Diagnostic Performance of IOTA-SRs and RMI 4 For Diagnosis of Malignancy in Ovarian Masses Comparison with Histopathology

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Abstract

Background: The discrimination between benign and malignant ovarian masses is essential for clinical management and surgical planning. This study aimed to compare the International Ovarian Tumor Analysis (IOTA) Simple Rules (SRs) and Risk of Malignancy Index (RMI) 4 as a diagnostic method to preoperative evaluation of malignant ovarian tumours by correlating with the postoperative histopathology reports.

Materials and methods: This prospective observational study was conducted in the Obstetrics & Gynecology Department of Chittagong Medical College Hospital, Chattogram. 45 women with ovarian masses were included. Ultrasound examinations were performed. Demographic data and preoperative CA 125 levels were recorded. IOTA SRs and RMI-4 scoring were applied to predict malignancy. The final diagnosis was based on the histopathological diagnosis. Diagnostic accuracy in terms of sensitivity, specificity, Positive Predictive Value (PPV) Negative Predictive Value (NPV) and accuracy of each predictive tool was compared.

Results: There were 28 (62.2%) subjects with benign tumours and 17 (37.8%) subjects with malignant tumours. The sensitivity, specificity, PPV, NPV and accuracy for the IOTA SRs were 94.1%, 92.9%, 88.9%, 96.3% and 93.3% respectively. For the RMI 4, with a cut-off value of 450 these were 52.9%, 85.7%, 69.2%, 75.0% and 73.3% respectively.

Conclusion: IOTA SRs had higher diagnostic accuracy than RMI 4 to discriminate benign and malignant ovarian masses preoperatively.

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Submitted on : 30.09.2022
Accepted on : 30.11.2022

Key words: Adnexal mass; IOTA simple rules; Ovarian masses; RMI 4.

Introduction

Adnexal masses are one of the most common problems that gynaecologists encounter in the In-patient Department of obstetrics and gynaecology. The most prevalent type of pelvic mass is ovarian malignancy. According to Globocan 2018, ovarian cancers are the 7th most common cancers in females worldwide. But it has the highest mortality rate among all gynaecological cancers.[1] Ovarian cancer is an alarming health problem in Bangladesh. According to NICRH statistics from 2014-2018, the total number of ovarian malignancy was 6114, representing 22% of gynaecologicalmalignancies.The estimated incidence of ovarian cancer in Bangladesh in 2020 was 3122, with mortality of 2096 cases.[2]

The prognosis of ovarian malignancy is directly dependent on the disease stage at the time of diagnosis. Most of the cases are diagnosed at an advanced stage, which leads to poor outcomes of this disease.[3] The majority of ovarian malignancies are epithelial ovarian cancers, which are rapidly progressing tumours. A timely diagnosis of the nature of the mass ensures appropriate referral to a gyne-oncologist and treatment.[4] Moreover, preoperative differentiation between malignant and benign adnexal mass is essential for proper management and counselling of patients as approaches to treat the two conditions are often different. Functional ovarian cysts are usually treated with expectant management and benign ovarian tumour like dermoid cysts or serous cysts may need simple cystectomy via either laparoscopic surgery or laparotomy that general surgeons can perform, in contrast, malignant ovarian tumor requires extensive surgery or complete surgical staging, which typically requires expert consultation or referral to a tertiary center employing gynecologic oncologists.[3] Preoperative diagnosis of ovarian malignancy is found to be most challenging. Various diagnostic tests available to date are not

very dependable. The commonly available tests are tumour markers or radiological imaging. CA-125 is the most common tumour marker in all the cases, but it has also been shown to have false-positive results, as may be raised in many nonmalignant pathologies too.[5] Among the imaging modalities, Ultrasonography (USG) whether trans-vaginal or trans-abdominal, is the first-line preoperative investigation for ovarian masses. However, USG-based assessment depends on the sonologist's experience, hence it is operator dependent.

These led to different types of scoring systems for categorizing ovarian masses into benign and malignant. Risk of Malignancy Index (RMI) and International Ovarian Tumor Analysis (IOTA) simple rules are the two commonly used predictive models recognized by the RCOG.

