Comparison of International Ovarian Tumor Analysis -Simple Rules (IOTA-SR) with Risk of Malignancy Index IV (RMI IV) to Predict Ovarian Cancer

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ABSTRACT

Background

Ovarian cancer is globally third most common cancer in women. The incidence of a symptomatic ovarian cyst in a premenopausal female being malignant is approximately 1:1000 which increases to 3:1000 at the age of 50.

Objective

To compare the diagnostic accuracy of International Ovarian Tumor Analysis (IOTA) simple rules and risk of malignancy index (RMI) IV scoring to differentiate between benign and malignant adnexal masses pre-operatively.

Method

An observational analytical study carried out to compare two cancer prediction tools among the ovarian tumor patients undergoing surgery in the Department of Obstetrics and Gynecology at Nobel Medical College, Biratnagar in the year 2024 and 2025. The diagnostic accuracy of risk of malignancy index IV and international ovarian tumor analysis SR was compared using SPSS version 16. Histopathology was the gold standard for the final diagnosis. Ethical approval was taken from institution review committee.

Result

Out of total 52 cases, 20 cases were classified as malignant tumors by international ovarian tumor analysis simple rules that was confirmed by histopathology in only 17 cases. 32 cases predicted by international ovarian tumor analysis SR was confirmed to be benign in 31 cases reporting Sensitivity of international ovarian tumor analysis SR to be 94.4%, specificity of 94.2%, Positive predictive value of 89.5%, negative predictive value of 96.9% and Diagnostic accuracy of 94.23%. On calculation of risk of malignancy index IV and comparing it with the histopathology report, sensitivity of 88%, specificity of 91.2%, positive predictive value of 84.2%, negative predictive value of 94% and diagnostic accuracy of 90.38%. The risk of malignancy index IV showed the highest Area Under Curve (AUC) of 0.936 followed by CA 125 of 0.783 area under curve and size of tumor demonstrated area under curve of 0.662 in the present study. International ovarian tumor analysis had better diagnostic performance than risk of malignancy index IV (chi squared test 36.45 vs 32.53).

Conclusion

Diagnostic performance of international ovarian tumor analysis SR is relatively better for prediction of adnexal mass in comparison to risk of malignancy index IV.

KEY WORDS

Adnexal mass, IOTA simple rules, Ovarian tumor, Risk malignancy index IV

INTRODUCTION

Ovarian cancer is globally third most common cancer in women. The overall incidence of ovarian cancer in Nepal is 3-4% being 60% diagnosed in advanced stages with an unfavorable prognosis.[1] The incidence of a symptomatic ovarian cyst in a premenopausal female being malignant is approximately 1:1000 which increases to 3:1000 at the age of 50.[2]

With an effective tool for assessing adnexal masses pre-operatively, patients can get first-line treatment in the early stages increasing their survival and reducing mortality and morbidity. Risk assessment of ovarian masses are done by the following methods-tumor markers, RMI, Imaging and ROMA. RCOG guideline advocates use of RMI I whereas SOGC recommends RMI II for evaluation of adnexal mass to predict malignancy. RMI method being simple does not provide any diagnostic advantages due to high dependency on Serum CA-125. Also it has poor sensitivity for early-stage invasive and borderline illness particularly in pre-menopausal women.[3] RMI-4 was computed using formula by Yamamoto et al.[4] A total score of > 450 was indicative of malignancy. 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.

Till date, not many studies have compared the performance of IOTA Simple Rules with RMI-4, particularly in the context of Nepalese population with high burden of patients and also limited resources. The aim of the study was to compare the diagnostic accuracy of International Ovarian Tumor Analysis simple rules and risk of malignancy index IV scoring to differentiate between benign and malignant adnexal masses pre-operatively.

METHODS

An observational analytical study was carried out among all patients diagnosed with adnexal mass and planned for staging surgery admitted in Nobel Medical College Teaching Hospital from September 2024 - April 2025. Convenient sampling technique was done. Ethical approval was taken from Institution Review Committee of the college. Demographic data were collected. Ultrasound evaluation was done according to IOTA simple rules and peripheral blood sample was collected for serum CA 125 measurement and RMI IV was calculated. During ultrasound evaluation, the morphology of the adnexal masses was assessed using 2D real-time and color Doppler ultrasound. Adnexal masses were described according to origin, position, number of lesions, type of lesions, size, volume, intracystic fluid echogenecity, number of locations; presence and size of septations, presence, number, size of solid papillary projections, largest solid component; presence of ascites. Noted parameters were designated according to the IOTA-SR group. Size of Tumor, CA 125, Age, Menopause and histopathology report variables were studied. Demographic data were expressed in frequencies and mean. Sensitivity, specificity, positive predictive value (PPV), negative predictive values (NPV) and Diagnostic Accuracy (DA) of RMI IV and IOTA type were calculated. Paired T test was applied to compare size of tumor and CA 125. Chi Square test was applied in comparison of categorial data. The area under the reciever operating characteristic curve (AUROCs) curve was used to compare diagnostic accuracy of RMI IV and IOTA-SR. Statistical analysis were performed using 95% CI, considering $p < 0.05$ and comparing the clinical characteristics of groups classified as benign or malignant, using SPSS version 16. Histopathological report of the sample collected during the surgery was the final diagnosis. Tumors were classified according to the WHO histopathological classifcation.

