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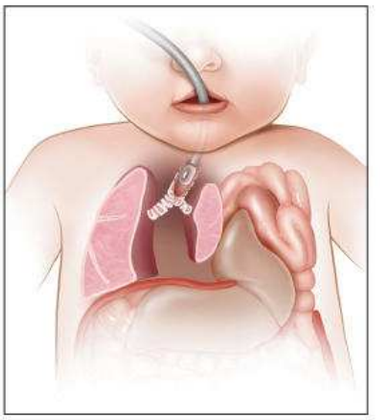

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Performance of the Risk of Malignancy Index for Discriminating Malignant Tumors in Women With Adnexal Masses

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Objectives—We examined the performance of 4 risk of malignancy index (RMI) variants in a medium-resource gynecologic cancer center.

Methods—A total of 158 women referred for adnexal masses were evaluated before surgery by the 4 RMI variants. Physicians with varied experience in ultrasound assessment of adnexal masses performed ultrasound examinations. We compared the performance of the 4 RMI variants using receiver operating characteristic curve analyses followed by calculation of sensitivity, specificity, and positive and negative likelihood ratios using the pathologic diagnosis of the masses as the reference standard.

Results—Among the 158 women with adnexal masses included in this study, 51 (32%) had malignant tumors; 26 (51%) of them were stage I. All RMI variants performed similarly (accuracy range, 74%–83%), regardless of menopausal status. Considering all women included, the positive likelihood ratios of the 4 RMI variants ranged from 3.52 to 4.41. In subset analyses, all RMI variants had decreased sensitivity for stage I malignant tumors and for those of nonepithelial histologic types.

Conclusions—The 4 RMI variants performed acceptably in a medium-resource setting where ultrasound examiners were physicians with varied experience. This finding indicates a good tradeoff between performance and feasibility, since ultrasound RMI protocols are of low complexity.

Key Words—cancer antigen 125; diagnosis; gynecologic ultrasound; malignancy; ovarian tumor

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Abbreviations

AUC, area under the curve; CA-125, cancer antigen 125; CI, confidence interval; IOTA, International Ovarian Tumor Analysis; RMI, risk of malignancy index; ROC, receiver operating characteristic

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There is no current strategy for ovarian cancer ultrasound screening in the general population,[1] although ultrasound imaging is a widely available examination, and with it, approximately 2.7% to 8% of women will have diagnosis of an adnexal mass at some point in their lives.[2–4] As a result, 1 in 10 women are still undergoing surgery for an adnexal mass, and devising strategies for better selecting women who will benefit from a surgical approach, which must be relatively inexpensive and simple enough to promote widespread acceptance by the medical community, is necessary.[5] This problem is especially true in medium-income countries such as Brazil, where the demographics are now close to those of developed countries, but human and economic resources are still scarce. Approximately 5680 ovarian cancers are expected in Brazil in 2014, with an estimated risk of 6 cases per 100,000 women.[6] In excess of 3000 deaths due to the disease were recorded in Brazil during 2012.[6]

In the last 30 years, several models, including tumor markers and ultrasound descriptors and scores, have been devised for better characterizing adnexal masses (ie, discriminating clinically relevant adnexal tumors from most benign masses). All of these prediction models are currently undergoing testing as potential tools for discerning the 20% to 35% of adnexal masses that are malignant ovarian tumors.[7–9]

Since 1990, several mathematical models and scoring systems have been developed to be used for discrimination between benign and malignant adnexal masses.[9–13] Encouraging results were obtained with the risk of malignancy index (RMI), which was first developed in 1990 and received subsequent adjustments during the last 20 years,[7,10–12,14–16] and with a variety of models developed and/or tested by the International Ovarian Tumor Analysis (IOTA) group, notably the simple rules, subjective assessment, and the logistic regression model.[9,17] Studies by the IOTA group suggested that subjective assessment, logistic regression, and the simple rules may perform better than the RMI[9,18] in premenopausal women. In a previous study based on the IOTA results,[19] we tested the simple rules in 103 women and obtained sensitivity of 90%, specificity of 87%, a positive predictive value of 69%, and a negative predictive value of 97%.[20] However, 17.3% of the women had adnexal tumors that were not classifiable by the simple rules, which prompted the need for an examiner experienced in the ultrasound evaluation of adnexal masses: a professional not widely available in our country. On the other hand, the RMI is a scoring system that is derived from a formula that combines menopausal status with serum cancer antigen 125 (CA-125) values and ultrasound variables of low complexity.[7,10–12,14,21,22] Because the ultrasound variables used in the RMI are simpler than those used in IOTA models, and because the RMI includes easily obtainable laboratory data (CA-125 levels), it is sensible to infer that these models are well suited for medium-income settings.

