Comparison of four malignancy risk indices in the detection of malignant ovarian masses

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Objective: The aim of this study was to evaluate the ability of four risk of malignancy indices (RMI) to detect malignant ovarian tumors.

Methods: This is a prospective study of 100 women admitted to the Department of Obstetrics and Gynecology of Gulhane Military Medicine Academy for surgical exploration of pelvic masses. To diagnose malignant ovarian tumors, the sensitivity, specificity, negative and positive predictive values and diagnostic accuracy of four RMIs (RMI 1, RMI 2, RMI 3, and RMI 4) were obtained.

Results: In our study we found that there is no statistically significant difference in the performance of four different RMIs in discriminating malignancy. We think that malignancy risk indices is more reliable than the menopausal status, serum CA-125 levels, ultrasound features and tumor size separately in detecting malignancy.

Conclusion: We concluded that any of the four malignancy risk indices described can be used for selection of cases for optimal therapy. These methods are simple techniques that can be used even in less-specialized gynecology clinics to facilitate the selection of cases for referral to an oncological unit.

Keywords: Ovarian cancer, Pelvic mass, Risk of malignancy index
of CA-125. This has given much better results than a single parameter [18-23]. The RMI can be applied in less specialized centers. The risk of malignancy index is the product of the ultrasound scores (U), the menopausal score (M), and the absolute value of serum CA-125 levels: \( \text{RMI} = U \times M \times |CA-125| \).

In the 1990s, Jacobs et al. [18] originally developed the RMI, which is now termed RMI 1. Tingulstad et al. [19] developed their version of the RMI in 1996 and it is known as RMI 2. In 1999, Tingulstad et al. [20] modified the RMI, which is termed RMI 3. Yamamoto et al. [24] created their own model of a malignancy risk index. They added the parameter of the tumor size (S) to the RMI and have termed it RMI 4.

The purpose of this study was to evaluate the ability of the four malignancy risk indices to discriminate a benign from a malignant pelvic mass and to evaluate the performances of the four malignancy risk indices.

**MATERIALS AND METHODS**

The clinical data of 100 women with pelvic masses appointed for laparotomy or laparoscopy between October 1, 2008, and February 3, 2010, to our hospital were obtained. We began our trial to compare RMI 1, RMI 2, and RMI 3 with each other. During the data collection period, in 2009, Yamamoto et al. [24] published their study about RMI 4. So we calculated RMI 4 scores of masses retrospectively before 2009 and prospectively after that year. Preoperative serum CA-125 levels, ultrasound findings, and menopausal status were noted. The ultrasound was performed transvaginally by a 7.5-MHz transducer (Siemens, Antares Sonoline, CA, USA). A transabdominal repeat examination with a full bladder was obtained if a mass was found to be too large to be observed completely transvaginally. A score was assigned for the following ultrasound features suggestive of malignancy: the presence of a multilocular cystic lesion, solid areas, bilateral lesions, ascites, and intraabdominal metastases, scored as one point for each. A total ultrasound score (U) was thus calculated for each patient. Tumor size (S) was measured by ultrasound for each patient. Postmenopausal status was defined as more than 1 year of amenorrhea or age older than 50 years in women who had undergone hysterectomy. All other women were considered premenopausal. Serum samples were collected preoperatively and serum CA-125 levels were measured using Electrochemiluminescence Immunoassay (ECLIA) (Roche Elecsys E 170-1) in accordance with the manufacturer's instructions. Based on the data obtained, RMI 1, RMI 2, RMI 3, and RMI 4 were calculated for all patients together with the sensitivity, specificity, diagnostic accuracy and positive and negative predictive values of the four methods as follows:

1. \( \text{RMI 1 (Jacobs et al. 1990)} = U \times M \times |CA-125| \), where a total ultrasound score of 0 made \( U = 0 \), a score of 1 made \( U = 1 \), and a score of \( \geq 2 \) made \( U = 3 \); premenopausal status made \( M = 1 \) and postmenopausal \( M = 3 \). The serum level of CA-125 was applied directly to the calculation [18].
2. \( \text{RMI 2 (Tingulstad et al. 1996)} = U \times M \times |CA-125| \), where a total ultrasound score of 0 or 1 made \( U = 1 \), and a score of \( \geq 2 \) made \( U = 4 \); premenopausal status made \( M = 1 \) and postmenopausal \( M = 4 \). The serum level of CA-125 was applied directly to the calculation [19].
3. \( \text{RMI 3 (Tingulstad et al. 1999)} = U \times M \times |CA-125| \), where a total ultrasound score of 0 or 1 made \( U = 1 \), and a score of \( \geq 2 \) made \( U = 3 \); premenopausal status made \( M = 1 \) and postmenopausal \( M = 3 \). The serum level of CA-125 was applied directly to the calculation [20].
4. \( \text{RMI 4 (Yamamoto et al. 2009)} = U \times M \times S \) (size in centimeters) \( \times |CA-125| \), where a total ultrasound score of 0 or 1 made \( U = 1 \), and a score of \( \geq 2 \) made \( U = 4 \). Premenopausal status made \( M = 1 \) and postmenopausal status made \( M = 4 \). A tumor size (single greatest diameter) of \( < 7 \) cm made \( S = 1 \), and \( \geq 7 \) cm made \( S = 2 \). The serum level of CA-125 was applied directly to the calculation [24].