RESULTS

The mean age of the patient was 42.67 ± 16 years (range 11-78) years. Out of the 52 women en-rolled in the study, 34 (65.38%) had benign tumors and 18 (34.6%) had malignant tumors. The youngest patient in the study was 11 years old and the eldest was 78 years old. Malignant tumors were seen maximum 27.7% (5/18) in the age group of 40-49 years. The maximum age distribution was presented between (21/52) 40-49 years (Table 1).

Table 1. Age distribution of ovarian mass (n=52)

		Final HPE		Total
		Benign	Malignant	
	< 20	2	2	4
	20-29	5	2	7
	30-39	4	4	8
	40-49	16	5	21
	50-59	1	2	3
	> 60	6	3	9
Total	34	18	52	
Menopausal Status	Pre-menopausal	25	9	34
	Post-menopausal	12	6	18
Total		37	15	52

There was no family history of any type of cancer. The major presenting features were lower ab-dominal pain 16 (30.8%), pelvic mass 10 (19.2%) and menstrual complaints 14 (26.9%). Other pre-senting complaints were abdominal distention 9 (17.3%), postmenopausal bleeding 1 (1.9%). 2(3.8%) cases presented as incidental findings on abdominal ultrasound (Fig. 1).

Among total 52 women, 7 (13.5%) were unmarried, 1 (1.9%) cases were nulliparous and majority 43 (82.7%) were parous women with maximum women being parity of three 43(82.7%).

Out of 34 benign tumors, the majority 25 (48%) were in the premenopausal age group by histo-pathology. Whereas

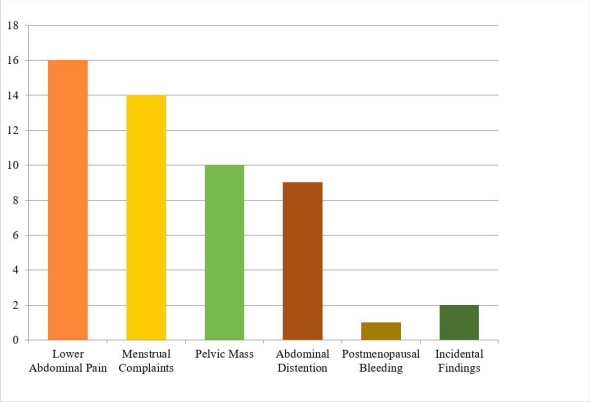

Figure 1. **Presenting features of adnexal mass**

there were 6 cases of malignant tumor in Postmenopausal women with all being Epithelial tumors. These findings showed that malignancy was more common in premeno-pausal group 12/18 (66.67%) than postmenopausal group 6/18 (33.33%).

There were equal number of benign and malignant tumors (13 Vs 12) in tumors larger than 7 cm in size. On Ultrasonography, solid components were found in 16 cases out of total 18 malignant cases. Increased blood flow in doppler was found in 7 cases out of 18 malignant ovarian tumor cases. Also, papillary projections were present in 1 case of malignant tumor.

Ultrasound- based IOTA and histopathological diagnosed ovarian pathology were compared. Out of total 52 cases, 20 cases were classified as malignant tumors by IOTA simple rules that was confirmed by histopathlogy in only 17 cases and 32 cases predicted by IOTA SR was confirmed to be benign in 31 cases. Sensitivity of IOTA SR was found to be 94.4%, specificity of 94.2%. Positive predictive value was 89.5%, negative predictive value of 96.9% and Diagnostic accuracy of 94.23% (Table 2).

Table 2. **Comparison of ovarian mass assesment by IOTA SR and RMI IV**

		Final HPE		Total
		Benign	Malignant	
IOTA SR	B Features	31	1	32
	M Features	3	17	20
	Total	34	18	52
RMI IV	< 450	31	2	33
	≥ 450	3	16	19
	Total	34	18	52

Different multiples of normal levels of serum CA 125 showed that only 20 out of 52 patients had normal CA 125 level whereas 18 cases were malignant. Among them, 17 had benign and 3 pa-tients had malignant tumor.