In this study, we examined whether the outstanding results obtained and reported by RMI creators are reproducible in a different set of premenopausal and postmenopausal Brazilian women with adnexal masses who underwent surgical interventions for these masses. We also examined the factors associated with RMI failure in diagnosing malignant tumors and at ruling out malignancy, such as the tumor histologic type and stage.

Materials and Methods

Patient Selection

We conducted an analysis of prospectively collected data on 158 nonconsecutive women who underwent surgery for an adnexal mass. The women had been referred to the gynecologic oncology clinics of the State University of Campinas for adnexal masses detected by an ultrasound or clinical examination from January 2010 through January 2014.

After the initial interview, including an explanation of the study's research methods and purpose, all women gave written informed consent to participate. An ultrasound evaluation was scheduled, and peripheral blood was collected for serum CA-125 measurements. When indicated, women were informed that surgery had to be performed to treat their adnexal masses. Patients underwent surgical intervention, and the pathologic specimens were sent for histopathologic analysis. The study was approved by the faculty's Research Ethics Committee (number 008/2010).

Ultrasound Examinations

Ultrasound evaluations were performed in the Ultrasound Technical Section of the State University of Campinas, using one of the ultrasound machines available in the section: Accuvix V10 (Medison Corporation, Ltd, Seoul, Korea), Nemio XG (Toshiba Corporation, Tokyo, Japan), and Voluson Expert 730 (GE Healthcare, Milwaukee, WI), all equipped with convex transvaginal broadband high-resolution multifrequency transducers and all with amplitude spectral Doppler capability.

In Brazil, there are no sonographers. Performance and interpretation of ultrasound examinations are considered medical procedures. In our study, all examinations were performed by obstetrician-gynecologists who had between 2 and 12 years of experience in performing and interpreting gynecologic ultrasound examinations at a referential center. These examiners were previously enrolled in at least a 1-year ultrasound training course. The training course offered a theoretical program, which included 2 hours of lectures and 2 hours of paper discussions per week, and a practical program, which consisted of an average of 100 supervised hands-on pelvic, breast, and obstetric ultrasound examinations per trainee per week. The trainees were systematically evaluated by seniors in practical skills, and there was a final theoretical examination each year. The same physician performed and evaluated the ultrasound examination for each case. The ultrasound scores were evaluated by that physician prospectively.

The ultrasound evaluation was performed with the woman in a supine position. Initially we used a transabdominal approach, with the woman's bladder full; she was then asked to empty her bladder, and we performed a supplementary transvaginal examination. Adnexal masses were described according to origin (ovarian, extraovarian, or

indefinite), position (right, left, or bilateral), number of lesions, type of lesion (unilocular, unilocular-solid, multilocular, multilocular-solid, or solid), size in 3 dimensions (longitudinal, anteroposterior, and transverse diameters), volume (calculated electronically by the ultrasound device), presence and size of the largest solid component (3 diameters), presence and measurement of fluid volume in the posterior cul-de-sac, and presence and location of lesions suggestive of metastases. The adnexal masses were always assessed with color Doppler imaging, which was given a subjective qualitative classification (score of 1, no blood flow; 2, minimal blood flow; 3, moderate blood flow; or 4, marked blood flow) and was contained in the ultrasound report. Doppler parameters were assessed, as we routinely do, but as they were not included in the calculation of the RMI, they were not used for the analysis.

Patients presenting with at least 1 adnexal mass were eligible for inclusion in the study, and when there was more than 1 mass, the mass with the most complex morphologic characteristics or, in cases of similar morphologic characteristics, the largest one was considered for statistical analysis, as suggested by Sayasneh et al.[23] More than 1 adnexal mass was detected in 20 women.

Risk of Malignancy Index Variants

The RMI is a scoring system that is derived from a formula that combines menopausal status with serum CA-125 values and ultrasound variables. An ultrasound score is assigned for the following features suggestive of malignancy: presence of a multilocular cystic lesion, solid areas, a bilateral lesion, ascites, and intra-abdominal metastasis. The presence of each of the previous parameters adds 1 point to the ultrasound score. Based on the data obtained, 4 variants of the RMI (RMI1–4) were calculated for premenopausal and postmenopausal women according to the original criteria and those of Yamamoto et al[14] and Aktürk et al.[15] In brief, all RMI variants are based on multiplication of an ultrasound score by an arbitrary value given to menopausal status by the CA-125 level. For RMI4, tumor size is added. Table 1 shows the parameters used for the calculations of each RMI variant: RMI1 (Jacobs et al[10]), RMI2 (Tingulstad et al[11]), RMI3 (Tingulstad et al[12]), and RMI4 (Yamamoto et al[14] and Aktürk et al[15]).

