The Journal of Obstetrics and Gynecology of India (March–April 2024) 74(2):158–164
https://doi.org/10.1007/s13224-023-01890-5

ORIGINAL ARTICLE

Comparison of Simple Ultrasound Rules by International Ovarian Tumor Analysis (IOTA) with RMI-1 and RMI-4 (Risk of Malignancy Index) in Preoperative Differentiation of Benign and Malignant Adnexal Masses

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Received: 16 August 2023 / Accepted: 17 October 2023 / Published online: 11 December 2023

Abstract

Background IOTA proposed Simple Ultrasound Rules in 2009 for preoperative diagnosis of ovarian masses based on ultrasound only. It is an accurate, simple and inexpensive method. RMI, however, requires CA125 level. While RMI-4 is the latest, RMI-1 is still the most widely used method. The present study was done to compare IOTA Rules with RMI-1 and RMI-4.

Purpose To differentiate benign and malignant adnexal masses preoperatively using IOTA simple rules and compare its accuracy with RMI-1 and RMI-4.

Methods A prospective observational study was performed from 1st November 2019 to 31st March 2021 in the Department of Obstetrics and Gynaecology, ABVIMS and Dr. RML Hospital, New Delhi. This study was conducted on 70 patients with adnexal masses who underwent pre-operative evaluation using IOTA Simple Rules, RMI-1 and RMI-4. Histopathology was used to compare the results.

Results Out of 70 patients, 59 (84.3%) cases were benign and 11 (15.7%) were malignant. The IOTA Rules were applicable to 60 cases (85.7%), and the results were inconclusive in 10 cases (14.3%). Where applicable, the sensitivity and specificity of the IOTA Rules (88.9% and 94.1%, respectively) were significantly higher than RMI-1 (45.5% and 93.2%, respectively) and RMI-4 (45.5% and 89.8%, respectively). When inconclusive results were included as malignant, the sensitivity of the IOTA Rules increased (88.9% vs 90.9%); however, the specificity decreased (94.1% vs 81.4%).

Conclusion IOTA Simple Rules were more accurate at diagnosing benign from malignant adnexal masses than RMI-1 and RMI-4. However, the rules were not applicable to 14% of the cases.

Keywords IOTA · Simple Rules · Adnexal mass · RMI-1 · RMI-4 · Ovarian mass

Introduction

Ovarian cancer is a common and lethal disease which has the highest mortality rate of all gynaecological cancers. Currently, there is no effective strategy for ovarian cancer screening. Primary goal for these patients is to detect the disease at an early stage. It is crucial to accurately characterize and differentiate an adnexal tumor into benign and malignant before deciding the plan of management. While conservative management is a possibility for benign masses, more extensive surgeries and staging are needed for malignant masses, preferably to be done by gynaecological oncologists. RMI is one of the most utilized methods for triage of patients with ovarian masses. RMI was originally developed by Jacob et al [1] in 1990 and has subsequently evolved into RMI II, III and IV. Tingulstad et al. developed RMI-2 in 1996 and further modified it into RMI-3 in 1999 [2, 3]. RMI-4, which includes tumor size score (S) in the calculation, was introduced by Yamamoto et al. in 2009 [4]. The study concluded that RMI-4 had more accuracy than RMI-1. However, only RMI I and II have received adequate validation to date [5]. Its major limitation is that it relies on CA125 levels, which

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is neither specific nor sensitive. CA125 is elevated in epithelial ovarian malignancies only and not in germ cell tumors. Additionally, numerous benign conditions like fibroids, adenomyosis, endometriosis and pelvic infections can have raised CA125 levels. In spite of this, RMI is the most widely used method. A systemic review by Geomini et al. in 2009 concluded that RMI (Risk of Malignancy Index) is the best test to classify patients with ovarian malignancies [6]. However, subjective assessment on ultrasonography by an expert examiner is still believed to be the best way to classify adnexal masses [7]. Unfortunately, an expert examiner is not always accessible, particularly in resource limited nations.