The histopathological diagnosis was considered as the gold standard for definite outcome. We did not include borderline tumors in our study. When a gynecological cancer was found, it was staged according to the International Federation of Gynecology and Obstetrics classification [21]. All statistical analyses were performed using the SPSS ver. 15.0 (SPSS Inc., Chicago, IL, USA). The \( \chi^2 \) test was used to test differences in distribution of age, menopausal status, and ultrasound score. The Mann-Whitney U-test was applied when testing differences in distribution of CA-125 among women with benign and malignant pelvic masses. The McNemar’s test was used when testing differences in performances between RMI 1, RMI 2, RMI 3, and RMI 4. The sensitivity was defined as the percentage of patients with malignant disease having a positive test result. The specificity was defined as the percentage with benign disease having a negative test result. The positive predictive value was defined as the percentage of patients with a positive test result having malignant disease and the negative predictive value was defined as the percentage of patients with a negative test result having benign disease.

**RESULTS**

As a result of the histological examination of the surgical specimens of 100 patients, 80 (80%) had benign and 20 (20%)...
had malignant disease (Table 1). The histopathological classification of all cases and the stage distribution of malignant ones are given in Table 1. The distribution of benign and malignant cases by age, menopausal status, tumor size and ultrasound score is described in Table 2. In univariate analysis a significant linear trend for malignancy was found by increasing ultrasound score and the occurrence of malignancy in the pre- and postmenopausal patients. Although the risk of malignancy was increasing by age, it did not reach the statistical significance (p=0.051).

The mean serum level of CA-125 was significantly higher among women with malignancy when compared with women with benign tumors (329.2310 U/mL vs. 28.0374 U/mL). The sensitivity, specificity, and positive and negative predictive values and diagnostic accuracy of serum CA-125 level of 35 U/mL, the ultrasound score of 2, postmenopausal status and the size of 7 centimeters are reported in Table 3. When individual parameters were compared in Table 3, CA-125 had better sensitivity than the ultrasound score, size and menopausal status, even though the others had higher specificity.

### Table 1. Histopathological classification and stage distribution of cases

| Histological diagnosis            | No. (%) |
|----------------------------------|---------|
| Ovarian cancer                   |         |
| Stage I                          | 12 (60) |
| Stage II                         | 2 (10)  |
| Stage III                        | 4 (20)  |
| Stage IV                         | 2 (10)  |
| Total malignant cases            | 20 (20) |
| Serous cystadenocarcinoma        | 8       |
| Mucinous cystadenocarcinoma      | 10      |
| Ovarian lymphoma                 | 1       |
| Krukenberg's tumor               | 1       |
| Total benign cases               | 80 (80) |
| Simple cyst                      | 5       |
| Endometriosis                    | 27      |
| Dermoid cyst                     | 14      |
| Serous cystadenoma               | 8       |
| Mucinous cystadenoma             | 7       |
| Fibroma                          | 3       |
| Tekoma                           | 2       |
| Corpus luteum                    | 4       |
| Paratubal cyst                   | 5       |
| Leiomyoma                        | 2       |
| Struma ovarii                    | 1       |
| Tuboovarian abscess              | 2       |

### Table 2. The distribution of benign and malignant cases by age, menopausal status, serum CA-125, tumor size and ultrasound score

| Variables                        | Benign | Malignant | Test/p-value |
|----------------------------------|--------|-----------|--------------|
| Age (yr)                         |        |           | x²/0.051     |
| <20                              | 6      | 1         |              |
| 21-40                            | 34     | 4         |              |
| 41-50                            | 28     | 5         |              |
| >50                              | 12     | 10        |              |
| Menopausal status                |        |           | x²/0.002     |
| Premenopausal                    | 64     | 9         |              |
| Postmenopausal                   | 16     | 11        |              |
| Ultrasound score                 |        |           | x²/<0.001    |
| 0                                | 50     | 3         |              |
| 1                                | 19     | 6         |              |
| 2-5                              | 11     | 11        |              |
| CA-125 (U/mL)                    |        |           | U test/<0.001|
| Mean                             | 28.0374| 329.2310  |
| Minimum                          | 3.14   | 12        |
| Maximum                          | 120    | 2,821     |
| Standard deviation               | 23.7557| 648.0259  |
| Size (cm)                        |        |           | x²/<0.002    |
| <7                               | 68     | 7         |              |
| ≥7                               | 12     | 13        |              |