RMI was developed to improve diagnostic accuracy in predicting ovarian malignancy and has been in use for many years in low-income countries. Initially, the RMI system was developed by Jacob et al on 1990 based on the combination of sonographic findings, menopausal status and serum levels of CA 125. Four versions of RMI have been proposed till now i.e RMI 1, RMI 2, RMI 3 and RMI 4. The sensitivity and specificity of each version of RMI have been studied in various studies. RMI 4 is the recent version that includes tumour size and is considered more reliable than previous versions.[6] As RMI depends upon serum CA 125 levels, this limits their utility, particularly in women of reproductive age. Serum CA 125 levels are frequently normal in borderline tumours and early-stage invasive ovarian cancer. They can show a false positive increase in numerous benign tumours or conditions that irritate the pelvic peritoneum (e.g Endometriosis, fibroids, pregnancy, infection and surgery).[7,8]

Therefore, the International Ovarian Tumour Analysis (IOTA) group developed a prediction model called "Simple Rules" (SR). This rule is based on five sonographic features typical for benign tumours called the B-features and five features typical for malignant tumours termed M-features. Based on B- or M-features, tumours are classified as benign, malignant or inconclusive (If both B and M-features are present).[9] The IOTA SR model achieves both high sensitivity and specificity in recent studies and therefore discriminates well between benign and malignant ovarian tumours than the RMI.[10-15]

However, most of the studies using IOTA simple rules were conducted in American and European countries and it has not been studied enough in other parts of the world. Unfortunately, there is no data that compare the diagnostic performance of IOTA simple rules and RMI-4 scoring systems and their applicability in the Bangladeshi population. Though IOTA SR can be more feasible as a prediction method in a low resource country like Bangladesh as it is more cost effective.

The study was designed to compare the IOTA Simple Rules and RMI 4 in predicting malignant ovarian tumours in patients attending the Department of Obstetrics and Gynecology of a public tertiary care hospital in Bangladesh.

Materials and methods

This prospective observational study was conducted in the Obstetrics & Gynecology Department of Chittagong Medical College Hospital (CMCH) in Chattogram, Bangladesh from August 2019 to July 2020. Forty-five women with ovarian masses were included and were subjected to surgery in the study. Patients who already had preoperative FNA, ovarian tumor with pregnancy, mass found to be arising from other structure than ovary were excluded. Written informed consent was obtained prior to enrollment in the study. On admission, detailed history was taken and complete examination was performed.

The patients were subjected to ultrasonographic examination done by single expert radiologist of Radiology Department of CMCH. The sonologist was blind to the patient's clinical information. 3D ultrasound with color Doppler study was done by Philips Affiniti 30 ultrasound machine.

Trans abdominal ultrasonography was done to evaluate the following criteria like multilocularity, consistency, papillary structures, blood flow, acoustic shadows, solidity, bilaterality, ascites, presence of intra-abdominal metastasis and size of the tumor.

2 ml of peripheral venous blood was collected for estimation of serum CA 125.

RMI-4 score was calculated according to the following chart :-

Risk of Malignancy Index variants

Variant	Ultrasound score (U)	Menopausal score (M)	Tumor size (S) mm (Single greatest diameter)
RMI4(U×M×S×CA125)[6]	U=1(0 or 1 parameter) U=4 (≥2 parameter)	M=1(Premenopausal) M=4 (Postmenopausal)	S=1(<70) S=2(≥70)

IOTA simple rules were described as malignant or benign masses preoperatively according to the following table

Rules for predicting a malignanttumour (M-rules)	
M1	Irregular solid tumor
M2	Presence of ascites
M3	At least four papillary structures
M4	Irregular multilocular solid tumor with the largest diameter ≥100 mm
M5	Very strong blood flow (Colour score 4)
Rules for predicting a benign tumour (B-rules)	
B1	Unilocular
B2	Presence of solid components with the largest diameter < 7mm
B3	Presence of acoustic shadows
B4	Smooth multilocular tumor with the largest diameter < 100 mm
B5	No blood flow (Colour score 1)

In the event of bilateral ovarian masses, the mass with the most complex USG morphology was included. If both masses showed similar ultrasound morphology, the large one or the one most accessible by ultrasound was included. On application of one or more M-rules in the absence of a B-rule or one or more B-rules in the lack of an M-rule, the mass was classified as malignant or benign, respectively. If both M-rules and B-rules are applicable or if no rule applies, the mass waslabeled as inconclusive.

