Ovarian cancer (OC) is the most fatal of all gynaecologic malignancies in women. Optimal cytoreductive surgery is the most significant prognostic factor in the management of OC (Harlan et al., 2003; Gultekin et al., 2009). In the event of high index of suspicion for ovarian cancer, patients should undergo surgery in tertiary care units where optimal cytoreductive surgery could be performed.

Cancer antigen 125 (CA-125) is a cell surface glycoprotein of 220-kDa molecular weight. Elevated CA-125 levels are found in 80% of non-mucinous epithelial ovarian cancers. A cut-off value of 35U/mL yields 83.1% sensitivity but low specificity (39.3%) (Benjapibal and Neungton, 2007). Menopausal status provides limited information about the nature of the adnexal masses. Menopausal status yields 55% sensitivity and 80% specificity in differentiating benign from malignant adnexal masses (Aktürk et al., 2011). Ultrasonography (USG) is the most commonly performed imaging modality used to evaluate pelvic pathologies and adnexal masses (Khattak et al., 2013). Hafeez et al. (2013) reported that USG provides 91% diagnostic accuracy in adnexal masses depending on the structure pattern of the mass. However, this high rate applies only to experienced radiologists. Inexperienced physicians attain lower success rate in recognising the mass pattern and operator-dependent subjective nature precludes reliable use of this method.

In the past 20 years, various investigators have proposed risk of malignancy indexes (RMIs) to

*[1]Department of Obstetrics and Gynaecology, Düzce University Faculty of Medicine, Düzce, [2]Department of Obstetrics and Gynaecology, Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara, [3]Department of Obstetrics and Gynaecology, Medicana International Istanbul Hospital, Istanbul, Turkey *For correspondence: draliyavuzcan@yahoo.com*

successfully differentiate benign from malignant masses on an objective basis (Jacobs et al., 1990; Tingulstad et al., 1996; Tingulstad et al., 1999; Yamamoto et al., 2009). Four different indexes utilizing CA-125 levels, menopausal status and findings of malignancy on performed USG as the basic variables have yielded a sensitivity ranging from 71-86.8%, and a specificity ranging from 91-96% (Jacobs et al., 1990; Tingulstad et al., 1996; Tingulstad et al., 1999; Yamamoto et al., 2009). On the other hand, some studies indicate that RMI is not a sensitive tool in certain populations while other studies call for a change in universally accepted cut-off values to differentiate benign from malignant lesions (Ashrafgangooei and Rezaeezadeh, 2011; Ong et al., 2013).

In this study, our aim was to evaluate the efficiency of four different malignancy indexes in a homogeneous population.

Materials and Methods

Medical records of the patients, who underwent a surgery with the pre-diagnosis of adnexal mass in the Department of Obstetrics and Gynaecology in Düzce University Faculty of Medicine and in Ankara Zekai Tahir Burak Training and Research Hospital between November 2009 and May 2013, were retrieved from the hospital records. We evaluated a total of 153 non-pregnant women who did not have a history of malignancy and who were above 18 years of age. All patients were evaluated by USG 2 weeks prior to surgery. All patients provided written informed consent. Surgical staging was performed in accordance with International Federation of Gynaecology and Obstetrics if the diagnosis from frozen section examination was suggestive of malignancy (Benedet et al., 2000). Invasive malignant neoplasms, metastatic masses and borderline ovarian lesions which did not invade epithelial basement membrane were considered as malignant adnexal mass (Andersen et al., 2003). All other masses were considered benign lesions. A total of 32 patients (20.9%) appeared to have a malignant lesion and 121 patients (79.1%) had benign lesion. Histopathological diagnoses of the adnexal masses are presented in Table 1.

In our study, patients were considered postmenopausal in the absence of menstrual flow for the last 1 year. The women above 50 years of age who underwent hysterectomy and those above 55 years of age and who do not remember the date of their last period were also considered postmenopausal (Ashrafgangooei and Rezaeezadeh, 2011). CA-125 levels were determined using electrochemiluminescence immunoassay and expressed in IU/mL. Upper limit of normal for serum CA-125 was set at 30IU/mL.