The graphical representation of multiples of CA-125 values alongside the nature of an ovarian tumor can be visualized as a graph. Two lines were drawn to show the relationship between CA-125 levels and tumor nature, indicating that higher CA-125 levels are associated with malignant tumors (Fig. 2).

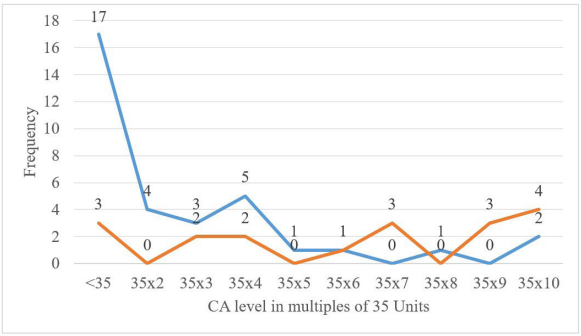

Figure 2. **Multiples of CA 125 value and nature of tumor (n=52)**

The histopathological diagnosis of benign ovarian mass shows that the most common is Serous Cystadenoma (12/34) followed by Endometrioma (10/34) and cases of Mucinous Cystadenoma with 9 out of 34 benign ovarian masses. Among Malignant tumors, the most common was Mucinous carcinoma (7/18) followed by Serous Adenocarcinoma(4/18).

On calculation of RMI IV and comparing it with the histopathology report, 33 cases out of total 34 benign cases had RMI IV < 450 whereas 19 malignant cases had RMI IV score of ≥ 450 which was confirmed by histopathology in 31 benign cases and 16 malignant cases only giving positive predictive value of 84.2%, negative predictive value of 94%. Sensitivity was found to be 88%, specificity of 91.2% and Diagnostic accuracy of 90.38%.

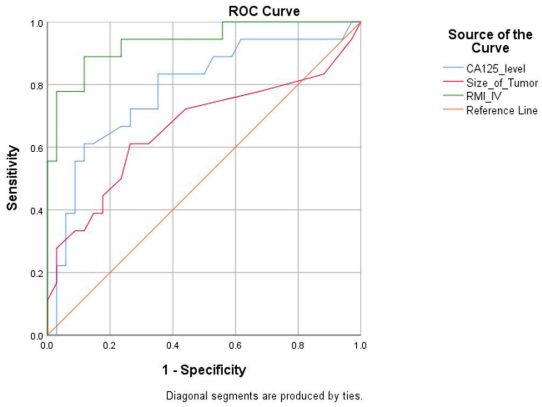

Figure 3. **Performance of Different Indexes in Predicting Ovarian Cancers**

In the above mentioned figure, all predictors demonstrated higher AUCs in discriminating benign and malignant ovarian masses. The RMI IV showed the highest AUCs of 0.936 followed by CA 125 of 0.783 AUC and Size of Tumor demonstrated AUCs of 0.662 in the present study. IOTA had better diagnostic performance than RMI IV (chi square test 36.45 Vs 32.53).

Table 3. Efficacy of IOTA and RMI IV scoring.

	TP	FP	TN	FN	PPV	NPV	Sensitivity	Specificity	Diagnostic Accuracy
IOTA SR	17	2	32	1	89.5%	96.9%	94.4%	94.2%	94.23%
RMI IV	16	3	31	2	84.2%	94%	88%	91.2%	90.38%

DISCUSSIONS

The mean age of the patient in current study was 42.67 ± 16 years which is simlar to several studies conducted in countries of Asian population, which does not comply with the study in Turkey by Guvey et al. where it was much higher of 54.4 ± 9.0 years.[2-12] The youngest patient in the study was 11 years and the eldest was 78 years old reflecting the broad age spectrum of ovarian tumor presentations which was similar to several studies (range 14-76) of nepal, (18-77) India, (19-75) Thailand.[6,9,10] This is due to the geographical difference as Turkey lies in western asia and europe with maximum incidence. This could also be explained by the differences in life expectancy among diverse geographical population distribution.

Most women were parous (82.7%), with only a small fraction being nulliparous (1.9%) and unmarried (13.5%). This high parity rate may reflect regional reproductive patterns, but also underscores the importance of considering reproductive history in ovarian tumor risk stratification.