The patients were subjected to either laparotomy or laparoscopy surgery and tissue excised was sent for histopathological analysis. Histopathological diagnosis is considered the gold standard for a definite outcome.

The diagnostic accuracy of the IOTA simple rules & RMI 4was calculated for sensitivity, specificity, positive and negative predictive values. An agreement between the IOTA and RMI methods was done using the kappa statistics. p value was considered as statistical significance when it is <0.05 and confidence interval was set at 95% level. Before commence the study, clearance letter of ERB of CMC was taken (Memo no CMC/PG/2021 dt 15.11.2021)

Results

In the present study, 45 patients with ovarian mass subjected to surgery in CMCH were included. Histopathology reports of the surgical specimens revealed benign tumours in 28 cases and malignant in the rest of the 17 cases. The results and observations of the present study were presented in the following Tables and Graphs.

Table I RMI-4 scores of the patients with ovarian mass

RMI-4 score	Frequency	Percentage
Median (IQR)	200 (80-511)	
Range	25-4800	
Score >200	24	53.3
Score >400	15	33.3
Score >450	13	28.9

RMI 4 score range between 25 and 4800 in the study. Fifteen (33.3%) and 13 (28.9%) of the patients had RMI 4 score >400 and >450 respectively (Table I).

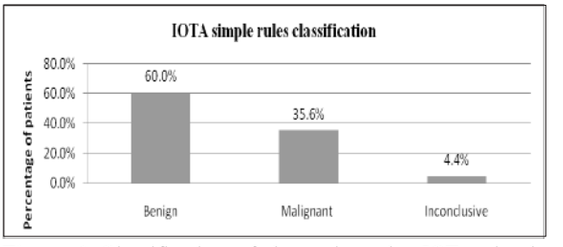

Figure 1 Classification of the patients by IOTA simple rules findings

IOTA simple rules could be applied to 95.6% (43) masses and were inconclusive for 4.4% (2). Figure 1 shows that 35.6% (16) were malignant and 60.0% (27) cases were benign as per IOTA simple rules.

Table II Comparison of IOTA simple rules findings to histopathology report

IOTA-simple rules	Histopathology report		
	Benign	Malignant	p-value*
Benign	26 (93.3)	1 (3.7)	
Inconclusive	0 (0)	2 (100.0)	<0.001
Malignant	2 (12.5)	14 (82.4)	

*Chi-square test.

Out of 27 benign cases according to IOTA simple rules, 26 (93.3%) were found benign on histopathology report. Out of 16 malignant cases according to IOTA simple rules, 14 (82.4%) were found malignant on histopathology report. Two inconclusive cases were found to be malignant on histopathology report (Table II).

Table III Comparison of RMI 4 scores to histopathology report

RMI 4 score	Histopathology report		
	Benign (n=28)	Malignant (n=17)	p-value
Median (IQR)	502.0 (138.4-1808)	178.8 (60.0-385.9)	<0.001*
Range	25-4660	60-4800	
Score >200	16 (57.1)	8 (47.1)	0.544†
Score >400	5 (17.9)	10 (58.8)	0.005†
Score >450	4 (14.3)	9 (52.9)	0.006†

*p-value was derived from Mann-Whitney U test, †Chi-square test.

Median RMI 4 score was significantly higher in patients with a malignant tumour on histopathology report than patients with a benign lesion on histopathology report (Table III). 10 (58.8%) of the malignant cases were correctly classified with the cut-off value of RMI >400. When the cut-off value was 450, then 9 (52.9%) of the malignant cases were classified correctly.

