Singapore Med J 2013; 54(3): 136-139
doi:10.11622/smedj.2013046

Comparison of risk of malignancy indices in evaluating ovarian masses in a Southeast Asian population

Clara Ong[1], MBBS, MRCOG, *Arijit Biswas*[1,2], MRCOG, FRCOG, *Mahesh Choolani*[1,2], FRCOG, FRANZCOG, *Jeffrey Jen Hui Low*[1,2], FRCOG, FRANZCOG

INTRODUCTION The risk of malignancy index (RMI) is a scoring system used to triage benign from malignant ovarian masses. We compared the specificity and sensitivity of the four indices (RMI 1, RMI 2, RMI 3 and RMI 4) to discriminate a benign ovarian mass from a malignant one in a Southeast Asian population.

METHODS This was a five-year retrospective study of women who were admitted for surgery due to ovarian masses. RMI scores were calculated based on standardised preoperative cancer antigen (CA)-125 levels, ultrasonography findings, menopausal status and tumour size based on ultrasonography. Postoperative histopathologic diagnosis was regarded as the definite outcome. Data were analysed using the Statistical Package for the Social Sciences, and Mann-Whitney U test was used to compare the individual RMI scores between the benign and malignant cases.

RESULTS Out of the 480 patients reviewed, 228 women aged 10–65 years were included in the study. Of these, 17 (7.5%) had malignant disease and 211 (92.5%) had benign pathology. There was no statistical difference in the RMI 1, 2, 3 and 4 scores between the benign and malignant cases. Individual variables that were analysed showed significant differences in median CA-125 level and tumour size ($p = 0.044$ and $p < 0.0005$, respectively) between the benign and malignant cases.

CONCLUSION Our study shows that RMI is not a valuable triage tool for our Southeast Asian population. Further prospective validation, with regard to standardising results in different patient populations and centres, is required.

Keywords: CA125, ovarian cancer, risk of malignancy index, ultrasonography

INTRODUCTION

The incidence of ovarian cancer among Singapore women has been rising over the past four decades, with the local incidence rate falling between those of Western Europe and the USA.[1] In Singapore, ovarian cancer accounts for 5.7% of all female cancers and ranks as the fifth most common cancer among Singapore women (breast cancer ranks first, followed by colorectal, lung and uterine cancer).[2] Most ovarian cancers are epithelial in origin. The presenting symptoms are often ill-defined in the early stages. Thus, the majority are diagnosed at an advanced stage, resulting in a poor overall five-year survival rate of less than 45%.

It has been shown that women with ovarian cancer have a better prognosis if the full surgical staging procedure is carried out initially by a trained gynaecological oncologist.[3] Therefore, preoperative knowledge of the nature of the adnexal mass is necessary so that optimal surgery can be planned at the time of initial treatment. The challenge for general gynaecologists has been how to differentiate a benign adnexal mass from a malignant one so that an appropriate referral can be made preoperatively. The risk of malignancy index (RMI) has been shown to be a triage tool with the potential to reduce the workload in a busy gynaecological unit.

The aim of this study was to determine the value of the RMI as a triage tool by evaluating the four indices (RMI 1, RMI 2, RMI 3, and RMI 4) and comparing their specificity and sensitivity in discriminating a benign ovarian mass from a malignant one.

METHODS

This was a five-year retrospective study conducted from November 2004 to October 2009 in female patients who were admitted to our hospital for surgery due to ovarian masses. Only patients who had both cancer antigen (CA)-125 tests and ultrasonography performed in the same hospital were included in the study. The local research ethics committee had deemed that no ethics approval was required, as this was a retrospective review of patients' case notes.

RMI was calculated by multiplying the results of ultrasonography score (U) by menopausal status (M) and blood levels of ovarian CA-125 (measured in U/mL). All RMI used the same basic formula but differed in the scores that were assigned to U and M. RMI 4 included tumour size (S) measured by ultrasonography (Table I). Total ultrasonography scores were calculated by giving one point for each of the ultrasonographic features suggestive of malignancy on transvaginal ultrasonographic examination. These features included the presence of a multilocular cystic lesion, solid areas, bilateral lesions, ascites, and intra-abdominal metastases.

The standardised preoperative serum CA-125 levels, age and menopausal status of the patients were recorded.

[1]Department of Obstetrics and Gynaecology, National University Hospital, [2]Department of Obstetrics and Gynaecology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
Correspondence: A/Prof Jeffrey Low, Senior Consultant and Head, Division of Gynaecologic Oncology, Department of Obstetrics and Gynaecology, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074. jeffrey_low@nuhs.edu.sg

Table I. Risk of malignancy index (RMI) scoring systems.