Analysis of RMI

RMI score was calculated by multiplying transvaginal USG results (U), menopausal status (M) and preoperative CA-125 levels (IU/mL). For this calculation, different coefficients were used in each RMI scale (RMI-1, RMI-2 and RMI-3) (Jacobs et al., 1990; Tingulstad et al., 1996; 1999). In RMI-4, the calculation also included mass size (S) as one of the variables that is measured on transvaginal ultrasonography (Yamamoto et al., 2009) (Table 2). The total USG scores (U) were constructed on the basis of the findings on transvaginal USG that would be suspicious for malignancy. These findings included appearance of multilocular cystic lesions, solid area, bilaterality, ascites and presence of intra-abdominal metastasis.

Statistical analysis

Descriptive statistics included mean, standard deviation, minimum and maximum values, median, proportion and frequency. The level of impact was measured using ROC curve analysis. Kappa analysis was used to assess agreement. The p values <0.05 were considered statistically significant. SPSS 21.0 statistical software was used in statistical analyses.

Results

Mean age of the study participants was 46.0±11.3years. Mean size of the adnexal masses was 84.4±39.2mm. Mean preoperative CA-125 level was 75.8±112.5IU/mL. Of the patients, 54 (35.3%) were menopausal. General features of the patients are shown in Table 3.

In our study, Kappa value was 0.691 (p=0.000) for RMI-1. A cut-off value of 200 (Jacobs et al., 1990) for RMI-1 yielded 90.0% specificity, 97.3% negative predictive value, 88.5% sensitivity and 65.7% positive predictive value. While evaluating an adnexal mass preoperatively based on RMI-1 in our study, a cut-off value of 250 provided statistically higher agreement with histopathological results (Kappa: 0.734/p=0,000). A cut-off value of 250 provided 95.9% inter-observer agreement, yielding 95.9% specificity, 93.5% negative predictive value, 75.0% sensitivity and 82.8% positive predictive value. According to our findings, a cut-off value of 250

Table 1. Histopathological Diagnoses of Adnexal Masses

	n	(%)
Non-invasive lesions		
Benign Brenner tumour	1	(0.7%)
Corpus haemorrhagicum cyst	6	(3.9%)
Corpus luteum cyst	3	(2.0%)
Endometrioma	24	(15.6%)
Fibroma	1	(0.7%)
Follicular cyst	6	(4.2%)
Mature cystic teratoma	21	(13.7%)
Mucinous cyst	4	(2.8%)
Mucinous cystadenoma	5	(3.5%)
Uterine fibroids	4	(2.8%)
Paraovarian cyst	2	(1.4%)
Paratubal cyst	7	(4.9%)
Serous cyst	12	(7.8%)
Serous cystadenoma	14	(9.2%)
Serous papillary cystadenoma	4	(2.8%)
Struma ovarii	1	(0.7%)
Thecoma	1	(0.7%)
Tuba-ovarian abscess	5	(3.5%)
Invasive malignant lesions		
Borderline mucinous tumour	1	(0.7%)
Borderline serous tumour	7	(4.9%)
Clear cell carcinoma	1	(0.7%)
Endometrioid-type carcinoma	3	(2.0%)
Malignant mesenchymal tumour	1	(0.7%)
Malignant mucinous carcinoma	3	(2.1%)
Serous cystadenocarcinoma	16	(10.4%)

for RMI-1 showed high performance in preoperative diagnosis of invasive malignant lesions.

Kappa value for RMI-2 was 0.539 (p=0.000) with a cut-off value of 200 (Tingulstad et al., 1996). Inter-observer agreement has been 87.0% for RMI-2 with a cut-off value of 200, which yielded 85.1% specificity, 98.2% negative predictive value, 75.0% sensitivity, and 57.1% positive predictive value. While evaluating an adnexal mass preoperatively based on RMI-2 in our study, a cut-off value of 350 provided good agreement with histopathological results (Kappa: 0.700/p=0.000). A cut-off value of 350 provided 94.5% inter-observed agreement, yielding 94.2% specificity, 93.4% negative predictive value, 75.0% sensitivity and 77.4% positive predictive value. RMI-2 showed the higher performance when the cut-off value was set at 350.

Kappa value for RMI-3 was 0.579 (p=0.000) with a cut-off value of 200. Inter-observer agreement has been 89.0% for RMI-3 with a cut-off value of 200 (Tingulstad et al., 1999), which yielded 87.6% specificity, 93.0% negative predictive value, 71.0% sensitivity, and 61.5% positive predictive value. While evaluating an adnexal mass preoperatively based on RMI-3 in our study, a cut-off value of 250 provided good agreement with histopathological results (Kappa: 0.717/p=0.000). A cut-off value of 250 provided 95.2% inter-observer agreement, yielding 95.0% specificity, 93.2% negative predictive value, 75.0% sensitivity, and 88.0% positive predictive value. In our study, RMI-3 showed the highest performance to diagnose malignant adnexal masses when the cut-off value was set at 250.