Cancer Antigen 125 Measurement

An automated CA125 analysis was performed by electrochemiluminescence using the Cobas e411 test (Roche Diagnostics GmbH, Mannheim, Germany) according to the manufacturer's instructions and using its reagents and equipment. Values were expressed in units per milliliter. Postmenopausal status was defined as more than 1 year of amenorrhea or age older than 50 years in women who had undergone hysterectomy.

Surgery and Pathologic Analysis

Surgery for diagnosis, treatment, or both was performed at our institution, and the techniques and surgical procedures were chosen and performed according to medical indications. The mean time elapsed between the ultrasound examination and surgery was 73 days, ranging from 24 hours or less for emergency procedures to a maximum of 119 days. Patients who had lesions that were more likely to be benign but with indications for surgical treatment waited for nonpriority surgeries. Patients who had lesions with moderate and high risks of malignancy underwent surgery earlier. The reference standard was the histopathologic diagnosis of surgical specimens, all performed in the Department of Pathologic Anatomy of the State University of Campinas School of Medicine, following the guidelines of the World Health Organization's International Classification of Ovarian Tumors.[24] For statistical purposes, borderline tumors were classified as malignant. Malignant ovarian tumors were staged according to the 2014 International Federation of Gynecology and Obstetrics staging system.[25]

Table 1. Risk of Malignancy Index Variants

Variant	Ultrasound Score (U)[a]	Menopausal Score (M)	Tumor Size (S), mm (Single Greatest Diameter)
RMI1 (U × M × CA-125) Jacobs et al[10]	U = 0 (0 parameter) U = 1 (1 parameter) U = 2 (≥2 parameters)	M = 1 (premenopausal) M = 3 (postmenopausal)	Not applicable
RMI2 (U × M × CA-125) Tingulstad et al[11]	U = 1 (0 or 1 parameter) U = 2 (≥2 parameters)	M = 1 (pre-menopausal) M = 4 (postmenopausal)	Not applicable
RMI3 (U × M × CA-125) Tingulstad et al[12]	U = 1 (0 or 1 parameter) U = 3 (≥2 parameters)	M = 1 (premenopausal) M = 3 (postmenopausal)	Not applicable
RMI4 (U × M × S × CA-125) Yamamoto et al[14] Aktürk et al[15]	U = 1 (0 or 1 parameter) U = 4 (≥2 parameters)	M = 1 (premenopausal) M = 4 (postmenopausal)	S = 1 (<70) S = 2 (≥70)

[a]Parameters: presence of a multilocular cystic lesion, solid areas, a bilateral lesion, ascites, and intra-abdominal metastasis.

Statistical Analyses

All statistical calculations were performed in the R environment[26] for data analyses. Ninety-five percent confidence intervals (CIs) were used throughout, and a $P < .05$ was considered significant. We first compared the proportions of the main clinical and pathologic features according to the pathologic status (malignant versus benign) of their tumors using a χ^2 test for categorical data and the Kruskal-Wallis test for continuous data. Next, we calculated the performance of the RMI variants for detection of malignant tumors using standard receiver operating characteristic (ROC) curves. We then compared the areas under the curves (AUCs) for the RMI variants in a pair-wise manner using the Venkatraman projection-permutation test. Next, we calculated performance indicators (sensitivity, specificity, and positive and negative likelihood ratios) using the cutoff values determined by ROC analyses. Then we recalculated the performance indicators at recommended cutoff points (200 for RMI1–3 and 450 for RMI4).[14,15]

Results

Table 2 lists the key clinical and pathologic characteristics of the women. The prevalence of malignant tumors was 32%. Patients with malignant tumors were significantly older than their counterparts with benign adnexal masses. Most (77%) malignant tumors were epithelial, although 7 of 51 (13%) originated in the stroma. Approximately half of the malignant primary ovarian tumors were stage I. Endometriomas were the most frequent (43%) nonneoplasic adnexal masses. Women with malignant tumors had significantly higher CA-125 levels, ultrasound scores, and tumors larger than 7 cm in diameter than women with benign masses.

In Table 3, we compare the performance of the RMI variants using the optimal cutoff points as determined by ROC analyses. In the general population (premenopausal and postmenopausal women), RMI variants yielded similar performance indicators. In the subset of premenopausal women, the best sensitivity was obtained with RMI2 (90%; 95% CI, 83%–97%) and RMI4 (89%; 95% CI, 81%–97%). Specificity for the RMI variants did not differ significantly. Similar performance was obtained for the RMI variants in premenopausal and postmenopausal women. The 4 RMI variants had similar positive likelihood ratios, ranging from 2.92 to 5.68.