Parameter	RMI 1	RMI 2	RMI 3	RMI 4
Ultrasonography score (U)				
No feature	0	1	1	1
1 feature	1	1	1	1
≥ 2 features	3	4	3	4
Menopausal status (M)				
Premenopausal	1	1	1	1
Postmenopausal	3	4	3	4
CA-125 (U/mL)	-	-	-	-
Tumour size (S)				
< 7 cm	-	-	-	1
≥ 7 cm	-	-	-	2

Formula for RMI 1, 2 and 3: U × M × CA-125
Formula for RMI 4: U × M × CA-125 × S

Table II. Distribution of diagnoses among the 228 patients in the study.

Diagnosis/stage of disease	No. of patients (%)		
	Premenopausal (n = 214)	Postmenopausal (n = 14)	Total (n = 228)
Benign disease	200 (93.5)	11 (78.6)	211 (92.5)
Simple cyst	10 (4.7)	2 (14.3)	12 (5.7)
Paratubal cyst	2 (0.9)	1 (7.1)	3 (1.4)
Fimbrial cyst	2 (0.9)	0	2 (0.9)
Tubo-ovarian abscess	1 (0.5)	0	1 (0.5)
Endometriosis	160 (74.8)	2 (14.3)	162 (76.8)
Dermoid cyst	12 (5.6)	1 (7.1)	13 (6.2)
Fibroma	2 (0.9)	1 (7.1)	3 (1.4)
Serous cystadenoma	7 (3.3)	2 (14.3)	9 (4.3)
Mucinous cystadenoma	4 (1.9)	2 (14.3)	6 (2.8)
Malignant disease	14 (6.5)	3 (21.4)	17 (7.5)
Stage 1 – invasive	3 (1.4)	1 (7.1)	4 (23.5)
Stage 1 – borderline	10 (4.7)	1 (7.1)	11 (64.7)
Stage 2	0	0	0
Stage 3	1 (0.5)	1 (7.1)	2 (11.8)
Stage 4	0	0	0

Table III. Area under the receiver-operator characteristic (ROC) curve for RMI 1, 2, 3 and 4.

Variable	Area	Std. error*	Asymptotic	
			Sig.†	95% CI
RMI 1	0.519	0.070	0.800	0.382, 0.656
RMI 2	0.431	0.082	0.355	0.270, 0.592
RMI 3	0.426	0.079	0.322	0.271, 0.580
RMI 4	0.558	0.080	0.436	0.402, 0.715

*Under the nonparametric assumption. †Null hypothesis: true area = 0.5.
Area under the ROC curve showed no statistical difference in RMI 1, 2, 3 and 4 between benign and malignant cases.
The test result variable(s): RMI 1, 2, 3 and 4 have at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

Ultrasonographic examinations were performed transvaginally at the hospital's antenatal diagnostic centre, and abdominal imaging was conducted, when indicated. Tumour size was measured by ultrasonography for each patient. A GE Voluson 730 Pro was used with a 2–7 MHz AB2-7 transabdominal probe and a 3.7–9.3 MHz IC 5-9H transvaginal probe (General Electric Healthcare, Tokyo, Japan). Peripheral venous blood samples were drawn preoperatively. Serum CA-125 levels were measured in the hospital's biochemistry laboratory by CA-125 chemiluminescence immunoassay (AccuBioTech, Newark, DE, USA). Postoperative histopathologic diagnosis was regarded as the definite outcome.

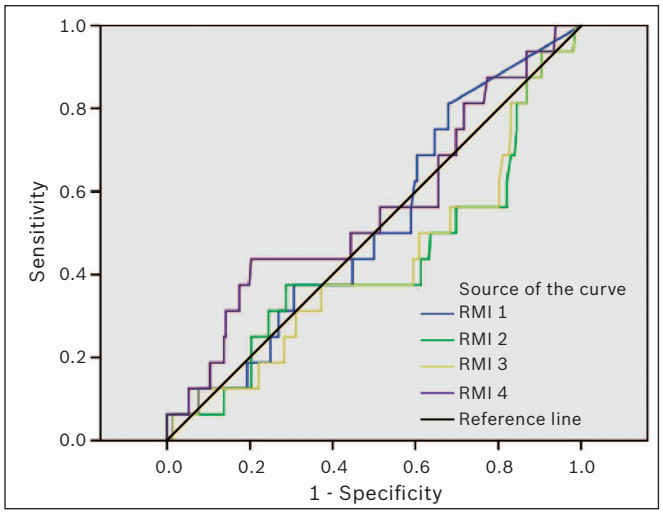

Fig. 1 Receiver-operator characteristic (ROC) curve shows the relationship between specificity and sensitivity for RMI 1, 2, 3 and 4.