In our study, Kappa value for RMI-4 was 0.684 (p=0.000) when the cut-off value was set at 450 (Yamamoto et al., 2009). Inter-observer agreement has been 93.8% for RMI-4 with a cut-off value of 450, which yielded 93.4% specificity, 93.4% negative predictive value, 75.0% sensitivity, and 75.0% positive predictive value. In our study, RMI-4 showed similar statistical performance when the cut-off value was set at 400 ([Kappa: 0.684/p=0.000] , yielding 93.8% inter-observer agreement, 93.4% specificity, 93.4% negative predictive value, 75.0% sensitivity, and 75.0% negative predictive value).

Table 2. Coefficients in RMI Indexes

Parameter		RMI 1[a]	RMI 2[b]	RMI 3[c]	RMI 4[d]
USG score	No feature	0	1	1	1
(U)	1 feature	1	1	1	1
	≥ 2 features	3	4	3	4
Menopausal score	Premenopausal State	1	1	1	1
(M)	Postmenopausal State	3	4	3	4
	CA-125 (U/mL)	-	-	-	-
Size of mass	<7 cm	-	-	-	1
(S)	≥7 cm	-	-	-	2

[a]Jacobs et al. (1990); [b]Tingulstad et al. (1996); [c]Tingulstad et al. (1999); [d]Yamamoto et al. (2009)

Table 3. General Features of the Patients

	N (%)	Mean±Std. Deviation
Age (years)	153 (100%)	46.0±11,3
Menopause	54 (35.3%)	
Gravida	153 (100%)	2.9±1.9
Parity	153 (100%)	2.4±1.6
CA-125 (IU/mL)	153 (100%)	75.8±112.5
Measured Size on USG (mm)	153 (100%)	84.4±39.2

Table 4. Evaluation of the Efficiencies of RMI 1-4 with Different Cut-off Values

		Histopathologic agreement	Kappa	Specificity	NPV	Sensitivity	PPV	p value
RMI 1	≤200	91.1%	0.622	90.1%	93.2%	75.0%	66.7%	0
	≤250	95.9%	0.734	95.9%	93.5%	75.0%	82.8%	0
RMI 2	≤200	87.0%	0.539	85.1%	92.8%	75.0%	57.1%	0
	≤350	94.5%	0.700	94.2%	93.4%	75.0%	77.4%	0
RMI 3	≤200	89.0%	0.579	87.6%	93.0%	75.0%	61.5%	0
	≤250	95.2%	0.717	95.0%	93.5%	75.0%	80.0%	0
RMI 4	≤450	93.8%	0.684	93.4%	93.4%	75.0%	75.0%	0
	≤400	93.8%	0.684	93.4%	93.4%	75.0%	75.0%	0

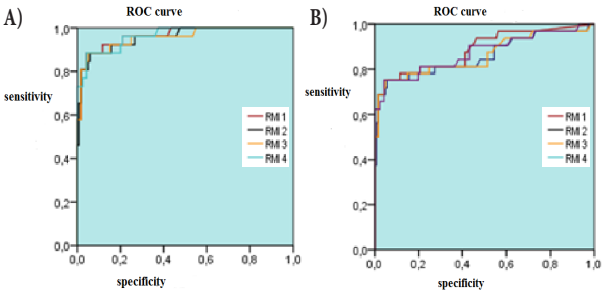

Figure 1. Comparison of A) New cut-off Values for RMI 1-4 in this Study with B) Traditional cut-off Values

Discussion

Early diagnosis is crucial in OC (Ashrafgangooei and Rezaeezadeh, 2011). Early detection of ovarian cancer offers as high as 80% cure rate and the mortality rate declines by half (Zalel et al., 1996). There is no screening test for routine use to diagnose OC. CA-125 has a low specificity in early stages of the disease and may also be found elevated in other conditions such as benign ovarian cysts, irregular cycles, and anaemia, which do not require surgical intervention (Cure et al., 2012). CA-125 levels increase with increasing age. Hormone replacement therapy and smoking reduce CA-125 levels in menopausal women (Dehaghani et al., 2007). On the other hand, Alcázar et al. (2013) reported false positive results by non-expertized ultrasonography operators to be as high as 12% even in the presence of findings strongly suggestive of malignancy such as ascites, bilaterality, solid component, septa formation and metastasis or even if pattern recognition method has been used.