Table 4 shows the performance indicators of RMI variants at progressive cutoff points in the general (premenopausal and postmenopausal) population. The standard (literature-recommended) cutoff point for RMI1–3 is 200, and for RMI4, it is 450. At these recommended cutoff points, the sensitivity of the different RMI variants ranged from 68% to 78%, and the specificity ranged from 82% to 87%. At these recommended cutoff points, the positive likelihood ratio was approximately 4.0 for all RMI variants.

Table 5 shows how RMI variants classified benign, borderline, and malignant ovarian tumors at recommended cutoff points. Values above reference points corresponded to false-positive results for benign tumors and true-positive results for borderline and malignant tumors. The worst correspondence between RMI values and final pathologic diagnoses was obtained for borderline tumors,

Table 2. Key Clinical Features of Women With Benign and Malignant Ovarian Tumors

Characteristic	Benign [n (%): 107 (67.8)]	Malignant [n (%): 51 (32.2)]	*P*
Mean age (SD), y	45.9 (15.0)	55.7 (16.2)	<.001
Menopausal status, n (%)			
Premenopausal	65 (61)	20 (40)	.01
Postmenopausal	42 (39)	31 (60)	
Familial ovarian or breast carcinoma, n (%)			
No	90 (84)	43 (84)	>.99
Yes	9 (9)	5 (10)	
Unknown	8 (7)	3 (6)	
Histologic type, n (%)			
Epitheliala	37 (35)	39 (77)	
Stromal	17 (16)	7 (13)	
Germ cell tumor	21 (20)	1 (2)	
Metastasis	0	3 (6)	
Extraovarian	2 (2)	1 (2)	
Other	2 (2)	0	
Non-neoplastic, n (%)			
Endometriomas	12 (43)	0	
Functional cyst	5 (18)	0	
Other	11 (39)	0	
Disease stage, n (%)[b]			
I	0	26 (51)	
II	0	5 (10)	
III	0	12 (23)	
IV	0	2 (4)	
Metastasis and extraovarian		4 (8)	
Mean CA-125 (SD), U/mL	63 (168)	919 (2538)	<.01
<35, n (%)	78 (73)	13 (25)	<.01
≥35, n (%)	29 (27)	38 (75)	
Ultrasound score, n (%)			
0–1	83 (78)	18 (35)	<.01
≥2	24 (22)	33 (65)	
Tumor size, n (%)			
<7 cm	38 (36)	10 (20)	<.01
≥7 cm	69 (64)	41 (80)	

[a]Among epithelial malignant tumors, there are 8 borderline tumors.
[b]Metastasis and extraovarian tumors were not staged.

which were incorrectly classified in 50% of the cases when using RMI1 and RMI3 and 37% of cases when using RMI2 and RMI4. Similar proportions of correctly and incorrectly classified benign and malignant tumors were obtained with the 4 RMI variants.

Table 6 shows how the RMI variants classified nonepithelial and epithelial malignant tumors. Clearly, the RMI classified epithelial tumors much better than nonepithelial tumors.

Table 7 shows diagnostic failures (false-positive and -negative results) of the RMI variants at recommended cutoff points, according to tumor histologic types. RMI1 and 3 and RMI2 and 4 showed very similar false-positive and -negative results. The false-negative rate was higher for stromal tumors: 5 of 7 granulosa cell tumors were incorrectly classified as benign by the 4 RMI variants. As shown in Table 4, borderline tumors were also incorrectly classified as benign in 37% to 50% of the cases depending on the RMI variant used.

Table 8 shows that false-negative rates for the RMI variants were higher in women with stage I tumors compared to women with more advanced stages (significant *P* values for all variants). RMI1 and RMI3 incorrectly classified most stage I tumors as benign; RMI2 was the variant that best classified stage I tumors. It is worth noting that all 7 granulosa cell tumors were stage I.

In Figure 1, we show an ROC curve analysis of RMI variants for discrimination of women with malignant tumors from those with benign tumors. All pair-wise comparisons between the curves returned nonsignificant results.

Discussion

Our study confirms that the RMI is a valuable tool in medium-resource settings such as the typical Brazilian health care system. In this sample of women with adnexal masses, all RMI variants performed similarly (accuracy range, 74%–83%), regardless of menopausal status. At the standard cutoff points, the sensitivity and specificity of all RMI variants were good, with positive likelihood ratios in excess of 4.0 for all variants. It is important to note, however, that RMI variants had decreased sensitivity for stage I malignant tumors and in women with nonepithelial tumors.

