Original Research Article

Diagnostic accuracy of the risk of malignancy index 1 compared to the more recent IOTA ADNEX model in discriminating benign from malignant adnexal masses: a multi-centric study

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ABSTRACT

Background: Identification of the nature of an adnexal mass can ensure optimum management. Single parameters as well as diagnostic models using a combination of several parameters are in use. The International Ovarian Tumor Analysis (IOTA) consortium has developed and published the Assessment of Different NEoplasias in the adneXa (ADNEX) model, which differentiates between benign and malignant masses. Authors conducted this study with the aim of finding a cut off value for this model in the study population and comparing the diagnostic accuracy of this model to that of the risk of malignancy (RMI).
Methods: Women with adnexal masses admitted to the 3 medical college affiliated hospitals for surgical management were included in this study. Appropriate investigations were done to calculate the RMI-I and ADNEX score for each participant. A cut off score for the ADNEX model was determined and diagnostic accuracy tests were done for comparison.
Results: At a cut-off of 29 for the ADNEX model and 200 for RMI model the sensitivity was 75% and 77.8, specificity 100% and 80.6%; Positive Predictive Value (PPV) 100% and 60%; Negative Predictive Value (NPV) 91% and 90.6%; Positive Likelihood ratio of infinity and 4 and a negative Likelihood Ratio of 2.8 and 2.5 respectively.
Conclusions: The ADNEX model rates higher than the RMI in almost all tests of diagnostic accuracy and can be used for triaging, framing a referral policy and prioritizing surgery.

Keywords: Adnexal mass, IOTA ADNEX model, Risk of Malignancy Index (RMI), Tests of diagnostic accuracy

INTRODUCTION

Ovarian masses are one of the most common problems faced by a practicing gynecologist. Single parameters as well as diagnostic models using a combination of several parameters are in use to distinguish benign from malignant.[1-4] The Royal College of Obstetrics and Gynecologist (RCOG) recommends RMI I as a validated tool to distinguish benign from malignant masses. A cut off of 200 with a sensitivity of 78% and a specificity of 87%, or a cut off of 250 with a lower sensitivity (70%) but higher specificity (90%) are equally good to plan management The American College of Obstetricians and Gynecologists (ACOG) in its guidelines advocates referring the patient to an oncology centre if the CA-125 is greater than 35 in a post-menopausal woman and greater than 200 in a premenopausal woman.[5,6] Recently the International Ovarian Tumor Analysis (IOTA)

consortium has developed and published the Assessment of Different Neoplasias in the adnexa (ADNEX) model, which differentiates between benign and four types of malignancy namely borderline, stage I cancer, stage II-IV cancer, and secondary metastatic cancer. As with other models it suggests that every clinical setting should define their own cut offs for management as well as referrals.[7] Knowing the nature of the mass goes a long way in the preparedness for dealing with it. Whether they should be operated, who should operate, where and how the operation needs to be done and how the patient and her attendants are to be counselled are important questions that need answers.[1] This combined with the fact that the cut off for diagnostic models should be determined as per the clinical setting authors conducted this study with the aim of finding a cut off for the IOTA model in present study population and comparing the diagnostic accuracy of this model with that of the RMI-1 model which authors had been being used for planning the management of adnexal masses. The objectives of the present study are determining a cut off for the IOTA ADNEX model, to distinguish between benign and malignant adnexal masses in the study population and comparing the diagnostic accuracy of RMI 1 with the IOTA ADNEX model using the above cut off.

METHODS

Data collection

Women with adnexal masses admitted to the 3-medical college affiliated hospitals for surgical management were included in this study. Women with adnexal masses who were either managed conservatively, were not fit for surgery or denied surgery were excluded. Informed consent (Appendix-1) was obtained from all participants.

Transvaginal ultrasound was performed and if the mass was too big to be observed completely a trans-abdominal scan was also done. Serum CA-125 levels were measured using Electro-Chemi-LuminescenceImmuno-Assay (ECLIA). Based on the data collected the RMI-1 Score and IOTA ADNEX percentage for each participant was calculated (Appendix-2 and Appendix-3 respectively).