Based on the data obtained, the RMI 1, 2, 3 and 4 scores were calculated. An RMI value ≥ 200 was considered to be a high risk of malignancy and a value < 200 was considered to be a low risk of malignancy.[4-6] The data were analysed using the Statistical Package for the Social Sciences version 17, and Mann-Whitney U test was used to compare the individual RMI between the benign and malignant cases. A p-value < 0.0.5 was considered to be statistically significant.

RESULTS

The clinical records of 480 patients were reviewed. Out of these, 228 (47.5%) patients who had both CA-125 tests and ultrasonography performed in the same hospital were included based on the selection criteria. Out of 228 patients, 17 (7.5%) had malignant disease and 211 (92.5%) had benign pathology. The distribution of diagnoses and stages of disease in the cohort is shown in Table II.

Our study showed no statistical difference in RMI 1, 2, 3 and 4 scores between the benign and malignant cases (Table III, Fig 1). The distribution of benign and malignant cases by age, menopausal status, ultrasonography score and tumour size is shown in Table IV. Individual variables analysed showed significant differences in median CA-125 and tumour size ($p = 0.044$ and $p < 0.0005$, respectively) between the benign and malignant cases (Table IV). The performance of RMI 1, 2, 3 and 4 at different cut-off levels showed improved sensitivity but with a corresponding loss in specificity (Table V).

DISCUSSION

RMI is a straightforward algorithm that is simple to apply in clinical practice. It uses inexpensive tests that are commonly available and easily reproducible. The risk of malignancy index (RMI 1) was originally developed by Jacobs et al in 1990.[4] Subsequently, Tingulstad et al developed RMI 2 in 1996,[5] and modified it to derive RMI 3 in 1999.[6] The difference among

Table IV. Distribution of age, menopausal status, ultrasonography score, tumour size and serum CA-125 levels in patients with benign and malignant pelvic masses (n = 228).

Variable	No. of patients (%)		p-value
	Benign (n = 211)	Malignant (n = 17)	
Age (yrs)			0.25*
≤ 30	62 (29.4)	5 (29.4)	
31–40	68 (32.2)	2 (11.8)	
41–50	72 (34.1)	7 (41.2)	
≥ 50	9 (4.3)	3 (17.6)	
Menopausal status			
Premenopausal	200 (94.8)	14 (82.4)	
Postmenopausal	11 (5.2)	3 (17.6)	
Ultrasonography score			0.103*
0	69 (32.7)	2 (11.8)	
1	92 (43.6)	8 (47.0)	
2	47 (22.3)	6 (35.3)	
3–5	3 (1.4)	1 (5.9)	
Tumour Size (cm)			< 0.0005*
< 7	129 (61.1)	1 (5.9)	
≥ 7	82 (38.9)	16 (94.1)	
CA-125 (U/mL)			0.044*
Mean	64.86	37.96	
Median	35.80	18.75	
Range	1–991	5–228	

*Data was analysed using the U test.

Table V. Specificity and sensitivity of RMI 1, 2, 3 and 4 at different cut-off points of RMI.

RMI cut-off points	RMI 1		RMI 2		RMI 3		RMI 4	
	SEN	SPEC	SEN	SPEC	SEN	SPEC	SEN	SPEC
50	37.5	62.7	37.5	50.9	37.5	54.2	56.3	44.8
75	31.3	72.6	37.5	64.2	31.3	67.9	43.8	58.5
100	18.8	77.4	37.5	70.3	18.8	74.1	43.8	62.7
125	12.5	82.1	25	76.4	12.5	79.7	43.8	65.6
150	12.5	84	25	79.2	12.5	82.5	43.8	71.2
175	12.5	86.3	12.5	82.1	12.5	85.8	43.8	75.9
200	12.5	89.6	12.5	84.9	12.5	90.1	43.8	78.8

RMI: risk of malignancy index; SEN: sensitivity; SPEC: specificity

these three indices lies in the scoring given to ultrasonography findings and menopausal status. The RMI 2 score gives greater weight to ultrasonography findings and menopausal status than RMI 1. All indices presented a significantly better performance in detecting malignancy than the use of a single parameter. Tested by Morgante et al on another population with evident malignant criteria on ultrasonography, such as hepatic or distant metastases, it was found that RMI 2 yielded better performance for detecting ovarian malignancy.[7] Yamamoto et al published their own model (termed RMI 4) in 2009, which added tumour size score measurement on ultrasonography.[8]

It has been shown that using a cut-off value of 200 (regardless of scoring system) for an RMI score achieves sensitivities ranging from 70% to 87%, and specificities from 89% to 97%.[4-7] However, RMI uses ultrasonography imaging, which is subject to interpreter variability between and within centres, as well as variation between patient populations. Using data obtained within the same hospital, Jacobs et al reported a sensitivity and specificity of 85.4% and 96.9%, respectively, using an RMI score of 200, but a sensitivity and specificity of 95.1% and 76.5%, respectively, with an RMI score of 50.[4] Manjunath et al[9] reported a sensitivity and specificity of 73% and 91%, respectively, attributing the lower sensitivity to a higher percentage of premenopausal ovarian cancer patients compared to that of earlier studies by Jacobs et al and Davies et al.[4,10]