Table 3. Performance of RMI Variants in Premenopausal and Postmenopausal Women at Cutoff Points Determined by ROC Analyses

Group	Index	AUC	Cutoff	Sensitivity, %	Specificity, %	Accuracy, %	LR+	LR–
All women	RMI1	0.85 (0.78–0.91)	93.9	82 (75–90)	77 (67–88)	79	3.67	0.22
	RMI2	0.85 (0.78–0.91)	195.7	78 (71–86)	82 (72–92)	81	4.41	0.26
	RMI3	0.85 (0.78–0.91)	93.9	82 (75–90)	77 (65–86)	78	3.52	0.23
	RMI4	0.85 (0.77–0.92)	250.4	83 (76–90)	81 (69–90)	81	4.29	0.21
Premenopausal	RMI1	0.84 (0.78–0.91)	93.9	70 (59–81)	88 (74–100)	83	5.68	0.34
	RMI2	0.85 (0.74–0.96)	50.8	90 (83–97)	69 (59–84)	74	2.92	0.14
	RMI3	0.84 (0.73–0.95)	93.9	70 (59–81)	89 (76–100)	76	3.46	0.32
	RMI4	0.86 (0.72–0.98)	101.8	89 (81–97)	78 (63–93)	78	4.19	0.32
Postmenopausal	RMI1	0.81 (0.72–0.91)	238.5	74 (61–87)	78 (64–93)	77	3.46	0.32
	RMI2	0.81 (0.71–0.91)	424.0	71 (57–85)	81 (67–95)	77	3.72	0.36
	RMI3	0.81 (0.71–0.91)	238.5	74 (61–87)	79 (64–93)	76	3.46	0.32
	RMI4	0.79 (0.68–0.90)	848.0	73 (60–87)	82 (69–96)	78	4.19	0.32

Values in parentheses are 95% CIs. LR indicates likelihood ratio.

Table 4. Performance of RMI Variants at Progressing Cutoff Points for the Detection of Malignant Ovarian Tumors

Cutoff		Sensitivity, %				Specificity, %				Positive Likelihood Ratio				Negative Likelihood Ratio			
RMI1–3	RMI4	RMI1	RMI2	RMI3	RMI4	RMI1	RMI2	RMI3	RMI4	RMI1	RMI2	RMI3	RMI4	RMI1	RMI2	RMI3	RMI4
50	300	86	96	88	79	60	52	57	81	2.14	2.01	2.05	4.29	0.22	0.07	0.21	0.25
100	350	78	82	78	77	78	73	77	81	3.64	3.03	3.49	4.17	0.27	0.24	0.27	0.28
150	400	74	78	74	77	84	80	83	82	4.68	3.99	4.42	4.41	0.30	0.27	0.31	0.28
200[a]	450[a]	68	78	69	75	87	82	87	82	5.24	4.41	5.24	4.29	0.36	0.26	0.36	0.30
250	500	67	74	67	73	89	83	89	83	5.94	4.42	5.94	4.41	0.37	0.31	0.37	0.32
300	550	63	69	63	71	89	85	89	85	5.59	4.58	5.59	4.86	0.42	0.37	0.41	0.34
350	600	63	67	63	71	90	85	90	85	6.10	4.45	6.10	4.86	0.41	0.39	0.41	0.34
400	650	61	65	61	71	91	88	91	85	7.22	5.32	7.22	4.86	0.43	0.40	0.43	0.34

[a]Standard (literature-recommended) cutoff points for premenopausal and postmenopausal women with adnexal masses.

In our study, the AUC observed for RMI1–4 was 0.85, albeit the RMI4 AUC was slightly higher than that of RMI2. Van den Akker et al[27] compared RMI3 and RMI4, and both proved to be capable of discriminating benign and malignant adnexal lesions with similar performance, both with an AUC of 0.86. In the same year, Aktürk et al[15] repeated the performance evaluation of the RMI but found no significant differences between the 4 different indices. It is worth noting that our ROC analysis showed that optimal cutoff points for premenopausal women were substantially lower than those established for the general population. At the standard cutoff levels, our results closely reproduced, in a population with a diverse epidemiologic background, those described by Geomini et al[7] in a systematic review evaluating the accuracy of risk scores, in which 200 was used as the cutoff level. In that analysis, the pooled estimates were 78% and 87% for sensitivity and specificity, respectively.