As being the basic components of RMI scales, serum CA-125 levels and positive findings on USG show extensive variability depending on numerous factors and this seems to be affecting the reliability of RMIs. In a study conducted in Thailand, Moolthiya et al. (2009) used a cut-off value of 200 and found lower sensitivity rates for RMI-1 and RMI-2 as compared to the studies conducted in European countries (Jacobs et al., 1990; Tingulstad et al., 1996; Andersen et al., 2003). The study by Ong et al. (2013) conducted in Singapore yielded 12.5% sensitivity and 84.9-90.1% specificity for RMI 1-3. The results suggest that these values are of no diagnostic value in

women of Singapore. In our study, a cut-off value of 200 yielded 90.1% specificity and 75.0% sensitivity. Jacobs et al. (1990) reported 71% sensitivity and 96% specificity when they first used RMI-1. The investigators, who proposed the use of RMI-2, reported 92% specificity and 80% sensitivity with a cut-off value of 200 (Tingulstad et al., 1996). According to our findings, a cut-off value of 200 did not show good performance, and yielded 85.1% specificity and 75% sensitivity. The cut-off value of 200 for RMI-3 yielded 71% sensitivity and 92% specificity for differentiation of benign from malignant adnexal masses (Tingulstad et al., 1999). However, the efficacy of the same cut-off value was found to be lower for RMI-3 in our study (87.6% specificity and 75.0% sensitivity). RMI-4, which is thought to possess the highest efficacy, has been advocated to yield 86.8% sensitivity and 91.0% specificity with a cut-off value of 450 (Yamamoto et al., 2009). However, in our study, we found higher specificity (91.0%) but lower sensitivity (75.0%) for RMI-4 as compared to previous reports.

Many studies evaluating RMI scales in Asian and Pacific countries have reported different cut-off values compared to those originally reported by the investigators who proposed these indexes at the first place (Lou et al., 2010; Ashrafgangooei and Rezaeezadeh, 2011; Bouzari et al., 2011). On the other hand, according to the report by van den Akker et al. from Holland, a cut-off value of 200 for RMI-3 and 450 for RMI-4 showed the best performance and yielded success rates similar to that reported by the original investigators (Tingulstad et al., 1999; Yamamoto et al., 2009; van den Akker et al., 2011). In England, Bailey et al. (2006) reported 88.5% sensitivity for RMI with a cut-off value of 200. This finding was similar to that was found in other European studies (Jacobs et al., 1990; Tingulstad et al., 1996; 1999). However, we found cut-off values for RMI 1-4 different than the other studies. We used a cut-off value of 250 for RMI-1 and 3, 350 for RMI-2, and 400 for RMI-4. With these cut-off values, specificity ranged from 94.3-95.9% and sensitivity was 75%. A cut-of value of 400 or 450 for RMI-4 does not produce significant difference in terms of efficiency. But, new cut-off values set in our study for RMI 1-3 yielded better PPV and NPV. When a cut-off value is set at 250 for RMI-1 and 250 for RMI-2, a patient with the pre-diagnosis of OC is more likely to be diagnosed with OC during surgery. Besides, these new cut-off values would reduce the number of redundant surgeries in asymptomatic patients with benign adnexal mass. Similar to our study, Ashrafgangooei and Rezaeezadeh (2011) reported a cut-off value of 238 for RMI-1 to be performing better in their population. Likewise, Bouzari et al. (2011) reported a cut-off value of 265 for RMI-1 and 3, and 355 for RMI-2 in their study conducted in Iran which is Turkey's neighboring country.

In this study, we showed successful utilization of RMIs in preoperative differentiation of benign from malignant masses. Many studies conducted in Asian and Pacific countries have reported different cut-off values as was the case in our study. We think that it is difficult to determine universally accepted cut-off values for RMIs for common use around the globe.

References

Aktürk E, Karaca RE, Alanbay I, et al (2011). Comparison of four malignancy risk indices in the detection of malignant ovarian masses. *J Gynecol Oncol*, **22**, 177-82.

Alcázar JL, Pascual MA, Olartecoechea B, et al (2013). IOTA simple rules for discriminating between benign and malignant adnexal masses: a prospective external validation. *Ultrasound Obstet Gynecol*, **42**, 467-71.