In 2008, the International Ovarian Tumor Analysis (IOTA) group published Simple Ultrasound Rules based on specific ultrasound findings [8]. It identifies an adnexal tumor as benign, malignant or indeterminate based on five benign (B-features) and five malignant (M-features). These Simple Rules have been validated in several studies by both expert and non-expert examiners with varying degrees of training and experience. The Simple Rules have gained widespread acceptance among clinicians, and the Royal College of Obstetricians and Gynaecologists (RCOG) in the United Kingdom has incorporated them into their Green Top guideline on the assessment and management of ovarian masses in premenopausal women [5]. In 2016, the American College of Obstetricians and Gynaecologists integrated the Simple Rules into their clinical guidelines on the evaluation and management of adnexal masses. [9]

The purpose of the current study was to compare Simple Ultrasound Rules with RMI-1 and RMI-4 and to identify a quick, affordable and reliable method for the diagnosis of ovarian malignancy in resource poor countries. To date, many studies of the IOTA simple rules have been published. However, studies are restricted to a few groups only and have rarely been examined in other parts of the world [10], especially among the Indian population. Also, other systems, such as RMI, have rarely been used to compare the performance of IOTA Simple Rules within the same study group.

Materials and Methods

The present study was a prospective observational study conducted in the Department of Obstetrics and Gynaecology, ABVIMS and Dr. Ram Manohar Lohia Hospital, New Delhi. The study comprised a total of 70 patients with an adnexal mass or masses on examination who were scheduled for surgery. The study excluded pregnant women, prior history of adnexal mass surgery or who failed to undergo surgery within 120 days of ultrasonography. The study was conducted from 1st November 2019 to 31st March 2021. After taking written informed consent, a thorough history and examination were done, followed by relevant investigations. CA125 level was done for all patients to calculate RMI. The patients were evaluated by radiologists at Dr. RML Hospital using either transabdominal (3–5 MHz) or transvaginal (5–8 MHz) ultrasound or both as deemed necessary, as well as a color doppler scan. Morphological features of adnexal mass were recorded as per the three scoring methods. In cases of bilateral masses, the larger one or one with a more complex morphology was chosen.

For IOTA Rules, findings were recorded using the tick box system (Table 1), and the following rules were applied according to descriptions by Timmerman et al [8]: (a) if ≥ 1 malignant feature was present, with no benign features, the mass was categorized as malignant; (b) if ≥ 1 benign feature was present, with no malignant features, it was classified as benign; (c) if both features or none were present, the findings were inconclusive.

As described by Jacob et al [1], RMI-1 was calculated using the formula $U \times M \times$ serum CA 125 (U/mL), where U was determined using the following five ultrasound characteristics: multilocularity, solid areas, bilateral masses, ascites and evidence of metastases. $U = 0$ when no feature is present; $U = 1$ if 1 feature is present; and $U = 3$ if ≥ 2 features are present. M stands for menopausal status, with a score of 1 for premenopausal and 3 for postmenopausal women. CA125 level was multiplied directly in the formula. An RMI score of ≥ 200 was indicative of malignancy.

Table 1 IOTA Simple Rules [8]

Benign features	±	Malignant features	±
B1—Unilocular cyst		M1—irregular solid tumor	
B2—Presence of solid Components (largest diameter < 7 mm)		M2—ascites	
B3—presence of acoustic shadowing		M3—At least four papillary structures	
B4—Smooth multilocular tumor with largest diameter < 100 mm		M4—Irregular multilocular Solid tumor with largest diameter ≥ 100 mm	
B5—no blood flow (Color Score 1)		M5—very strong blood flow (Color Score 4)	

RMI-4 was computed using formula by Yamamoto et al [4]: U × M × S × CA125 level (U/ml), where U = 1 in case of 0 or 1 ultrasonography feature and U = 4 in case of 2 or more features. M = 1 for premenopausal and 4 for postmenopausal women. S = 1 with a tumor size (single greatest diameter) of < 7 cm and S = 2 with a size of ≥ 7 cm. Serum CA125 was multiplied directly in the formula. A total score of > 450 was indicative of malignancy.