Using Histopathology as the reference standard, the data analysis was done in two parts:

- Finding the cut off for the IOTA model using a ROC curve.
- Comparing the RMI model with the IOTA using different tests of diagnostic accuracy

Choosing a cut off for the ADNEX model

Using the sensitivities and specificities of the IOTA ADNEX an ROC curve was plotted (Appendix 4). Area Under Curve (AUC) value 0.978 (p value<0.001) shows that IOTA has a very good predictive ability to discriminate benign from malignant adnexal masses.

For present study authors chose the cut off value as 29.29 which had a sensitivity of 75% and a specificity of 100%. This is quite comparable to the sensitivity and specificity values for the RMI cut off of 200.

Table 1: For analysis of the data.

		The gold standard test (histopathology)		
The test to be assessed (RMI or IOTA)		Disease (Number)	Non- disease (Number)	Total (Number)
	Positive (Number)	A (true positive)	B (false positive)	Test positive
	Negative (Number)	C (true negative)	D (false negative)	Test negative
		T (disease)	T (non-disease)	Total

Sensitivity= (a / a+c) x 100, Specificity= (d/ b+d) x 100, Positive predictive value= (a/a+b) x100, Negative predictive value = (d/c+d) x100, Positive Likelihood Ratio = Sensitivity / 1-Specificity, Negative Likelihood Ratio=1-Sensitivity/Specificity, Diagnostic accuracy = (a+d)/Total

Thus, participants having a risk calculation of 29 and above were taken as having malignant masses and those with calculation below 29 were taken to be benign.[5] The centers where this study was done are not oncology centers. Suspected malignancies requiring surgery are referred to an oncology centre where the management is done by a multidisciplinary team. One of the main reasons why the study was done was to improve triaging, referrals and prioritizing surgeries. The 29 cut off has the maximum sensitivity for 100% specificity. Comparing the RMI model with the IOTA using different tests of diagnostic accuracy. There are several measures that relate to the different aspects of the diagnostic procedure. For present study authors calculated the sensitivity, specificity, positive and negative likelihood ratios, positive predictive value (PPV) and negative predictive value (NPV) and diagnostic accuracy. Discriminatory tests like sensitivity and specificity are not affected by disease prevalence whereas tests used to assess the predictive ability are affected by disease prevalence.[8,9] Sensitivity, specificity and the likelihood ratios are methods that can be used to frame policies for triaging patients. Since these values are not affected by disease prevalence they can also be extrapolated to other

populations.[10,11] PPV, NPV and diagnostic accuracy are predictive methods which are useful in predicting the probability of malignancy in an individual case and could help the clinician in counseling the woman and her family. Since these values are dependent on disease prevalence, they are useful in knowing the probability of malignancy in a particular individual and are not applicable to other settings. In this study of diagnostic accuracy, authors have also included all the items listed in STARD: Standards for Reporting Diagnostic accuracy studies. (Appendix-5) This list of items was developed to contribute to the completeness and transparency of diagnostic accuracy studies.[10,11]

RESULTS

The mean age of the participants was 44 years with a Standard Deviation (SD) of 14.86 (Table 2). Using

Histopathology as the gold standard for diagnosing malignancy the RMI had 21 true positives (a), 14 false positives (b), 6 true negatives (c) and 58 false negatives (d) (Table 3).

Table 2: Age distribution.

	Mean	Standard Deviation (SD)
Age (in years)	44.65	14.86

Table 3: Cross tabulation for risk of malignancy index (RMI).

		Cancer		
		Yes	No	Total
RMI	Positive	21 (a)	14 (b)	35 (a+b)
	Negative	6 (c)	58 (d)	64 (c+d)
	Total	27 (a+c)	72 (b+d)	99 (Total)

Table 4: Summary measures for risk of malignancy index (RMI).