Better triaging tools and protocols can assist in the referral process for women with adnexal masses to health care facilities with the necessary capabilities and avoid potential surgical failures and unnecessary overloading of oncology centers with women who have benign conditions.[28] We detected only minimal performance variability between the 4 RMI variants in this analysis on a relatively homogeneous set of women with adnexal masses who were treated at a single institution and thus subjected to similar treatment protocols. RMI4 was slightly superior to RMI2, but only by a very nonsignificant small margin. These findings are in accordance with those of Yamamoto et al,[14] who demonstrated that RMI4 was better than RMI1–3 using cutoff values of 450 for RMI4 and 200 for the other variants. They observed that the sensitivity, specificity, positive predictive value, and negative predictive value of RMI4 were 86%, 91%, 63%, and 97.5%, respectively. We obtained sensitivity of 83%, specificity of 81%, a positive predictive value of 84%, and a negative predictive value of 60% using RMI4. Figures 2 and 3 show ultrasound images of cases with true-positive and true-negative RMI results, respectively.

In our study, of the 51 malignant tumors, 31 were of epithelial origin, 8 were borderline ovarian tumors, and 8 were germ cell or stromal tumors. Meray at al[29] demonstrated that RMI1 is not adequate for detection of malignancy in a population with a high prevalence of borderline or nonepithelial tumors. In a population with 30% nonepithelial tumors, the sensitivity, specificity, and positive and negative predictive values were 60%, 88%, 57.1%, and 89.9%, respectively. When these nonepithelial tumors were excluded from the performance analyses, these indicators changed to 76.9%, 88.7%, 52.6%, and 95.9%.

Table 5. Proportions of Benign, Borderline, and Malignant Tumors at Recommended Cutoff Points for RMI Variants

RMI Variant	Stratum	Total	Pathologic Status, n (%)		
			Benign (n = 107)	Borderline (n = 8)	Malignant (n = 43)
RMI1	< 200	109	93 (87)	4 (50)	12 (28)
	≥200	49	14 (13)	4 (50)	31 (72)
RMI2	< 200	99	88 (82)	3 (37)	8 (19)
	≥200	59	19 (18)	5 (63)	35 (81)
RMI3	< 200	109	93 (87)	4 (50)	12 (28)
	≥200	49	14 (13)	4 (50)	31 (72)
RMI4	< 450	101	88 (82)	3 (37)	10 (23)
	≥450	57	19 (18)	5 (63)	33 (77)

Table 6. Proportions of Nonepithelial and Epithelial Ovarian Malignant Tumors at Recommended Cutoff Points for RMI Variants

RMI Variant	Stratum	Total	Primary Ovarian Malignancy, n (%)		
			Nonepithelial	Epithelial	*P*
RMI1	< 200	16	5 (63)	10 (27)	.132
	≥200	32	3 (37)	29 (73)	
RMI2	< 200	11	5 (63)	6 (15)	.014
	≥200	37	3 (37)	34 (85)	
RMI3	< 200	16	5 (63)	11 (27)	.132
	≥200	32	3 (37)	29 (73)	
RMI4	< 450	12	5 (63)	8 (20)	.04
	≥450	33	3 (37)	32 (80)	

With standard cutoff points, the sensitivity of all RMI variants may be severely compromised in premenopausal women with stage I disease, stromal tumors, or even both. Van Gorp et al[30] obtained 76% sensitivity and 92.4% specificity in the general population, but sensitivity decreased to 64.1% in premenopausal women. Similar findings were reported by authors using IOTA models in a study that included 18 specialized centers in 6 different countries[9]: the sensitivity in the general population was 67.1% (95% CI, 61.4%–72.4%), and the specificity was 90.6% (95% CI, 76.7%–79.7%); however, in the subset of premenopausal women, the sensitivity decreased to 53% (95% CI, 46%–61%).

In our study, in most false-negative cases of epithelial, stage I, and stromal tumors, we found suspected ultrasound morphologic features, but CA-125 levels were low. Subjective assessment without the influence of CA-125 would perform better in these cases. Figure 4 shows an example of a false-negative result in a stage I cystadenocarcinoma.

False-positive results were frequently associated with the presence of ascites and elevated CA-125 levels in some benign tumors.[31] Fibromas associated with ascites are

Table 7. Diagnostic Errors of RMI Variants at Recommended Cutoff Points

Error	RMI1, 200	RMI2, 200	RMI3, 200	RMI4, 450
False-positive				
Fibroma	5	6	5	6
Brenner tumor	0	1	0	1
Endometrioma	3	4	3	4
Mucinous cystadenoma	2	3	2	3
Serous cystadenoma	3	4	3	4
Teratoma	1	1	1	1
Total	14	19	14	19
False-negative				
Granulosa cell tumor	5	5	5	5
Borderline serous	1	1	1	1
Borderline mucinous	3	2	3	2
Serous adenocarcinoma	3	1	3	3
Endometrioid adenocarcinoma	1	1	1	1
Mucinous adenocarcinoma	3	1	3	1
Total	16	11	16	13