Among total 52 women, 7 (13.5%) were unmarried, 1 (1.9%) case was nulliparous and majority 43 (82.7%) were parous women with maximum women being parity three 43 (82.7%). These findings doesn't comply with the study in developed countries where the incidence was 60-70% higher in unmarried women.[13]

Malignant tumors were seen maximum 27.7% (5/18) in the age group of 40-49 years. Malignancy was more common in 6th decade age group.[9] The maximum age distribution was presented between (21/52) 40-49 years which is similar to studies.[15]

In our study 6 cases out of 15 postmenopausal women were malignant similar to study.[7,12] Present study showed that malignancy was more common in premenopausal group 6/15 (40%) than postmenopausal group 9/15(60%). In contrary to our study, study resulted that malignancy was more common in postmenopausal patients (71.43%).[10] However our study sample size may not be adequate enough to draw inference in this regard. In addition, literature states that several reproductive and hormonal factors may lower risk, including parity while others such as older age at menopause and hormone replacement therapy confer increased risks.[13]

Out of the 52 women enrolled in the study, 34 (65.38%) had benign tumors and 18 (34.6%) had malignant tumors similar to several studies, that ranges from (47-98.3%) for benign cases and (5.3-23.5%) for malignant cases.[6-12,16] Our results were consistent with the existing literature that benign ovarian tumors are more common compared to malignant tumors. Overall the distribution of Ovarian Cancer aligns with global trends that report benign ovarian tumors are more prevalent.

On the other hand, results from seversl studies, are in contrary to ours.[15,17-19] Study by Pun et al. in 2018 found malignant tumors 56 (64.36%) more than benign ones 31 (35.6%) out of 87 cases.[15] This study was carried out at B.P. Koirala Memorial Cancer Hospital (BPKMCH), Chitwan, which is already an established comprehensive referral cancer center from throughout the peripheral hospitals of Nepal. Yet another study by Goel et al. at AIIMS new Delhi in 2019-2020 also had malignant tumors 43 (51.1%) more than benign 41 (48.8%) among total 84 ovarian tumors.[17] This is because AIIMS is a leading government medical institute known for its advanced cancer treatments, research, and comprehensive care with maximum referrals.

The major presenting features were lower abdominal pain 16 (30.8%), pelvic mass 10 (19.2%) and menstrual complaints 14 (26.9%). Other presenting complaints were abdominal distention 9 (17.3%), postmenopausal bleeding 1 (1.9%) and 2 (3.8%) cases presented as incidental findings on abdominal ultrasound. These nonspecific clinical features reinforce the diagnostic challenge posed by ovarian tumors, as symptoms often overlap between benign and malignant cases.

This study did not consider a family history of ovarian cancer, as none of the patients presented with a positive family history. Instead study conducted in Chennai, India had more than half (67.5%) of the study participants had reported to have a family history of carcinogenic lesions.[2] Literature mentions family history of the disease as one of the most significant risk factors for OC. Also, women in direct genetic lineage of family cancer syndromes have up to a 50% lifetime risk of ovarian cancer.[20]

Interestingly, 66.67% of malignant tumors were seen in premenopausal women, challenging the traditional notion that malignancies are more common in the postmenopausal group. However, this could reflect either a regional demographic shift or improved early diagnostic access in younger populations.

The histopathological diagnosis of benign ovarian mass shows that the most common is Serous Cystadenoma 35.29% (12/34) similar to studies and Endometrioma was most common benign lesion in study.[2,15,19] However in a study by Pradhan SB21 in Nepal and Tian et al. in China,

among the benign masses, ovarian dermoid cysts were the most common.[14]

Among Malignant tumors, the most common was Mucinous carcinoma 38.89% (7/18) in present study whereas Serous Adenocarcinoma was the most common in several other studies.[2,14,15,19]

In current study, 61.5% (32/52) of the study population had CA 125 values > 35 units per ml. Also in studies, the CA-125 concentration (U/mL) was significantly higher in malignant masses than in the benign group.[2,17] However, high levels of CA-125 may be found in endometriosis and especially so in cases of ruptured endometrioma and advanced stage. The suspicion of malignancy in reproductive age group women with adnexal mass, therefore should not be based only on CA- 125 levels because there are various non-malignant gynecological lesions that can also be associated with high CA-125 levels.[22]

The strength of the present study is that IOTA SR assesment and RMI IV scoring were applied to the same patients using the same ultrasound machine by an experienced radiologist allowing an ideal comparison. IOTA SR's sensitivity was found to be signifcantly greater than RMI-4's (80% vs 60.7%) when used by senior physicians in a study by Guo et al. in 2022, while specifcity was only slightly lower (92.4% vs 95.3%).[23]

In the present study, the diagnostic accuracy of IOTA SR was superior to RMI-4 with 94.23% and 90.38% respectively. Diagnostic accuracy in present study of RMI IV was 90.38% and Yamamota et al. also calculated it to be 90.4% which is similar.[4]

Though, IOTA simple rules have been tested for effectiveness by several studies the findings of our study are comparable to them (Table 4).[7-12,14,16,19] The outcomes were comparable and diagnostic accuracy of IOTA SR ranges from (82.5-93.3%).