Statistics	Formula	Calculation	Value	95% CI
Prevalence	(Disease / Total) *100	(27/99) x 100	27.3 %	18.8-37.1 %
Sensitivity	(a / a+c) *100	(21/27) x 100	77.8 %	57.7-91.4 %
Specificity	(d/ b+d) *100	(58/72) x 100	80.6 %	69.5-88.9 %
Positive Predicted Value	(a/a+b)*100	(21/35) x 100	60 %	42.1-76.1 %
Negative Predicted Value	(d/c+d) *100	(58/64) x 100	90.6 %	80.7-96.5 %
Positive Likelihood ratio	Sensitivity / 1-Specificity	0.778/1-0.806	4	2.4-6.67%
Negative Likelihood ratio	1-Sensitivity/Specificity	1-0.778 / 0.806	0.28	0.13-0.56%
Accuracy	(a+d)/Total	(21+58)/99	79.8 %	70.5-87.2%

Table 5: Cross tabulation for IOTA ADNEX model.

		Cancer		
		Yes	No	Total
IOTA ADNEX	Positive	21 (a)	0 (b)	21 (a+b)
	Negative	7 (c)	71 (d)	78 (c+d)
	Total	28 (a+c)	71 (b+d)	99 (Total)

Table 6: Summary measures for IOTA ADNEX model.

Statistics	Formula	Calculation	Value	95% CI
Prevalence	(Disease / Total) *100	(28/99) x 100	28.3 %	19.7- 38.2 %
Sensitivity	(a / a+c) *100	(21/28) x 100	75 %	55.1-89.3 %
Specificity	(d/ b+d) *100	(71/71) x 100	100 %	94.9-100 %
Positive predicted value	(a/a+b)*100	(21/21) x100	100 %	83.9-100 %
Negative predicted value	(d/c+d) *100	(71/78) x100	91 %	82.4-96.3 %
Positive likelihood ratio	Sensitivity / 1-Specificity	0.75/1-1	Infinity	-
Negative likelihood ratio	1-Sensitivity/Specificity	1-0.75 / 1	0.25	0.13-0.47%
Accuracy	(a+d)/Total	(21+71)/99	%	86-97.1%

The RMI-1 model demonstrated a sensitivity of 77.8%; specificity of 80.6%; Positive Predictive value (PPV) 60%; Negative Predictive Value (NPV) 90.6%; Positive Likelihood ratio of 4, a Negative Likelihood Ratio of 2.5 and an accuracy of 79.8% in present study population

(Table 4). Again, using Histopathology as the gold standard for diagnosing malignancy the IOTA ADNEX Model had 21 true positives (a), 0 false positives(b) ,7 true negatives (c) and 71 false negatives (d) Table 5. The ADNEX model demonstrated a sensitivity of 75%;

specificity 100%; Positive Predictive Value (PPV) 100%; Negative Predictive Value (NPV) 91%; Positive Likelihood ratio of infinity, a negative likelihood ratio of 2.8 and an accuracy of 92.9% in present study population (Table 6).

DISCUSSION

An Area under Curve (AUC) value of 0.978 (p value<0.001) shows that IOTAADNEX has a very good predictive ability to discriminate benign from malignant adnexal masses

The overall findings demonstrated that the ADNEX Model is a better diagnostic tool as compared to RMI 1 and can help triage and counsel patients better . At a ≥29 cut off the specificity of the ADNEX Model is remarkably higher than the RMI and the sensitivity of both the models is quite comparable (75% and 77.8% respectively) Other Studies assessing the reliability of the ADNEX Model have also found that this model has a high performance when discriminating between benign and malignant adnexal masses.[12,13]

In present study using the cut off of 29 for the ADNEX model gives a 100% specificity and is much higher than that of RMI -1 (Specificity 80% CI 70 -89). Clinically this means that when an ADNEX score is < 29 % authors would confidently go for surgery at our centre and a referral to an oncology centre would not be required. In terms of sensitivity the RMI and ADNEX model are almost similar (77.8% and 75 %respectively). These findings could be extrapolated to other populations

Positive and negative likelihood ratios are also independent of disease prevalence. A positive likelihood ratio of more than 10 is the best indicator of ruling in the disease.[9,10] In present study the ADNEX had a positive likelihood ratio of infinity when compared with 4 of the RMI which indicates that an ADNEX score of ≥29 is the best indicator of malignancy in a woman with an adnexal mass, necessitating referral to an oncology centre. The Negative likelihood ratio: for ruling out malignancy (when the score is <29), although not ideal (<0.1), is slightly better for the ADNEX model (0.25) than for RMI 1 (0.29).