Table 8. Stage Distribution of Malignant Primary Ovarian Tumors at Recommended Cutoff Points for RMI Variants

RMI Variant	Stratum	Total	Stage, n (%)		
			I	II–IV	*P*
RMI1	<200	16	14 (54)	2 (10)	
	≥200	31	12 (46)	19 (90)	<.01
RMI2	<200	11	10 (38)	1 (5)	
	≥200	36	16 (62)	20 (95)	.02
RMI3	<200	16	14 (54)	2 (10)	
	≥200	31	12 (46)	19 (90)	<.01
RMI4	<450	13	12 (46)	1 (5)	
	≥450	34	14 (54)	20 (95)	<.01

Figure 1. Receiver operating characteristic curve analysis of RMI variants for discrimination of women with malignant tumors. A pair-wise comparison of the AUC for each variant was performed with the Venkatraman projection-permutation test. RMI4 was marginally superior to RMI2 ($P = .06$). Area under the curve values are shown in Table 2.

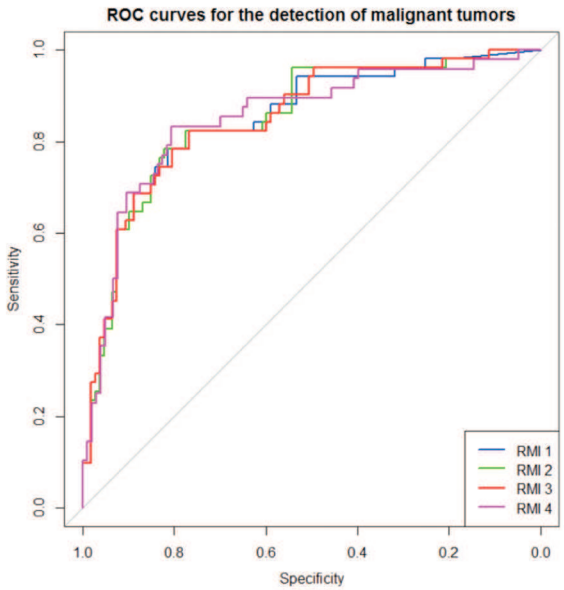
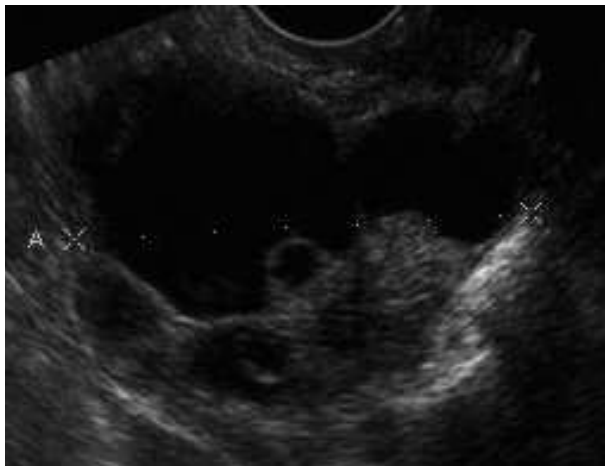


Figure 2. Illustrative case of a true-positive result according to all RMI variants. The patient was premenopausal. Ultrasound showed a multilocular-solid mass. The CA-125 value was 270.6 U/mL. Pathologic analysis confirmed a serous cystadenocarcinoma (stage IIIc).



examples of false-positive results, as illustrated in Figure 5. Another problem related to the RMI is that the score does not include Doppler parameters, which are currently almost mandatory in the evaluation of adnexal mass risk.

Our study was flawed by not discriminating the physicians who performed the study examinations according to their levels of expertise. A relatively small sample size and an unequal distribution of masses between 8 examiners did not allow us to get reliable results when studying them separately. On the other hand, this study was a single-institution trial with a relatively high percentage of stage I malignant tumors. As mentioned above, this particular group of patients poses a challenge to triaging methods, and our study corroborates the idea that the RMI may be not as good at diagnosing early-stage disease and nonepithelial ovarian tumors as originally thought. Our conclusions are weakened by the small sample size of nonepithelial tumors. For RMI purposes, an ultrasound score is assigned by considering the following features suggestive of malignancy: the presence of a multilocular cystic lesion, solid areas, a bilateral lesion, ascites, and intra-abdominal metastasis. Sharma et al[32] investigated 48,053 asymptomatic women who underwent ultrasound examinations, 4367 (9.1%; 95% CI, 8.8%–9.3%) of whom had abnormal adnexal morphologic characteristics. The strongest association between ovarian morphologic characteristics and epithelial ovarian cancer was the presence of "solid" elements. The relative risk of epithelial ovarian cancer within 3 years of the scan in women with solid elements compared to those with unilocular or multilocular cysts was increased 11.5-fold (95% CI, 5.9–22.5-fold).