In this study, CA125 levels were raised (> 35 U/ml) in 32 (61.5%) study subjects, among whom 26/32(81.25%) were premenopausal. Due to predominantly premenopausal patients, the sensitivity of RMI-4 might be raised. In the present study, RMI IV had lower diagnostic accuracy than IOTA simple rules (90.38% Vs 94.23%). There was no inconclusive cases in IOTA SR assesment resulting in higher diagnostic accuracy.

In the present study the median of the maximal diameter of the lesion was 7 cm. The minimum size was 3 cm and maximum was 30 cm of size of tumor. There were equal number of benign and malignant tumors (13 Vs 12) in tumors larger than 7 cm in size.

Also a study by Guvey et al. showed the median of the maximal diameters of the lesions was 7.8 cm.[12] The study also showed that preoperatively yielded sensitivity of 100% and specificity of 31.3% for the tumor size as determined by the ultrasound respectively.

Study suggested that International ovarian tumor analysis (IOTA) scoring system is a simple, clinically feasible diagnostic tool that accurately distinguishes benign from malignant adnexal pathologies.[24] IOTA simple rules had higher diagnostic accuracy compared with RMI to discriminate between benign and malignant adnexal masses resulting in inconclusive cases of nearly 20%, 11.9% and 6% in another study requiring expert opinion.[8,10,17] Our study had no inconclusive cases suggesting IOTA is highly effective.

For inconclusive cases, study concluded that Combining the IOTA simple rules with Contrast-enhanced Ultrasound (CEUS) significantly improves diagnostic accuracy in distinguishing benign from malignant adnexal masses.[14]

Both the IOTA-SR and RMI Index has good diagnostic predictive value with IOTA-SR having superior sensitivity and specificity in the diagnosis of adnexal malignancy. RMI Index is useful and superior in diagnosing serous malignancy, but IOTA-Simple Rules is able to diagnose all tumors such as serous, mucinous tumors, sex cord stromal tumors, and germ cell tumors as IOTA-SR is independent of CA-125. Use of IOTA-SR widely has chances to reduce inter-observer and Intra-observer variation. Hence this study recommends the use of IOTA-SR for diagnosis of ovarian malignancies in an early detectable stages.[2] Also study suggested IOTA SR as cost effective method with a short learning curve to differentiate the adnexal mass from a benign or malignant.[25]

Our findings are in contrast to the previous report of Sebina et al.[26] The efficacy of Ultrasound IOTA SR was sensitivity 90.90%, Specificity 60% and Diagnostic accuracy of IOTA SR was 79.24% whereas RMI 4 score had sensitivity 96.96% and specificity 60% and Diagnostic accuracy was 83.01% but here only 53 patients were involed over 3 years of study.

The study concluded that the most important factor in ovarian malignancy is time of detection.[9] Quality of cytoreductive surgery and surgical staging/lymph node dissection are important prognostic factors in ovarian cancer. Early detection and treatment would improve the survival significantly.

The overall diagnostic performance of IOTA SR and RMI IV for predicting ovarian Tumor was assesed by Area Under Reciever Operating Characteristic Curves (AUROCs). The RMI IV showed the highest AUCs of 0.936 followed by CA 125 of 0.783 AUC and Size of Tumor demonstrated AUCs of 0.662 in the present study. This study reveals that diagnostic performance of IOTA SR is better for prediction of adnexal mass in comparison to RMI IV(chi square test 36.45 Vs 32.53).

This study is limited by its sample size and single-center design, which may limit the generalizability of results.

CONCLUSION

Comparison of IOTA Simple Rules with histopathology showed excellent diagnostic performance. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy were 94.4%, 94.2%, 89.5%, 96.9% and 94.23%, respectively, indicating strong agreement with final histological diagnosis. Similarly, RMI IV demonstrated good diagnostic utility, with a sensitivity of 88%, specificity of 91.2%, PPV and NPV were 84.2% and 94%,and diagnostic accuracy of 90.38%. The higher Area Under the Curve (AUC) for RMI IV (0.936) compared to CA 125 (0.783) and tumor size (0.662) emphasizes the advantage of using composite indices over single-parameter tools. The IOTA Simple Rules outperformed RMI IV in terms of overall diagnostic efficacy emphasizing its value in preoperative evaluation of adnexal masses.

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