

Short Communication

Risk of malignancy index validity assessment in premenopausal and postmenopausal women with adnexal tumors

Milan Terzic^{a,b,*}, Jelena Dotlic^a, Ivana Likic^{a,b}, Natasa Brndusic^a, Igor Pilic^a,
Nebojsa Ladjevic^{b,c}, Sanja Maricic^d, Nebojsa Arsenovic^e, Zoran Maricic^a

^a Clinic of Obstetrics and Gynecology, Clinical Center of Serbia, Visegradska 26, Belgrade, Serbia

^b Medical Faculty, University of Belgrade, Dr Subotica 8, Belgrade, Serbia

^c Center for Anesthesiology and Resuscitation, Clinical Center of Serbia, Pasterova 2, Belgrade, Serbia

^d Occupational Health Department, General Health Center "Savski Venac", Pasterova 1, Belgrade, Serbia

^e Department of Cellular Pathology, PathLinks Pathology Services, Lincoln County Hospital, Greetwell Road, Lincoln LN2 5QY, UK

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Abstract

Objective: The aim of this study was to investigate the validity of the risk of malignancy index (RMI) in premenopausal and postmenopausal patients with adnexal masses.

Materials and Methods: The study involved all women treated for adnexal tumors throughout an 18-month period in the Clinic for Gynecology and Obstetrics, Clinical Center of Serbia (Belgrade, Serbia). On admission, detailed anamnestic and laboratory data were obtained and an expert ultrasound scan was performed. The RMI was calculated for all patients and the obtained data were related to histopathological findings of the tumors. For statistical analysis, we used descriptive and analytical statistics methods and an SPSS computer program.

Results: From a total number of 540 women, 85 women had malignant tumors; 20 women, borderline tumors; and 435 women, benign adnexal tumors. The RMI was reliable in 84.6% of all patients; in 77% of premenopausal patients, and in 81.1% of postmenopausal patients. The sensitivity of the RMI in the overall population was 83.81%; the specificity was 77.24%; the positive predictive value (PPV) was 47.06%, and the negative predictive value (NPV) was 95.18%. In premenopausal women, the RMI sensitivity was 83.87%; specificity, 80.31%; PPV, 28.89%; and NPV, 98.12%. In postmenopausal women the RMI sensitivity was 83.78%; specificity, 68.18%; PPV, 63.92%; and NPV, 74.71%.

Conclusion: The RMI was a reliable factor for differentiating benign from malignant adnexal masses in premenopausal and postmenopausal patients. Copyright © 2013, Taiwan Association of Obstetrics & Gynecology. Published by Elsevier Taiwan LLC. All rights reserved.

Keywords: adnexal masses; postmenopause; premenopause; risk of malignancy index

Introduction

Gynecologic malignancies from ovarian cancer remain a leading cause of death [1]. More than two-thirds of ovarian cancer cases are diagnosed when the disease has progressed to stage III or IV and has involved the peritoneal cavity or other organs [2]. Symptoms that are associated with ovarian cancer are typically nonspecific and the association is often not recognized until the disease has advanced. Therefore,

recognizing it at the early stage is of utmost importance. However, several features of ovarian cancer complicate its screening. Two-thirds of ovarian cancer cases are diagnosed in women over the age of 55 years [3]. The validity of the risk of malignancy index (RMI) in postmenopausal patients is well known and widely accepted. Its role in premenopausal patients remains undefined [3]. Furthermore, in recent years the incidence of ovarian cancer is increasing in younger women. The aim of this study was to verify the validity of RMI in discriminating between benign and malignant adnexal masses in clinical practice and to compare its value in premenopausal and postmenopausal women.

* Corresponding author. Clinic of Ob/Gyn, Medical Faculty, University of Belgrade, Dr Koste Todorovica 26, 11000 Belgrade, Serbia.

E-mail address: terzicmilan@yahoo.co.uk (M. Terzic).