### Table 3. The sensitivity, specificity, and positive (PPV) and negative (NPV) predictive values and diagnostic accuracy (DA) of serum CA-125, ultrasound score, postmenopausal status and tumor size

| Criteria          | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | DA (%) |
|-------------------|-----------------|-----------------|---------|---------|--------|
| CA-125 35 U/mL    | 75              | 75              | 92.3    | 42.9    | 75     |
| Ultrasound score  |                 |                 |         |         |        |
| ≥2                | 55              | 86.3            | 88.5    | 50      | 80     |
| Menopausal status |                 |                 |         |         |        |
| Postmenopausal    | 55              | 80              | 87.7    | 40.7    | 75     |
| Tumor size        |                 |                 |         |         |        |
| ≥7 cm             | 65              | 85              | 90.7    | 52      | 81     |
than CA-125, but with considerable loss of sensitivity which is important in suspecting a malignancy. The performance of RMI 1, RMI 2, RMI 3, and RMI 4 at different cutoff values is shown in Table 4. The overall best performance in RMI 1, RMI 2, and RMI 3 was obtained at a cutoff level of 200 and at 500 for RMI 4. Although, at a cutoff level of 200 for RMI 1, RMI 2, RMI 3, and at the level of 450 for RMI 4, RMI 4 looked like better than the others with its sensitivity, specificity and the diagnostic accuracy rates, direct comparison of the four indices revealed that there was no statistically significant difference in performance of the four methods (McNemar test, p=0.063). Receiver operating characteristic (ROC) analysis of the RMI 1, RMI 2, RMI 3, and RMI 4 showed that the values of area under the curve were significantly high with a value of 0.825, 0.806, 0.825, 0.856, respectively (p<0.001). Area under the curves values of menopausal status, serum CA-125, US features, and tumor size are 0.675, 0.750, 0.706, and 0.750, respectively. We think that risk of malignancy indices were more reliable in detecting malignancy in terms of area under the curves. The diagnostic performance of ultrasound score, CA-125, menopausal status, tumor size, RMI 1, RMI 2, RMI 3, and RMI 4 is shown in the receiver-operating characteristic curves (Fig. 1).

**DISCUSSION**

This study has revealed the usefulness of RMI to correctly discriminate benign from malignant pelvic masses. The RMI was

| Cutoff | Sensitivity | Specificity | PPV (%) | NPV (%) | DA (%) |
|--------|-------------|-------------|---------|---------|--------|
| RMI 1, 2, 3 | 85 | 90 | 85 | 72 | 85 | 35 | 42 | 44 | 51 | 94 | 96 | 96 | 95 | 64 | 73 | 75 | 81 |
| RMI 4 | 350 | 85 | 90 | 85 | 72 | 85 | 35 | 42 | 44 | 51 | 94 | 96 | 96 | 95 | 64 | 73 | 75 | 81 |
| 100 | 400 | 75 | 85 | 80 | 85 | 84 | 80 | 83 | 85 | 53 | 51 | 53 | 58 | 93 | 95 | 94 | 95 | 82 | 81 | 82 | 85 |
| 150 | 450 | 75 | 75 | 75 | 84 | 85 | 84 | 85 | 87 | 55 | 53 | 55 | 60 | 93 | 93 | 93 | 95 | 83 | 82 | 83 | 86 |
| 200 | 500 | 75 | 75 | 75 | 85 | 89 | 85 | 87 | 88 | 62 | 55 | 57 | 63 | 93 | 93 | 93 | 95 | 86 | 83 | 84 | 87 |
| 250 | 550 | 65 | 75 | 70 | 70 | 95 | 87 | 94 | 90 | 76 | 57 | 73 | 63 | 91 | 93 | 92 | 92 | 89 | 84 | 89 | 86 |
| 300 | 600 | 45 | 70 | 55 | 60 | 97 | 92 | 98 | 93 | 75 | 66 | 84 | 66 | 87 | 92 | 89 | 90 | 86 | 87 | 89 | 86 |
| 350 | 650 | 45 | 55 | 50 | 60 | 98 | 96 | 99 | 94 | 82 | 78 | 91 | 70 | 87 | 89 | 88 | 90 | 87 | 87 | 89 | 87 |
| 400 | 700 | 30 | 50 | 30 | 50 | 98 | 97 | 99 | 98 | 75 | 77 | 85 | 83 | 85 | 88 | 85 | 88 | 84 | 87 | 84 | 88 |

RMI, risk of malignancy index.

**Table 4.** Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values, and diagnostic accuracy (DA) for detecting malignancy at different cutoff levels of RMI 1, RMI 2, RMI 3, and RMI 4

**Fig. 1.** Receiver operator characteristic curve showing the performance of RMI 1, RMI 2, RMI 3, RMI 4, CA-125, tumor size, ultrasound score, and menopausal status. RMI, risk of malignancy index.
Risk of malignancy indices for detection of ovarian cancer

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The risk of malignancy index is a simple scoring system, appears to be very accurate, is useful in clinical practice, and should therefore be the test of choice in the preoperative evaluation of the adnexal mass. Any of the four malignancy risk indices (RMI 1, RMI 2, RMI 3, RMI 4) described can be used for selection of cases for optimal therapy. Since the specificity of risk of malignancy index is high, there is a potential role for this index in the selection of cases for conservative management or minimal invasive surgery of benign cases, like ultrasound guided aspiration or laparoscopic excision of other cysts.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.
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