The relative simplicity of the ultrasound parameters used to render the RMI is a strong advantage. Importantly, the RMI includes CA-125 levels in its formulas, and CA-125 determination is a standardized, easily reproducible, and relatively inexpensive procedure available even in low-resource settings. These features obviate the need for highly specialized examiners experienced in ultrasound evaluations of adnexal masses. The RMI still misses early-stage and borderline tumors, as well as nonepithelial neoplasms.

In conclusion, discriminating women with ovarian malignancies among those with adnexal masses may be difficult in medium-resource settings because of limitations

Figure 3. Illustrative case of a true-negative result according to all RMI variants. The patient was premenopausal. Ultrasound showed a multilocular cyst. The CA-125 value was 11.9 U/mL. Pathologic analysis confirmed a serous cystadenoma.

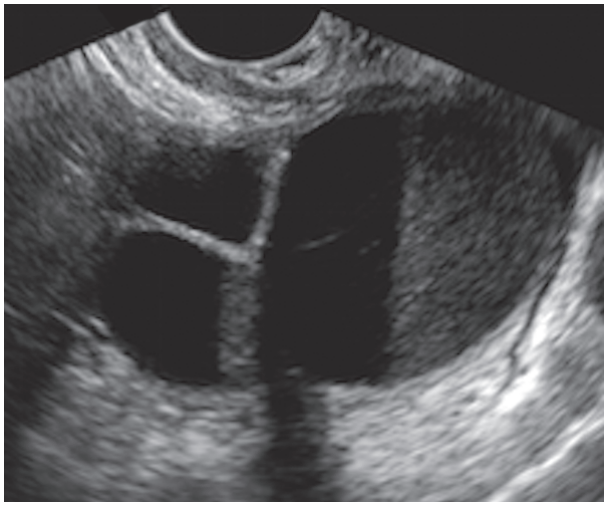


Figure 4. Illustrative case of a false-negative result according to all RMI variants. The patient was postmenopausal. Ultrasound showed a multilocular-solid mass. The CA-125 value was 12.86 U/ml. Pathologic analysis confirmed a serous cystadenocarcinoma (stage Ic).

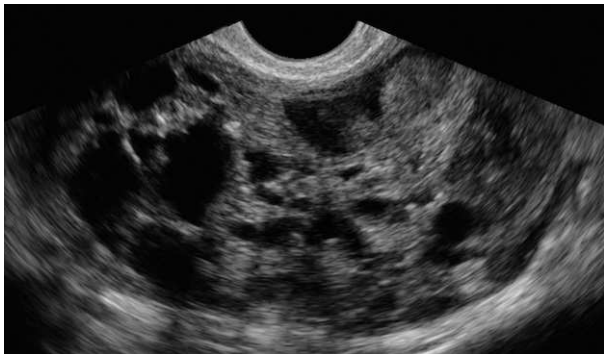
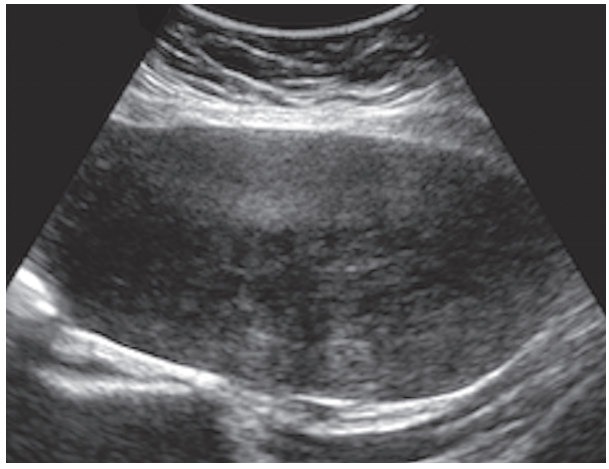


Figure 5. Illustrative case of a false-positive result according to all RMI variants. The patient was postmenopausal. Ultrasound showed a solid mass with smooth outlines and ascites. The CA-125 value was 232.2 U/mL. Pathologic analysis confirmed a fibroma (Meigs syndrome).



in ultrasound accuracy and the availability of specialized personnel. In our study, we found that the 4 RMI variants performed acceptably in a medium-resource setting where physician examiners had varied experience. This finding indicates a good tradeoff between performance and feasibility, since ultrasound RMI protocols are of low complexity.

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