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Original Article

Addition of parity to the risk of malignancy index score in evaluating adnexal masses

Ali Yavuzcan [a,*], Mete Çağlar [a], Emre Özgü [b], Yusuf Üstün [a], Serdar Dilbaz [a], Ismail Ozdemir [c], Tayfun Güngör [b], Selahattin Kumru [a]

[a] Department of Obstetrics and Gynaecology, Faculty of Medicine, Düzce University, Düzce, Turkey
[b] Department of Obstetrics and Gynaecology, Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara, Turkey
[c] Department of Obstetrics and Gynaecology, Medicana International Istanbul Hospital, Istanbul, Turkey

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ABSTRACT

Objective: The aim of our study was to evaluate the individual contribution of parity when incorporated as another parameter into the four risk of malignancy indices (RMI 1–4) to differentiate noninvasive benign lesions from invasive malignant ovarian lesions.

Materials and methods: After calculating RMI 1–4 for each patient included in this study, the resulting RMI scores were further multiplied by the parity score (*P*) of each patient to calculate the RMI parity (RMIP) score.

Results: A cutoff value of 300 for RMIP 1 yielded 95.0% specificity, 97.4% negative predictive value (NPV), 88.5% sensitivity, and 79.3% positive predictive value (PPV) and performed better than RMI 1 in the preoperative diagnosis of invasive malignant lesions. RMIP 2 with a cutoff value of 400 yielded 95.0% specificity, 97.4% NPV, 88.5% sensitivity, and 79.3% PPV, and it also performed better than RMI 2. A cutoff value of 400 for RMIP 3 provided 97.5% specificity, 97.5% NPV, 88.5% sensitivity, and 88.5% PPV and performed better than RMI 3. However, a cutoff value of 400 for RMIP 4 provided 90.0% specificity, 97.3% NPV, 88.5% sensitivity, and 65.7% PPV but did not perform better than RMI 4 in the preoperative diagnosis of invasive malignant lesions.

Conclusion: RMIP 1–3 scales were more reliable tools for the preoperative diagnosis of invasive adnexal masses compared with the traditional RMI 1–3 scales.

Introduction

Ovarian cancer (OC) ranks second among gynecological malignancies. Symptoms related to OC are typically nonspecific, and their association is often not recognized until the disease has reached an advanced stage. Recognizing OC at an early stage is very important [1], because the extent of disease at diagnosis is the primary determinant of survival [2]. Optimal debulking surgery performed in patients with OC is another significant prognostic factor [3], and accurate surgical staging of early-stage OC patients has great significance, permitting accurate estimation of the true extent of disease while detecting occult disease, and providing patients with appropriate information about prognosis and adjuvant treatment [4].

Ultrasonography (USG) and the measurement of serum cancer antigen-125 (CA-125) levels are commonly performed preoperatively to predict the histopathological nature of adnexal masses [5]. CA-125 levels >30 U/mL suggest a risk for malignancy [6], although patient age and menopausal status are also important factors in the preoperative evaluation of adnexal masses [7]. In 1990, Jacobs et al [6] introduced the Risk of Malignancy Index (RMI 1), which is based on serum CA-125 levels, menopausal status, and USG findings. Using the same parameters, Tingulstad et al [8,9] propounded RMI 2 and subsequently RMI 3. More recently, Yamamoto et al [10] suggested the use of RMI 4 for preoperative evaluation of malignant adnexal masses by incorporating the size of the adnexal mass on USG as a variable in the risk calculation.

The relationship between parity and epithelial ovarian cancer (EOC) has been demonstrated in numerous studies: the risk of OC decreases with increasing parity [11,12]. The birth of the first child,

* Corresponding author. Department of Obstetrics and Gynaecology, Faculty of Medicine, Düzce University, 81620 Konuralp, Düzce, Turkey.
E-mail address: draliyavuzcan@yahoo.com (A. Yavuzcan).

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in particular, reduces the risk of OC significantly, and the risk declines further with each full-term pregnancy [13]. However, Schüler et al [14] evaluated the relationship between OC and several reproductive factors, including parity, and their results were inconclusive. None of the indices that have been used previously to determine the malignancy risk of adnexal masses have evaluated the individual contribution of a healthy term pregnancy on the risk of malignancy [6,8–10].