Materials and methods

The study included all consecutive patients who had undergone surgery for adnexal tumors at the Clinic of Gynecology and Obstetrics, Clinical Center of Serbia (Belgrade, Serbia) during an 18-month period (July 1, 2010 to December 31, 2011). Written, informed consent was obtained from all patients for all necessary diagnostic methods, for surgery, and for inclusion into this study. On admission, all women underwent detailed anamnesis—especially in regard to the time of the last menstrual cycle—and all standard laboratory analyses (e.g., blood analysis, the CA-125 level as a tumor marker). Furthermore, expert clinical and ultrasound examinations were performed of the abdominal and pelvic organs (e.g., tumor diameter, multilocularity and bilaterality, solid/cystic components/parts, metastases and presence of ascites). The RMI was calculated for all patients by using the following formula: $RMI = U \times M \times CA-125$. In the formula, U represents the ultrasonographic index. Multilocular and bilateral tumors, the presence of solid parts in a tumor, metastasis and ascites are each marked with one point. The sum of these points, are scored so that in the formula U 0 = 0 points, U 1 = 1 point, and U 2–5 = 3 points. In the formula M represents menopausal status (1 for premenopausal and 3 for postmenopausal women). The CA-125 level is calculated directly into the equation. The patients were divided into three groups, according to the RMI values (low risk less than 25, intermediate risk 25–250, and high risk greater than 250). After surgery and the removal of the adnexal masses, the histopathological (HP) findings were analyzed to make a final diagnosis and determine the stage of the disease. After obtaining the HP verification of the tumor type and a specific diagnosis, the following were calculated: (1) sensitivity [i.e., (true positive/true positive + false negative) \times 100]; (2) specificity [i.e., (true negative/true negative + false positive) \times 100]; (3) positive predictive value [(true positive/true positive + false positive) \times 100]; and (4) negative predictive value [(true negative/true negative + false negative) \times 100]. The receiver operating characteristic (ROC) curves were then established for premenopausal and postmenopausal women, and for the whole population of the examined patients.

For statistical analysis of the achieved data we used descriptive statistics methods, the Kolmogorov-Smirnov Z test, Friedman's parametric ANOVA, the χ^2 test and threshold analysis. Data of the descriptive parameters were expressed as the mean \pm the standard deviation and the range, unless stated otherwise. For data analysis, an SPSS 15 computer program was used.

Results

The study involved 540 women. Of these, 356 were of reproductive age and 184 were in menopause. Malignancy was histopathologically present in 85 women, borderline tumors were present in 20 women, and benign tumors were present in 435 patients.

Table 1 shows the average age of the examined patients. High significant differences existed between the tumor types in regard to the woman's age ($F = 41.999$, $p < 0.001$). The youngest group was women with benign tumors. There were no significant differences between women with malignant tumors and women with borderline tumors. Most women with benign tumors were 30–39 years old, whereas most women with malignant or borderline tumors were 50–59 years old. The highest RMI levels were in women 50–59 years old and the lowest levels were in women younger than 19 years old ($\chi^2 = 55.401$, $p < 0.001$). A high risk for malignancy was more frequent in postmenopausal women, whereas low and intermediate risks were more usual in premenopausal women ($F = 27.781$, $p < 0.001$).

Table 1 presents the RMI levels of all examined women and in the groups of premenopausal and postmenopausal patients. Table 2 presents the number of patients in each risk categories (i.e., low, intermediate, and high), based on their RMI level.

There were significantly large differences between the tumor types in regard to the patients' RMI (for the overall examined population, $F = 40.692$ and $p < 0.001$; for postmenopausal women, $F = 13.182$ and $p < 0.001$; for premenopausal women, $F = 24.158$ and $p < 0.001$). The RMI values were significantly greater in women with malignant tumors than in women with other tumor types in all three examined populations. There were no significant differences between women with benign tumors and women with borderline tumors in all three examined populations (i.e., all, postmenopausal, and premenopausal women).

The RMI was reliable for 84.6% of all patients. In the examined postmenopausal patients, the RMI was accurate for 81.1% of the women, whereas the RMI was accurate for 77% of premenopausal women (Fig. 1). Table 3 presents the sensitivity and specificity of the RMI on cutoff at the recommended intermediate risk level of 25 and high risk level of 250. Furthermore, we assessed other cutoff points with a better sensitivity/specificity ratio obtained from the receiver operating characteristic (ROC) analysis. The RMI cutoff point of 29.6 had a sensitivity of 94.1% and a specificity of 29.7%. The RMI cutoff point of 107.4 had a sensitivity of 80.0% and a specificity of 70.3%. The RMI cutoff point of 204.2 had a sensitivity of 72.9% and a specificity of 84.8%. For premenopausal women, the most appropriate sensitivity/specificity

Table 1
Age and RMI level of the patients in the examined populations.