Table IV Agreement between IOTA simple rules and RMI 4 score for the prediction of malignant ovarian mass

RMI 4 score	IOTA-simple rules		
	Malignant (n=18)	Benign (n=27)	Kappa statistics
Cut-off value >200			
Malignant	10 (55.6)	12 (44.4)	0.107
Benign	8 (44.4)	15 (55.6)	
Cut-off value >400			
Malignant	9 (50.0)	6 (22.2)	0.286
Benign	9 (50.0)	21 (77.8)	
Cut-off value >450			
Malignant	8 (44.4)	5 (18.5)	0.272
Benign	10 (55.6)	22 (81.5)	

*Chi-square test.

Agreeemnt between IOTA-simple rules and RMI 4 score was the highset when the cut-off value of RMI 4 was >400 (Table IV).

Table V Comparison of the diagnostic performance of IOTA-SRs and RMI 4 for diagnosis of malignant tumors considering the histopathology as gold standard

Statistic	IOTA SRs		RMI 4 with cut-off value >400	
	Value	95% CI	Value	95% CI
Sensitivity	94.12%	71.31% - 99.85%	58.82%	32.92% - 81.56%
Specificity	92.86%	76.50% - 99.12%	82.14%	63.11% - 93.94%
PPV	88.89%	67.67% - 96.83%	66.67%	45.13% - 82.94%
NPV	96.30%	79.48% - 99.43%	76.67%	64.47% - 85.61%
Accuracy	93.33%	81.73% - 98.60%	73.33%	58.06% - 85.40%

PPV: Positive Predictive Value, NPV: Negative Predictive Value.

Table V depiceted that diagnostic performance of IOTA SRs in terms of sensitivity, specificity, PPV, NPV and accuracy was better than the RMI 4 score.

Discussion

The present prospective observational study investigated the diagnostic performance of two commonly used models, IOTA simple rules and RMI 4, to differentiate between benign and malignant ovarian masses. The primary purpose of this study was to identify the more accurate, predictive tool between these two. For this purpose, 45 cases with ovarian mass who were subjected to surgical management in the Obs and Gynae Department of CMCH were included in the study. The results of the present study demonstrated that IOTA simple rules were more effective than RMI 4 scoring at discriminating between benign and malignant ovarian masses preoperatively.

The proportion of malignancy in the current study was 37.8%. In the literature, this rate is reported to be 16.9%-48.7%.[11,13-15,17] These wide variations among study results were attributable to the study setting and the sample size.

In the present study, the sensitivity and specificity of RMI 4 to diagnose malignant disease were 58.8% and 82.14% for the cut-off value of 400 and 52.9% and 85.7% for the cut-off value of 450. Recently, Kaur et al reported that the RMI 4 at a cut-off level of 450 yielded a sensitivity of 72.73% and a specificity of 89.47% with a sample size of 30 patients.[17] Feharsal & Putra has yielded a sensitivity of 86% and specificity of 61%, sample size was119.[11] Yammamoto et al gained 86.8% sensitivity and 91% specificity.[6] Mulder et al showed 72% sensitivity and 90.7% specificity in their study with 202 patients.[15] Incomparison with theprevious studies, the sensitivity is comparatively lower in the present study may be due to the number of non-epithelial and borderline tumours. Non epithelial cancers often gives rise to false negative results in the RMI 4 group that led to missing ovarian cancer, resulting in inadequate treatment.

It was found that RMI 4 was the best predictive RMI for preoperative discrimination of benign from malignant at a cut-off level of 450.[16] In the present study, RMI 4 cut-off value of 400 and 450 had the highest sensitivity and specificity. These differences in the accuracy of different cut-off values of RMI 4 indicated that it is challenging to determine universally accepted cut-off values for RMI 4 score for everyday use around the globe.