The aim of our study was to evaluate the individual contribution of parity, when incorporated as another parameter into the four malignancy indices, in the differentiation of noninvasive benign lesions from invasive malignant ovarian lesions.

Materials and methods

This study included patients with a prediagnosis of an adnexal mass who underwent surgery in the Department of Obstetrics and Gynecology at Düzce University Faculty of Medicine (Düzce, Turkey) and in Ankara Zekai Tahir Burak Women's Health Education and Research Hospital (Ankara, Turkey) between November 2009 and May 2013. A total of 153 nonpregnant Caucasian women >18 years of age with no history of malignancy were evaluated. The data were retrieved retrospectively by reviewing the patients' medical charts. All patients provided written consent prior to the surgery. The patients were evaluated by USG 2 weeks before surgery and underwent an excision of the adnexal mass using surgical staging, performed in accordance with the guidelines of the International Federation of Gynecology and Obstetrics, if the diagnosis from the frozen section examination was malignant [15]. All benign lesions, tumors of borderline malignancy, and any other lesions that did not invade the epithelial basement membrane were classified as benign adnexal masses [16]. Invasive malignant neoplasms and metastatic masses were considered malignant adnexal mass. An invasive malignant mass was detected in 24 patients (15.8%), and noninvasive benign lesions were found in 129 patients (84.2%). The histopathological diagnoses of the adnexal masses are presented in Table 1.

Postmenopausal patients were defined as patients with an absence of menstrual flow for 1 year. The parity score was defined as the number of pregnancies that resulted in full-term births. CA-125 levels were determined using an electrochemiluminescence immunoassay and expressed in IU/mL. The upper limit of the normal range for the serum CA-125 level was set at 30 IU/mL.

Analysis of RMI

The RMI score was calculated by multiplying together the transvaginal USG results (U), menopausal status (M), and preoperative CA-125 levels (IU/mL). For this calculation, different coefficients were used for RMI 1, 2, and 3 [6,8,9]. For RMI 4, the calculation also included mass size (S) as one of the variables measured by transvaginal USG [10] (Table 2). The total USG scores (U) were determined based on the findings on transvaginal USG that were suspicious for malignancy. These findings included the appearance of multilocular cystic lesions, solid area, bilaterality, ascites, and presence of intra-abdominal metastasis.

Analysis of the RMI parity score

After calculating RMI 1–4 for each patient, the resultant RMI scores were further multiplied by the parity score (P) of the individual patient to calculate RMI parity (RMIP) 1–4. This P score was defined as 3 for nulliparous women, 2 for women with a parity of 1, and 1 for women with parity $\geq$2.

Statistical analysis

SPSS 21.0 was used for the statistical analyses (IBM Corp., Armonk, NY, USA). Means, standard deviations, minimum and maximum values, medians, proportions, and frequencies were used for the descriptive statistics. The level of impact was measured using receiver operating curve (ROC) analysis. Kappa (κ) analysis was used to assess agreement. A p value <0.05 was considered statistically significant.

Results

The mean age of the study participants was 46.05 ± 11.39 years, and 54 patients (35.3%) were postmenopausal. The mean parity of the patients was 2.46 ± 1.62, and the mean preoperative CA-125 level was 75.82 ± 112.53 IU/mL. The general characteristics of the patients are shown in Table 3.

We evaluated the power of RMIP 1–4 to differentiate noninvasive benign lesions from malignant invasive adnexal masses. RMIP 1 significantly differentiated invasive benign lesions from malignant adnexal masses [area under the curve (AUC) = 0.96; 95% confidence interval (CI), 0.92–1.00; $p = 0.000$). RMIP 2 successfully differentiated benign and malignant adnexal masses (AUC = 0.96; 95% CI, 0.91–1.00; $p = 0.000$). RMIP 3 showed a significant distribution for differentiation of benign from malignant lesions (AUC = 0.96; 95% CI, 0.91–1.00; $p = 0.000$). RMIP 4 was also found to be reliable for differentiating benign from malignant lesions (AUC = 0.97; 95% CI, 0.93–1.00; $p = 0.000$) (Graph).