Women with ≥ 1 year of missed period or age more than 50 years with hysterectomy were taken as postmenopausal. For all patients, surgery was performed within 120 days of evaluation. Histopathological examination (HPE) served as the gold standard for the final diagnosis. Tumors were classified according to the WHO histopathological classification. The collected data was statistically analyzed using the inter-rater kappa agreement and the McNemar test. Analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

A total of 70 patients fulfilling the inclusion criteria were enrolled. The patients ranged in age from 13 to 80 years, with a mean age of 33 years. Of those, 33 (47.1%) were nullipara. Fifty-seven (81.4%) patients were premenopausal, and 13 (18.6%) were postmenopausal. CA125 was raised (> 35 U/ml) in 24 patients; 22 of them were premenopausal. Out of these 24, 19 cases with elevated CA125 had benign histology results. On histopathology, 59 masses (84.3%) were benign and 11 masses (15.7%) were malignant, including four cases of borderline malignancy. Among 11 malignant tumors, nine (81.8%) cases were found in premenopausal women, while six cases (54.5%) were found in nulliparous women. Table 2 displays the demography of these tumors. On histology, malignant cases included three cases of adenocarcinoma, two cases each of borderline serous and borderline mucinous cancer, and one case each of serous carcinoma, mucinous carcinoma, yolksac tumor and granulosa cell tumor. Table 3 displays the HPE correlation of IOTA Rules, RMI-1 and RMI-4 (Fig. 1).

When the RMI-1 score was calculated, 61 masses were suggestive of benign nature (RMI-1 < 200) and nine masses of malignant nature (RMI-1 > 200). Following the comparison of outcome with HPE, the sensitivity and specificity of the RMI-1 score were 45.5% and 93.2%, respectively, and its NPV, PPV, and likelihood ratios were as given in Table 4.

Based on RMI-4, 59 masses were found to be benign (RMI-4 < 450), and 11 masses were found to be malignant (RMI-4 > 450). After comparing the results with HPE, the sensitivity and specificity of RMI-4 were 45.5% and 89.8%, respectively, and its NPV, PPV, and likelihood ratios were as depicted in Table 4.

The Simple Ultrasound Rules were applicable in 60 cases (85.7%), of which 49 cases were classified as benign by the Simple Rules (of which 48 were benign on histology) and

Table 2 Demography and distribution of age, parity and menstrual status and clinical characteristics

Parameters	HPE impression		*P* value
	Benign (n = 59)	Malignant/borderline (n = 11)	
Age (Years) (mean ± SD)	34.34 ± 14.86	31.91 ± 19.21	0.337 [1]
Age			0.246 [2]
≤ 20 Years	14 (23.7%)	5 (45.5%)	
21–30 Years	12 (20.3%)	2 (18.2%)	
31–40 Years	14 (23.7%)	0 (0.0%)	
41–50 Years	11 (18.6%)	3 (27.3%)	
51–60 Years	4 (6.8%)	0 (0.0%)	
61–70 Years	3 (5.1%)	0 (0.0%)	
71–80 Years	1 (1.7%)	1 (9.1%)	
Parity			0.592 [3]
Nullipara	27 (45.8%)	6 (54.5%)	
Multipara	32 (54.2%)	5 (45.5%)	
Menstrual status			1.000 [2]
Premenopausal	48 (81.4%)	9 (81.8%)	
Post-menopausal	11 (18.6%)	2 (18.2%)	
CA125 (mean ± SD)	41.93 ± 56.99	230.59 ± 384.88	0.605 [1]
Bilateral involvement	6 (10.2%)	3(27.3%)	

P value significant at $p < 0.05$, 1: Wilcoxon-Mann–Whitney U Test, 2: Fisher's Exact Test, 3: Chi-Squared Test

Table 3 Association of HPE Diagnosis with IOTA Simple Rules (SR), RMI-1 and RMI-4:

Parameters	HPE diagnosis		Total
	Benign (n = 59)	Malignant/borderline (n = 11)	
IOTA SR finding			< 0.001 [2] (*p* value)
Benign	48 (81.4%)	1 (9.1%)	49
Inconclusive	8 (13.6%)	2 (18.2%)	10
Malignant	3 (5.1%)	8 (72.7%)	11
RMI-1 score			0.003 [2] (*p* value)
≤ 200	55 (93.2%)	6 (54.5%)	61
> 200	4 (6.8%)	5 (45.5%)	9
RMI-4 score			0.003 [2] (*p* value)
≤ 450	53 (89.8%)	6 (54.6%)	59
> 450	6 (10.2%)	5 (45.4%)	11

11 cases were classified as malignant (of which eight were malignant on histology), as shown in Table 3. Where Simple Rules were applicable, the test's sensitivity and specificity were determined to be 88.9% and 94.1%, respectively, and its PPV, NPV, diagnostic accuracy, and likelihood ratios were as displayed in Table 4.

Ten cases (14.3%) were deemed to be inconclusive where the rules were not applicable or both M and B features were present. IOTA Simple Rules provided inconclusive results in two cases each of mature teratoma, endometriotic cyst and borderline serous cystadenocarcinoma, as well as one case each of serous cystadenoma, mucinous cystadenoma, haemorrhagic corpus luteal cyst and leiomyoma. When the inconclusive results were assumed to be malignant, the sensitivity and specificity of the IOTA Simple Rules were calculated as 90.9% and 81.4%, respectively (Table 4).

Discussion

The aim of the present study was to assess the diagnostic performance of IOTA Simple Ultrasound Rules, which is emerging as an efficient, simple and affordable diagnostic method for resource limited centres. This method relies solely on ultrasonography and requires no other tests. Our study compares the diagnostic performance of IOTA Simple Rules with that of RMI-1 and RMI-4. While RMI-1 is the most widely used model for predicting malignancy, RMI-4 has been found to be more accurate than other RMI scores.

The strength of the present study is that different scoring methods were applied to the same patients using the same ultrasound machine, allowing an ideal comparison. Till date, not many studies have compared the performance of IOTA Simple Rules with RMI-1 or RMI-4, particularly among the Indian population.

When RMI-1 was applied to 70 cases in our study, its sensitivity and specificity were found to be 45.5% and 93.2%, respectively. In the original study by Jacob et al [1], the sensitivity and specificity of RMI-1 were 85% and 97%, respectively. The findings of our study are comparable to a study done by Timmerman et al [11] in 2010, where the sensitivity and specificity of RMI-1 were 75% and 95%, respectively,