Besides RMI, a variety of methods for the detection of early ovarian cancer has been investigated. Human epididymis secretory protein 4 (HE4) is a recent example. Overexpressed in ovarian cancers, especially in serous epithelial tumours, this novel biomarker has been shown to have a sensitivity similar to CA-125 and a higher specificity than CA-125 in distinguishing between patients with ovarian cancer and those with benign gynaecologic conditions.[11] Recognising that HE4 was a promising tool, Moore et al created the risk of ovarian malignancy algorithm (ROMA), which utilises dual serum markers of HE4 and CA-125 combined with menopausal status. ROMA was shown to have a higher sensitivity for distinguishing benign ovarian masses from early ovarian cancer compared to RMI (94.3% versus 84.6%, at a set specificity of 75%; p-value = 0.0029).[12] Another proposed screening tool was the ovarian cancer symptom index developed by Andersen et al in 2008. The combination of the symptom index, CA-125 and HE4 reported a sensitivity of 84% and specificity of 98.5% when two of the three tests were positive.[13] Given the myriad of choices, further validation is needed before these screening tools can be added to clinical practice.

Our study was confounded by the large number of endometriotic cysts that presented as complex ovarian cysts with both high CA-125 levels and ultrasonography scores. These endometriotic cysts comprised 74.8% of benign cases and were the main limiting factor of our study. This calls into question how well RMI would perform in triaging cases of malignant ovarian cysts versus benign but complex-looking endometriotic cysts in our hospital. Other limiting factors in our study included its retrospective nature, the small sample size and possible interobserver variability among sonographers.

In conclusion, this study has shown that RMI is not a valuable tool in the triage of our Southeast Asian population. Further prospective validation is required with regard to the standardisation of results in different patient populations and centres.

REFERENCES

1. Trends in cancer incidence in Singapore 1968-2007. Singapore Cancer Registry Report Number 7. Singapore: National Registry of Diseases Office, 2010.
2. Singapore Cancer Registry interim report. Trends in cancer incidence in Singapore, 2004-2008. Singapore: National Registry of Diseases Office, 2010.
3. Junor EJ, Hole DJ, McNulty L, Mason M, Young J. Specialist gynaecologists and survival outcome in ovarian cancer: a Scottish national study of 1866 patients. Br J Obstet Gynaecol 1999; 106:1130-6.
4. Jacobs I, Oram D, Fairbanks J, et al. A risk of malignancy index incorporating

CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. Br J Obstet Gynaecol 1990; 97:922-9.
5. Tingulstad S, Hagen B, Skjeldestad FE, et al. 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 1996; 103:826-31.
6. Tingulstad S, Hagen B, Skjeldestad FE, et al. The risk-of-malignancy index to evaluate potential ovarian cancers in local hospitals. Obstet Gynecol 1999; 93:448-52.
7. Morgante G, la Marca A, Ditto A, De Leo V. Comparison of two malignancy risk indices based on serum CA125, ultrasound score and menopausal status in the diagnosis of ovarian masses. Br J Obstet Gynaecol 1999; 106:524-7.
8. Yamamoto Y, Yamada R, Oguri H, Maeda N, Fukaya T. Comparison of four malignancy risk indices in the preoperative evaluation of patients with pelvic masses. Eur J Obstet Gynecol Reprod Biol 2009; 144:163-7.
9. Manjunath AP, Pratapkumar, Sujatha K, Vani R. Comparison of three risk of malignancy indices in evaluation of pelvic masses. Gynecol Oncol 2001; 81:225-9.
10. Davies AP, Jacobs I, Woolas R, Fish A, Oram D. The adnexal mass: benign or malignant? Evaluation of a risk of malignancy index. Br J Obstet Gynaecol 1993; 100:927-31.
11. Molina R, Escudero JM, Augé JM, et al. HE4 a novel tumour marker for ovarian cancer: comparison with CA 125 and ROMA algorithm in patients with gynaecological diseases. Tumour Biol 2011; 32:1087-95.
12. Moore RG, Jabre-Raughley M, Brown AK, et al. Comparison of a novel multiple marker assay vs the Risk of Malignancy Index for the prediction of epithelial ovarian cancer in patients with a pelvic mass. Am J Obstet Gynecol 2010; 203:228.e1-6.
13. Andersen MR, Goff BA, Lowe KA, et al. Use of a Symptom Index, CA125, and HE4 to predict ovarian cancer. Gynecol Oncol 2010; 116:378-83.