According to IOTA simple rules, out of 45 patients, majority (60%) were classified as benign and 35.6% were malignant. Only two cases (4.4%) were inconclusive in the present study. Auekitrungrueng et al reported IOTA simple rules could be applied to 392 (81.8%) masses and were inconclusive for 87 (18.2%) cases.[13] In the study of Mulder et al, the IOTA simple rules showed a remarkably high rate of inconclusive results (38.7%), which distorts the test's diagnostic accuracy.[15] Inconclusive results are the main disadvantage of the IOTA simple rules. This indicates that specialist sonographers would need to be consulted in a significant number of cases. This disadvantage may raise concern for its more comprehensive application. In daily practice, an inconclusive result will most probably be considered as an indication for referral. Therefore, as in previous studies, we classified inconclusive tumours as malignant realizing that assuming malignancy would improve sensitivity but deteriorate specificity.[10,13,15,18]

The present study demonstrated good predictive value of IOTA SR at discriminating malignant from benign masses.Mulder et al has comparatively low specificity of 68.6% may be due to more inconclusive results.[15] Garget al in their study with 50 women found the sensitivity of 91% and specificity of 84%.[19] Solanki et al found a high sensitivity and specificity of 96% and 92%.[14] The present study shows a similar result of sensitivity of 94.1% and specificity of 92.9%.

Differences in performance of the IOTA simple rules between studies as observed, underscore the potential performance of image-based classification systems related to the patient population, practice setting and prevalence of cancer.[9]

The diagnostic accuracy of the IOTA SR is better than the RMI 4 in the present study, which was in agreement with two of the previous studies.[11,13] However, Mulder et al reported the diagnostic accuracy of the RMI is better than the IOTA SR in their cohort study.[15] These were the few studies that have compared the diagnostic performance of the IOTA simple rules with other conventional techniques, particularly RMI 4.

The present study findings had important clinical implications in our setting. The most crucial factor in ovarian malignancy is the time of detection. With early detection, it is possible to improve the survival of patients significantly. USG offers inherent advantages of easy availability, low cost and lack of radiation exposure but being more subjective than other modalities. IOTA simple ultrasound rules can eliminate this problem as they are highly sensitive and specific in predicting ovarian malignancy yet being reproducible, easy to train and use.Most of the studies using IOTA simple rules were conducted in American and European countries and it has not been studied enough in the Bangladeshi population. This prospective study planned to compare the efficacy of IOTA simple rules and the conventional RMI 4 scoring system in diagnosing ovarian masses is one of a kind. The present study recommends the findings of IOTA simple rules in predicting ovarian malignancy and concludes that these can be quickly learned and applied. It can be of great clinical value in deciding the nature of ovarian masses.

Limitation

- The study had a relatively small number of included patients.
- Samples were conveniently selected from a single tertiary care hospital.
- Unclassified tumours were classified as malignant for statistical analysis. This strategy has also been used in other previous studies.

Conclusion

In summary, IOTA simple rules scoring system had better sensitivity, specificity, positive predictive value, negative predictive value and accuracythan RMI-4.All these parameters indicated the higher effectiveness of the IOTA simple rules in predicting malignancy preoperatively in patients with ovarian masses.

Recommendation

Based on the study results, it could be suggested that, for countries with limited resources like Bangladesh, the IOTA simple rules may be incorporated in clinical practice as a tool for assessing an ovarian mass owing to its high effectiveness and lack of need for measurement of tumour markers. Nevertheless, considering the small sample size of the present study, more studies comparing diagnostic performance between the new method IOTA simple rules and RMI 4 still need to be conducted to accumulate enough data to evaluate their suitability before proper implementation.

Acknowledgement
Authors are grateful to all the women participated in this study. We are also thankful to all who participated in the preparation of this manuscript.

Contribution of authors
IJ- Conception, design, data collection, manuscript writing & final approval.
SA- Interpretation of data, critical revision & final approval.
ANH- Interpretation of data, Data analysis, drafting & final approval.
SM- Interpretation of data, data analysis, manuscript writing & final approval.
TA- Data collection, manuscript writing & final approval.
HAB- Data collection, manuscript writing & final approval.
IC- Data collection, manuscript writing & final approval.

Disclosure
All authors declared no conflict of interest.

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