Further analysis determined that the κ value for RMI 1 was 0.691 ($p = 0.000$). A cutoff value of 200 [6] for RMI 1 yielded 90.0% specificity, 97.3% negative predictive value (NPV), 88.5% sensitivity, and 65.7% positive predictive value (PPV) (Table 4). When evaluating an adnexal mass preoperatively based on RMIP 1, a cutoff value of 300 (if $\leq$300 was noninvasive and >300 invasive) provided good discrimination that correlated significantly with the histopathological results ($\kappa = 0.759$, $p = 0.000$). A cutoff value of 300 provided 95.0% interobserver agreement, yielding 95.0% specificity, 97.4% NPV, 88.5% sensitivity, and 79.3% PPV (Table 5). Our findings

Table 1
Histopathological diagnoses of adnexal masses.

Noninvasive benign lesions	n (%)	Invasive malignant lesions	n (%)
• Brenner tumor	1 (0.7%)	• Clear cell carcinoma	1 (0.7%)
• Borderline serous tumor	7 (4.9%)	• Endometrioid-type carcinoma	3 (2.0%)
• Borderline mucinous tumor	1 (0.7%)	• Malignant mesenchymal tumour	1 (0.7%)
• Corpus hemorrhagicum cyst	6 (3.9%)	• Malignant mucinous carcinoma	3 (2.0%)
• Corpus luteum cyst	3 (2.0%)	• Serous carcinoma	16 (10.4%)
• 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%)		

Table 2
Coefficients in RMI indexes.

Parameter	RMI 1 Jacobs et al [6]	RMI 2 Tingulstad et al [8]	RMI 3 Tingulstad et al [9]	RMI 4 Yamamoto et al [10]
USG score (*U*)				
No feature	0	1	1	1
1 feature	1	1	1	1
≥2 features	3	4	3	4
Menopausal score (*M*)				
Premenopausal state	1	1	1	1
Postmenopausal state	3	4	3	4
CA-125 (U/mL)	—	—	—	—
Size of mass (*S*)				
<7 cm	—	—	—	1
≥7 cm	—	—	—	2

CA-125 = cancer antigen-125; RMI = risk of malignancy index; USG = ultrasonography.

determined that RMIP 1 performed better than RMI 1 in the preoperative diagnosis of invasive malignant lesions.

The κ value for RMI 2 was 0.599 ($p = 0.000$). A cutoff value of 200 [8] yielded 85.0% specificity, 97.1% NPV, 88.5% sensitivity, and 56.1% PPV (Table 4). When evaluating an adnexal mass preoperatively based on RMIP 2, a cutoff value of 400 (if ≤400 was noninvasive and >400 invasive) provided good discrimination that correlated significantly with the histopathological results (κ = 0.799, $p = 0.000$). A cutoff value of 400 provided 93.8% interobserver agreement, yielding 95.0% specificity, 97.4% NPV, 88.5% sensitivity, and 79.3% PPV (Table 5). Our findings determined that RMIP 2 performed better than RMI 2.

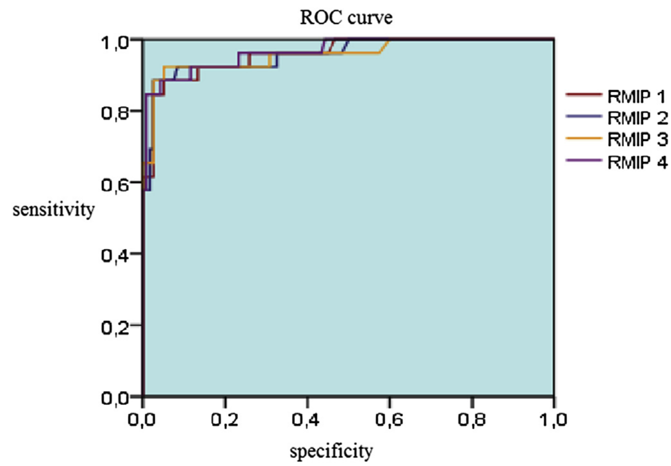
The κ value for RMI 3 was 0.643 ($p = 0.000$). A cutoff value of 200 [9] yielded 87.5% specificity, 97.2% NPV, 88.3% sensitivity, and 60.5% PPV (Table 4). In the preoperative evaluation of an adnexal mass based on RMIP 3, a cutoff value of 400 (if ≤400 was noninvasive and >400 invasive) provided good discrimination that correlated significantly with the histopathological results (κ = 0.860, $p = 0.000$). A cutoff value of 400 provided 95.9% interobserver agreement, yielding 97.5% specificity, 97.5% NPV, 88.5% sensitivity, and 88.5% PPV (Table 5). In our study, RMIP 3 showed a higher performance than RMI 3 in the preoperative diagnosis of invasive malignant lesions.