Parameters		Overall population	Premenopausal women	Postmenopausal women
Age	Mean	53.44	37.12	61.73
	SD	16.82	9.10	9.42
	Minimum	18	18	35
	Maximum	82	61	82
RMI	Mean	3065.53	212.67	2117.39
	SD	9171.38	697.27	6754.90
	Minimum	0.00	0.00	0.00
	Maximum	61305.00	8434.00	61305.00

RMI = risk of malignancy index; SD = standard deviation.

Table 2
Number of patients in the different risk categories, based on the RMI level.

Risk categories	Overall population	Premenopausal women	Postmenopausal women
Low	123	108	15
Intermediate	285	196	89
High	132	52	80

ratio had a RMI cutoff point of 99.5 and a sensitivity of 75% and a specificity of 72%.

By evaluating the relationships between RMI and HP in the examined populations, we have established the number of true-positive, false-positive, false-negative, and true-negative findings. From these values, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the RMI were calculated for the overall population, premenopausal women, and postmenopausal women. Table 4 presents these findings.

Discussion

Of all gynecological malignancies, ovarian cancer generally has the worst prognosis since it is usually diagnosed at an advanced stage [4]. A definitive diagnosis of ovarian cancer can be established as a rule only after surgery [5,6]. To detect the disease at a very early stage, several approaches have been used to triage women with suspicious ovarian tumors. These attempts include using a single cutoff for the serum CA-125 titer, ultrasonic morphology scoring systems, Doppler ultrasonic parameters, and complex statistical models developed from multivariate logistic regression [7,8].

According to the referral guidelines, for a newly diagnosed ovarian mass, patients are stratified on the basis of the woman's menopausal status. Women in menopause, a CA-125 level greater than 200 U/mL, the presence of ascites, evidence of abdominal or distant metastasis (by examination or imaging study) are usual indications for referral to gynecological oncologists since each of these parameters is significantly and

independently associated with the likelihood of malignancy [7,9]. However, none of these parameters examined alone have proven its accuracy in predicting the nature of the adnexal tumor. The risk of malignancy index incorporates all these parameters and is used to predict the likelihood of malignancy in patients presenting with an ovarian mass. The RMI (which is based on menopausal status), ultrasound findings, and serum CA-125 level are the most widely used methods for preoperatively differentiating between malignant and benign diseases [10,11]. The effectiveness of the RMI has also been validated in a number of studies, and has been proven as a simple, low-cost, and effective tool for triage and for managing ovarian masses in postmenopausal women [7,12].

The sensitivity of the RMI shows that it is able to label malignant tumors in high-risk cases, whereas its specificity shows it is able to label benign tumors as low-risk cases. The best result is when all examined parameters (i.e., sensitivity, specificity, PPV, and NPV) are high, but it is more important if the test has a high sensitivity. It is expected that specificity of the RMI would be lower than sensitivity since unreferred benign cases are not detected [7]. Our results were consistent with the expected lower specificity of the RMI in all three examined groups (i.e., overall population, premenopausal women, and postmenopausal women).

Numerous previous reports have tested the sensitivity and specificity of different RMI cutoff values in the overall population of women with adnexal masses. Most studies found the RMI had a high specificity when using a cutoff value of 25, 200, or 250 [7]. In available literature data, a cutoff level of 25 achieves a sensitivity of 98% and a specificity of 42%; this indicates that 98% of ovarian cancer cases have a RMI of more than 25 [10]. The results of our study for overall patients (sensitivity = 83.81%, specificity = 77.24%, PPV = 47.06%, NPV = 95.18%) are similar to the results reported in the medical literature. Furthermore, an appropriate high sensitivity was achieved in all three examined populations (i.e., overall population, premenopausal women, and postmenopausal women).

Some studies show that, in women with a RMI of less than 25, only few women (usually with borderline ovarian tumors) are misdiagnosed as having benign disease, which means that almost all patients with a RMI of less than 25 have a benign adnexal mass. Therefore, a RMI value of 25 appears to be a suitable threshold for determining which women would benefit from additional imaging. This was also confirmed in our study. Considering women with a RMI greater than 250 as having malignant disease resulted in just a couple of incorrect diagnoses. Therefore, it would seem reasonable for this group of women to be managed in a cancer unit by gynecological oncologist [10,13]. In our study, the recommended intermediate risk level of RMI 25 had higher sensitivity, which proved its reliability as a cutoff level. Almost all women with a RMI less than 25 had benign tumors. This was true for premenopausal and postmenopausal women, and for the overall population. In our study, the level of 29 furthermore showed the same sensitivity, but a somewhat higher specificity than did the RMI cutoff of 25. On the other hand, the recommended cutoff level for high risk (i.e., a RMI of 250) was less accurate. A