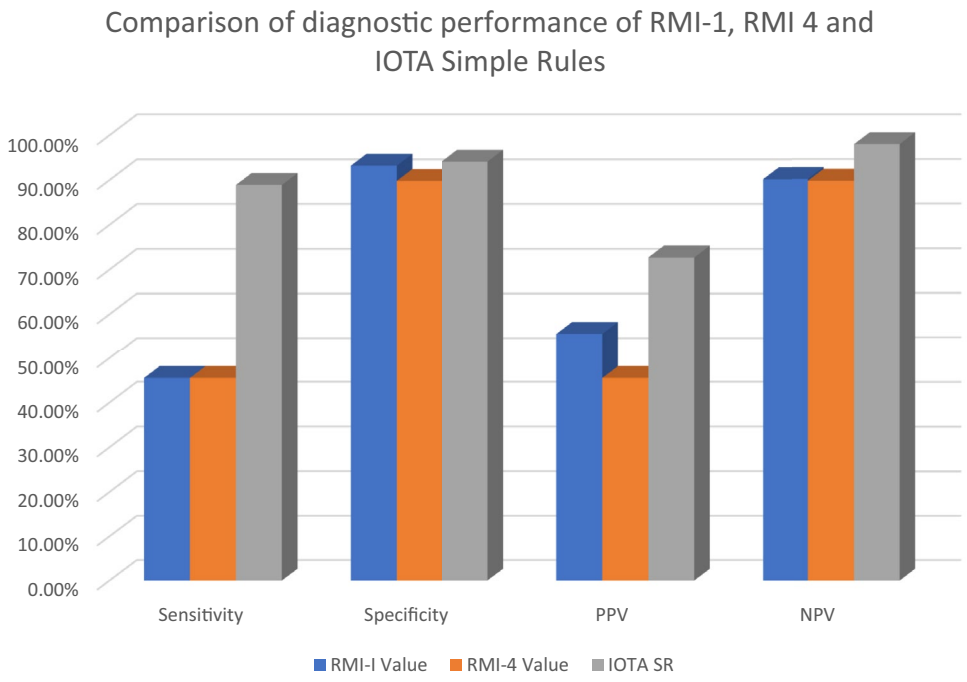

Fig. 1 Comparison of results of IOTA Rules, RMI-1 and RMI-4

Table 4 Comparison of Diagnostic Performance of IOTA Simple Rules with RMI-1 and RMI-4 in Predicting Malignant/borderline versus benign

Parameter	RMI-1 value (95% CI)	RMI-4 Value (95% CI)	IOTA SR	IOTA SR (inconclusive result included as malignancy)
Sensitivity	45.5% (17–77)	45.5% (16.7 to 76.6)	88.9% (52–100)	90.9% (59–100)
Specificity	93.2% (84–98)	89.8% (79 to 96)	94.1% (84–99)	81.4% (69–90)
PPV	55.6% (21–86)	45.5% (16.7 to 76.6)	72.7% (39–94)	47.6% (26–70)
NPV	90.2% (80–96)	89.8% (79 to 96)	98.0% (89–100)	98.0% (89–100)
Diagnostic Accuracy	85.7% (75–93)	82.9% (73.8 to 91.9)	93.3% (84–98)	82.9% (72–91)
+LR	6.70 (2.13–21.10)	4.47 (1.65–12.11)	15.11 (4.92–46.40)	4.88 (2.77–8.58)
-LR	0.59 (0.34–1.01)	0.61 (0.35–1.05)	0.12 (0.02–0.75)	0.11 (0.02–0.73)
Diagnostic Odds Ratio	11.46 (2.40–54.62)	7.36 (0.54–3.45)	128.00 (11.80–1388.19)	43.64 (5.04–377.44)

for overall study subjects. However, for just premenopausal patients, the sensitivity and specificity of RMI-1 were 55% and 96%, respectively.

When using RMI-4, with a cut-off of 450, we found sensitivity and specificity of 45.5% and 89.8%, respectively. Sensitivity and specificity were reported to be 86.8% and 91%, respectively, in a retrospective study done by Yamamoto et al. [4] In a study conducted by Hada et al [12] in 2020, the reported sensitivity and specificity of RMI-4 were 66.7% and 92.2%, respectively, for the overall study group. However, for premenopausal patients alone, the computed sensitivity and specificity were 42.9% and 90.6%, respectively. The specificity reported by our study was comparable to both studies; however, the sensitivity was lower.

In the present study, the sensitivity of both scoring systems, RMI-1 and RMI-4, was comparable. However, RMI-1 had higher specificity, PPV and NPV than RMI-4. In the study conducted by Hada et al [12], sensitivity of RMI-4 was marginally higher than that of RMI-1 (63% vs 66.7%), although RMI-4's specificity (93.8% vs 92.2%) and PPV (68% vs 64.3%) were marginally lower. NPV was comparable for both scores (92.3% vs 92.9%). (Table 4).

In the present study, the sensitivity and specificity of IOTA Simple Rules were 88.9% and 94.1%, respectively. The sensitivity was found to be lower than in prior IOTA studies, probably because of the low malignancy rate in the current study (15.7%). The study by Fathallah et al [13] reported a sensitivity of 73%, which was attributed to the study's low malignancy rate (11%). In the study by Nunes et al [14] in 2014, prevalence of malignancy was 44.3%, and the reported sensitivity of IOTA Rules was 96.2%. This was higher than the study by Timmerman et al [8], which reported a sensitivity of 95% and a malignancy prevalence of 29%.