Andersen ES, Knudsen A, Rix P, Johansen B (2003). Risk of malignancy index in the preoperative evaluation of patients with adnexal masses. *Gynecol Oncol*, **90**, 109-12.

Ashrafgangooei T, Rezaeezadeh M (2011). Risk of malignancy index in preoperative evaluation of pelvic masses. *Asian Pac J Cancer Prev*, **12**, 1727-30.

Bailey J, Tailor A, Naik R, et al (2006). Risk of malignancy index for referral of ovarian cancer cases to a tertiary center: does it identify the correct cases? *Int J Gynecol Cancer*, **16**, 30-4.

Benedet JL, Bender H, Jones H 3rd, Ngan HY, Pecorelli S (2000). FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO committee on gynecologic oncology. *Int J Gynaecol Obstet*, **70**, 209-62.

Benjapibal M, Neungton C (2007). Pre-operative prediction of serum CA 125 level in women with ovarian masses. *J MedAssoc Thai*, **90**, 1986-91.

Bouzari Z, Yazdani S, Ahmadi MH, et al (2011). Comparison of three malignancy risk indices and CA-125 in the preoperative evaluation of patients with pelvic masses. *BMC Res Notes*, **4**, 206.

Cure MC, Cure E, Kirbas A, Yazici T, Yuce S (2012). Requests for tumor marker tests in Turkey without indications and frequency of elevation in benign conditions. *Asian Pac J Cancer Prev*, **13**, 6485-9.

Dehaghani AS, Ghiam AF, Hosseini M, Mansouri S, Ghaderi A (2007). Factors influencing serum concentration of CA125 and CA15-3 in Iranian healthy postmenopausal women. *Pathol Oncol Res*, **13**, 360-4.

Gultekin M, Dursun P, Doğan NU, et al (2009). Debulking surgery for incompletely operated advanced epithelial ovarian carcinoma. *J Surg Oncol*, **100**, 258-60.

Hafeez S, Sufian S, Beg M, et al (2013). Role of ultrasound in characterization of ovarian masses. *Asian Pac J Cancer Prev*, **14**, 603-6.

Harlan LC, Clegg LX, Trimble EL (2003). Trends in surgery and chemotherapy for women diagnosed with ovarian cancer in the United States. *J Clin Oncol*, **21**, 3488-94.

Jacobs I, Oram D, Fairbanks J, et al (1990) A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. *Br J Obstet Gynaecol*, **97**, 922-9.

Khattak YJ, Hafeez S, Alam T, et al (2013). Ovarian masses: is multi-detector computed tomography a reliable imaging modality? *Asian Pac J Cancer Prev*, **14**, 2627-30.

Lou HY, Meng H, Zhu QL, Zhang Q, Jiang YX (2010). Application values of four risk of malignancy indices in the preoperative evaluation of patients with adnexal masses. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao*, **32**, 297-302.

Moolthiya W, Yuenyao P (2009). The risk of malignancy index (RMI) in diagnosis of ovarian malignancy. *Asian Pac J Cancer Prev*, **10**, 865-8.

Ong C, Biswas A, Choolani M, Low JJ (2013). Comparison of risk of malignancy indices in evaluating ovarian masses in a Southeast Asian population. *Singapore Med J*, **54**, 136-9.

Tingulstad S, Hagen B, Skjeldestad FE, et al (1999). The risk-of-malignancy index to evaluate potential ovarian cancers in local hospitals. *Obstet Gynecol*, **93**, 448-52.

Tingulstad S, Hagen B, Skjeldestad FE, et al (1996). Evaluation

of a risk of malignancy index based on serum CA125, ultrasound findings and menopausal status in the pre-operative diagnosis of pelvic masses. *Br J Obstet Gynaecol*, **103**, 826-31.

van den Akker PA, Zusterzeel PL, Aalders AL, et al (2011). External validation of the adapted risk of malignancy index incorporating tumor size in the preoperative evaluation of adnexal masses. *Eur J Obstet Gynecol Reprod Biol*, **159**, 422-5.

Yamamoto Y, Yamada R, Oguri H, Maeda N, Fukaya T (2009). Comparison of four malignancy risk indices in the preoperative evaluation of patients with pelvic masses. *Eur J Obstet Gynecol Reprod Biol*, **144**, 163-7.

Zalel Y, Tepper R, Altaras M, et al (1996). Transvaginal sonographic measurements of postmenopausal ovarian volumes as a possible detection of ovarian neoplasia. *Acta Obstet Gynecol Scand*, **75**, 668-71.