The κ value for RMI 4 was 0.761 ($p = 0.000$). A cutoff value of 450 [10] yielded 93.3% specificity, 97.4% NPV, 88.3% sensitivity, and 74.2% PPV (Table 4). In the preoperative evaluation of an adnexal mass based on RMIP 4, a cutoff value of 400 (if ≤400 was noninvasive and >400 was invasive) provided good discrimination that correlated significantly with the histopathological results (κ = 0.691, $p = 0.000$). A cutoff value of 400 provided 89.7% interobserver agreement, yielding 90.0% specificity, 97.3% NPV, 88.5% sensitivity, and 65.7% PPV (Table 5). Thus, RMI 4 was more reliable than RMIP 4.

Table 3
General features of the patients.

	n (%)	Mean ± SD
Age (y)	153 (100%)	46.05 ± 11.39
Menopause	54 (35.3%)	
Gravida	153 (100%)	2.99 ± 1.96
Parity	153 (100%)	2.46 ± 1.62
CA-125 (IU/mL)	153 (100%)	75.82 ± 112.53
Measured size on USG (mm)	153 (100%)	84.49 ± 39.20

CA-125 = cancer antigen-125; SD = standard deviation; USG = ultrasonography.



Graph. The power of RMIP 1–4 to differentiate noninvasive from invasive lesions. RMIP = risk of malignancy index parity.

Discussion

The RMI is used commonly in practice to differentiate benign from malignant adnexal masses. It is advantageous because it is a low-cost, objective, and readily applicable method. When the RMI was first introduced by Jacobs et al [6], they reported 85% sensitivity and 97% specificity using a cutoff value of 200 for RMI 1 [6]. In a study by Tingulstad et al [8], a cutoff value of 200 yielded 80% sensitivity, 92% specificity, and 83% PPV in the diagnosis of malignancy. Tingulstad et al [8] subsequently proposed RMI 3, which incorporated the USG score and menopause score into RMI 2, and reported 71% sensitivity and 92% specificity [9]. The most extensive modification in the traditional RMI 1–3 scales was made by Yamamoto et al [10], who proposed RMI 4, based on the assumption that the size of the adnexal masses could be associated with a higher risk of malignancy. A cutoff value of 450 for RMI 4 yielded 86.8% sensitivity, 91.0% specificity, 63.5% PPV, 97.5% NPV, and 90.4% accuracy in the preoperative diagnosis of malignant adnexal lesions [10]. Studies in subsequent years have also suggested that RMI 1–4 could be used reliably in the preoperative diagnosis of malignant adnexal masses [17,18]. This was supported by our study, which determined that RMI 1–4 was successful in differentiating benign from malignant invasive adnexal masses (Table 4).

After the progress made by Yamamoto et al [10], there have been no recent reports attempting to differentiate malignant adnexal lesions in the preoperative period more reliably and to improve the diagnostic efficiency of RMI. Instead, more complex and expensive tests have been introduced for the diagnosis of OC, such as human epididymis protein 4 (HE4) or the international ovarian tumor analysis (IOTA) logistic regression models [19]. In our study, we evaluated the influence of incorporating parity into RMI as a determinant of lifelong estrogen exposure and the total number of ovulations. Uninterrupted ovulation and excessive exposure to gonadotropin release are thought to play a major role in the development of OC [20]. Oral contraceptives inhibit ovulation, and a comprehensive report in 2013 determined that oral contraceptives were effective in the prevention of OC, but the duration of their use is the most important determinant of this [21]. Pregnancy reduces the risk of EOC by suspending ovulation and inhibiting the synthesis of gonadotropins, an effect similar to that of oral contraceptives. Moreover, because pregnancy raises estrogen and progesterone levels [14], the increased progesterone levels may prevent OC by inhibiting the proliferation of the ovarian epithelium, thereby accelerating cellular differentiation and promoting

Table 4
Evaluation of the reliability of RMI 1–4 in diagnosing malignant adnexal lesions.