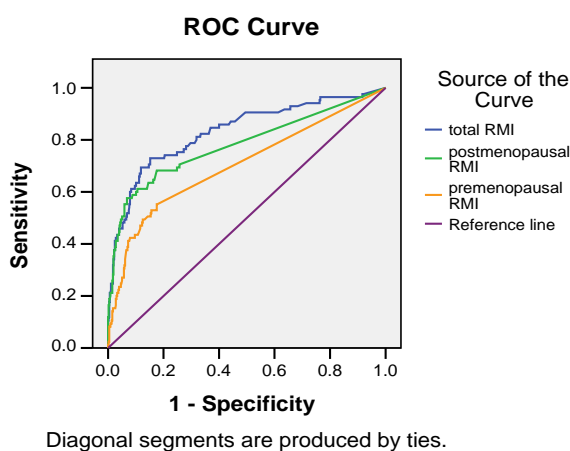


Fig. 1. The risk of malignancy index receiver operating characteristic (ROC) curves for the examined populations. RMI = risk of malignancy index.

Table 3
Sensitivity and specificity at different cutoff levels of the RMI.

RMI cutoff value	Overall population		Premenopausal women		Postmenopausal women	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
25	94.1	27.4	91.7	32.2	95.1	9.8
250	72.9	86.9	54.2	88.3	80.3	79.73

RMI = risk of malignancy index.

significant number of borderline and malignant cases was in the group of women with an intermediate risk (i.e., a RMI between 25 and 250). We advise that every finding of RMI above 100 should alert our attention. All such cases need further diagnostic evaluation.

The minimum PPV set by most epidemiologists to support a screening test is 10% [3]. Because of the low prevalence of ovarian cancer (40 cases/year per 100,000 women over the age of 50 years), a screening test must have both a high sensitivity and a high specificity to be clinically useful. It is estimated that a screening test for ovarian cancer would require a sensitivity of at least 75% and a specificity of more than 99.6% to achieve a PPV of 10%. In our study, the PPV of the RMI was 47.6% for the overall population, 28.89% for premenopausal women, and 63.92% for postmenopausal women. This is even higher than recommended. These findings confirm the previous RMI value for postmenopausal patients, with recommendation for its implementation for premenopausal women with adnexal masses.

Some studies report that the specificity of RMI is lower in younger women [14]. On the other hand, in our study, the RMI was reliable in 84.6% of both premenopausal and postmenopausal patients with adnexal masses. Moreover, the RMI is precise for 81.1% of postmenopausal women. These results are in agreement with the usual literature data that indicates that the RMI should be only used for postmenopausal women since it can show its full predictive power only in that population [3]. However, the RMI in our study also explained 77% of premenopausal cases. This is similar to some other investigations [14–16]. Therefore, the RMI can be accurately used for premenopausal women, which we recommend.

In conclusion, it can be said that there were no significant differences between women with malignant and borderline

tumors in regard to their age. However, women with benign tumors were younger. A high risk for malignancy was more frequent in postmenopausal women, whereas low and intermediate risks were more usual in premenopausal women. The RMI was reliable in 84.6% of cases in the overall population of premenopausal and postmenopausal patients; in 77% of premenopausal patients, and in 81.1% of postmenopausal patients. The sensitivity of the RMI was 83.81% in the overall population; 83.87% for premenopausal women; and 83.78% for postmenopausal women. It consequently can be concluded that the RMI is a reliable factor for differentiating benign from malignant adnexal masses in premenopausal and postmenopausal patients. Therefore, we recommend using the RMI during the preoperative triage of adnexal masses in premenopausal and postmenopausal patients.

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Table 4
Number of positive and negative findings and the sensitivity, specificity, positive predictive value, and negative predictive value of the RMI in the examined populations.

RMI	Overall population	Premenopausal women	Postmenopausal women
True positive findings (no.)	88	26	62
False positive findings (no.)	99	64	35
False negative findings (no.)	17	5	12
True negative findings (no.)	336	261	75
Sensitivity (%)	83.81	83.87	83.78
Specificity (%)	77.24	80.31	68.18
Positive predictive value (%)	47.06	28.89	63.92
Negative predictive value (%)	95.18	98.12	74.71

RMI = risk of malignancy index.

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