Many previously published studies have classified the inconclusive results of IOTA as malignant [11, 13–15]. When the present study included 10 cases with inconclusive results as malignant, the sensitivity of the test increased (from 88.9% to 90.9%). However, the specificity (94.1% vs 81.4%), PPV (72.7% Vs 47.6%) and diagnostic accuracy (93.3% Vs 82.9%) decreased significantly (Table 4).

The sensitivity and specificity of the IOTA Rules in the present study correlated well with the published data. The results were most closely related to the study done by Alcazar JL et al [15] in 2013, which reported sensitivity and specificity of 87.9% and 97.5%, respectively, when inconclusive results were excluded from analysis. Whereas, when the inconclusive results were included as malignant, the sensitivity and specificity were 93% and 81%, respectively. Table 5 provides a thorough comparison of the current study with the previously published articles.

On comparing the diagnostic performance of IOTA Simple Rules (after excluding inconclusive results) with RMI-1 and RMI-4, the results showed that IOTA Simple Rules performed better than RMI-1 and RMI-4 in terms of sensitivity, specificity, PPV, NPV and diagnostic accuracy (Table 4). The outcomes were comparable to those of a comparative study done by Rapeepat et al [10], that compared IOTA Simple Rules and RMI-1. Sensitivity and specificity of IOTA Rules (83.8% and 92.0%, respectively) were significantly higher than those of RMI-1 (77.2% and 86.8%, respectively). IOTA SR's sensitivity was found to be significantly greater than RMI-4's (80% vs 60.7%) when used by senior physicians in a study by Yuyang Guo et al [16] in 2022, while specificity was only slightly lower (92.4% vs 95.3%).

When inconclusive results were included as malignant in the present study, the sensitivity and negative predictive value of Simple Rrules were found to be better than RMI-I and RMI-4. Whereas the specificity, positive predictive value and diagnostic accuracy of RMI-1 were shown to be superior to those of IOTA Simple Rules and RMI-4, as demonstrated in Table 4.

The major limitation of the present study was its limited sample size. The majority of the patients in the study group were premenopausal (81.4%). CA125 may be falsely elevated in benign diseases in premenopausal patients. In

Table 5 Comparison of results of present study with the published data

Author and year of study	No. of cases	No. of cases where rules were applicable	Malignant tumors	Prevalence of malignancy (%)	Sensitivity (%)	Specificity (%)
Timmerman et el [8]	507	386	-	29	95	91
Timmerman et al [11]	1938	1501	542	25	92	96
Fathallah et al [13]	122	109	14	11.5	73	97
Hartman et al [17]	103	91	30	24.2	91	87
Alcazar et al [15]	340	270	55	16.2	87.9	97.5
Nunes et al [14]	303	237	135	44.3	96.2	88.6
Sugandha Garg et al [18]	50	45	14	28	91.6	84.84
Rapeepat et al [10]	479	392	-	30.3	83.8	92
Shetty et al [19]	205	183	39	25	92.8	92.9
Hiett et al [20]	150	113	40	26.7	100	95.6
Present study	70	60	11	15.7	88.9	94.1

this study, CA125 levels were raised (> 35 U/ml) in 24 study subjects, among whom 22 were premenopausal. Due to predominantly premenopausal patients, the sensitivity of RMI-1 and RMI-4 was highly decreased.

Conclusion

IOTA Simple Rules can be adopted as an efficient method to characterize ovarian masses because they are highly sensitive and specific. The advantage of this method is that all it requires is an ultrasound machine, which is readily available. The method is user-friendly and simple to learn and train. For low-income countries with limited resources, gynaecologists can adopt it as a first-line method. In the present study, IOTA Simple Rules had higher diagnostic accuracy than both RMI-1 and RMI-4. Nevertheless, the rules were not applicable to 14% of cases, despite high diagnostic accuracy.

Funding The study was not funded by anyone.

Declarations

Conflict of interest The authors have no conflicts of interest.

Ethical approval This study was performed in line with the principles of the Declaration of Helsinki (F No. TP (MD/MS) (70/2019)/ IEC/ ABVIMS/RMLH 734/19).

Informed consent All participants provided informed consent.

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