		Benign ($n = 129$)	Malignant ($n = 24$)	Specificity (%)	NPV (%)	Sensitivity (%)	PPV (%)	Kappa	p
RMI 1	≤200	117	3	90.0	97.3	88.5	65.7	0.691	<0.001
	>200	12	21						
RMI 2	≤200	111	3	85.0	97.1	88.5	56.1	0.599	<0.001
	>200	18	21						
RMI 3	≤200	114	3	87.5	97.2	88.5	60.5	0.643	<0.001
	>200	15	21						
RMI 4	≤450	121	3	93.3	97.4	88.5	74.2	0.761	<0.001
	>450	8	21						

NPV = negative predictive value; PPV = positive predictive value; RMI = risk of malignancy index.

Table 5
Evaluation of the reliability of RMIP 1–4 in diagnosing invasive malignant adnexal lesions.

		Benign ($n = 129$)	Malignant ($n = 24$)	Specificity (%)	NPV (%)	Sensitivity (%)	PPV (%)	Kappa	p
RMIP 1	≤300	123	3	95.0	97.4	88.5	79.3	0.799	<0.001
	>300	6	21						
RMIP 2	≤400	123	3	95.0	97.4	88.5	79.3	0.799	<0.001
	>400	6	21						
RMIP 3	≤400	126	3	97.5	97.5	88.5	88.5	0.860	<0.001
	>400	3	21						
RMIP 4	≤400	115	3	90.0	97.3	88.5	65.7	0.691	<0.001
	>400	12	21						

NPV = negative predictive value; PPV = positive predictive value; RMIP = risk of malignancy index parity.

apoptosis [22,23]. Thus, as parity increases, the duration of uninterrupted ovulation decreases.

Parity is a strong protective factor, particularly against EOC, and the effect is further intensified by increasing the number of births [24]. Pasalich et al [25] showed a 60% lower risk of EOC in women with parity ≥3 as compared with women with parity <1. The risk of OC is reduced by 80% in women with parity >5 [26], and increasing parity also protects women against the development of borderline tumors [27].

Our results describing the efficacy of RMI 1–4 are in agreement with previous case-control studies [6,8–10]. We assumed that parity could influence the risk of malignancy in a given adnexal lesion and, in contrast to other studies, determined that RMIP 1, 2, and 3 performed well in differentiating invasive malignant lesions with cutoff values of 300, 400, and 400, respectively. The concordance between preoperative diagnosis and histopathological diagnosis was higher for RMIP 1–3 compared with RMI 1–3 in our population. In addition, the specificities of RMIP 1–3 in diagnosing invasive malignant ovarian lesions were higher than those of RMI 1–3, with higher PPV. Furthermore, RMIP 4 offered significant advantages over RMI 4.

The diagnostic performances of the RMIP 1–3 scales in our study were superior to those of the RMI 1–3 scales reported in previous studies [6,8–10,16,18]. Thus, the use of RMIP 1–3 scales may result in greater diagnostic accuracy for malignancy in OC patients. Likewise, we showed that the number of patients undergoing an inadvertent operation despite the presence of a benign adnexal mass would be lower using RMIP 1–3. RMIP 1 with a cutoff value of 300 showed similar efficiency as RMIP 2 with a cutoff value of 400. RMIP 3 with a cutoff value of 400 offered the highest performance in differentiating benign from malignant adnexal masses in our study. Yamamoto et al [10] claimed that RMI 4 was more reliable than RMI 1–3, and that RMI 4 at a cutoff level of 450 yielded a sensitivity of 86.8%, specificity of 91.0%, and PPV of 63.5%. In our study, RMIP 3 at a cutoff level of 400 showed a sensitivity of 88.5%, specificity of 97.5%, and PPV of 88.5%.

The RMIP 1–3 scales are more reliable tools in the preoperative diagnosis of invasive adnexal masses compared with the traditional RMI 1–3 scales. The traditional RMI 4 scale was thought to be the most accurate index; however, our study demonstrated that RMIP 3 is more accurate in differentiating benign from malignant invasive adnexal masses, compared with the RMI 4 scale. Comprehensive studies performed in different populations are warranted to determine the use of these new indices as reliable alternatives to the traditional four malignancy risk indices.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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