The positive and the negative predictive values are dependent on disease prevalence and so these values from one study population cannot be extrapolated to other situations. Nevertheless, they can be used for counseling the woman and her relatives. In this study the positive predictive value of the ADNEX is 100% whereas that of the RMI is only 60%. So, a woman with an adnexal mass having an IOTA score ≥29 can be counseled for management in an oncology centre.

The negative predictive value of both the tools are quite high, as well as similar (ADNEX 91% and RMI 90.%) This means that a mass which has an ADNEX score of

<29 and an RMI score of <200 has a 90-91% chance of being benign. It has been seen in other studies that have used RMI as a diagnostic tool that endometriosis gives rise to a lot of false positive results which leads to decrease in the specificity of RMI 1. This study shows that using the IOTA can successfully overcome the specificity problem (eliminating the false positives).

Since the sensitivity still remains an issue with the IOTA ADNEX Model authors analyzed the 7 false negatives cases. Two were borderline tumors, one was a metastatic tumor from the stomach, 4 were unilocularmucinous cystadenocarcinomas with one to two papillary projections with a total diameter ranging from 7-10 and all of these four did not have an elevated CA-125 level.

These 4 mucinous cystadenocarcinomas most probably belonged to the that subgroup of mucinous ovarian malignancies which do not secrete CA-125 and instead are found to have an elevated CA 19.9 . Incorporating CA 19.9 into the IOTA model may make a difference to the sensitivity. However more studies need to be conducted on this subgroup of cases to justify including this parameter.

CONCLUSION

Adding tumor specific sonographic parameters has made the IOTA ADNEX Model a better diagnostic tool to assess the nature of an adnexal mass and it outperforms the RMI 1 on almost all tests of diagnostic accuracy.

When it comes to counselling individual patients since the ADNEX and RMI have a high Negative predictive value, either an ADNEX value of <20 or an RMI value of <200 or both together can be used to reassure the patient and her relatives about the benignity of the mass.

Since the positive predictive value of the IOTA is 100 % an IOTA value of ≥29 would help in counselling the patient and her relatives for immediate referral and request the referral centre for prioritizing the treatment to obtain optimal results.

Because ADNEX model has a much higher specificity it has helped in excluding many false positives due to endometriosis.

The sensitivity is still not ideal probably because border line and a subgroup of uniloculated, relatively small mucinous tumours, with one or two papillary projections were missed (false negatives). Addition of CA 19.9 which is found elevated in this subgroup of mucinous tumors may increase the sensitivity of this model.

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Appendix 1

Consent Form

Dear Participant,

This is a study on ovarian tumors being done at 3 medical colleges. As per this study all women like you who have an ovarian tumor and are about to undergo surgery will be included in this study. As a part of this study, data about the sonographic findings and blood test levels of women like you with ovarian tumors will be collected. The information gathered will not allow identification of you as an individual and will only be used for scientific purposes

Yours,

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Principal Researcher

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I ……………. give my consent for participation in this educational project. I understand that the data collected from the Questionnaire will be used for research purposes

Appendix 2

Risk of Malignancy Index - 1 (Jacobs et al. 1990)

The Risk of Malignancy Index was calculated by

U x M x CA-125, where a total ultrasound score of 0 made U =0, a score of 1 made U =1, and a score of ≥2 made U =3; premenopausal status made M =1 and postmenopausal M =3. The serum level of CA125 was applied directly to the calculation. The cut off level was selected at 200 above which was considered to indicate malignancy.

Appendix 3: IOTA ADNEX variables

Age in years (Range 14-100yrs)

Oncology Centre (Yes\No)

Maximum diameter of the lesion in mm (Range 8-400mm)

Maximum diameter of the solid part in mm (0 or ≥ 3mm)

More than 10 locules (Yes\No)

Papillary projections (none, one ,two, three or more than 3)

Acoustic shadowing (Yes\No)

Ascites (Yes\No)
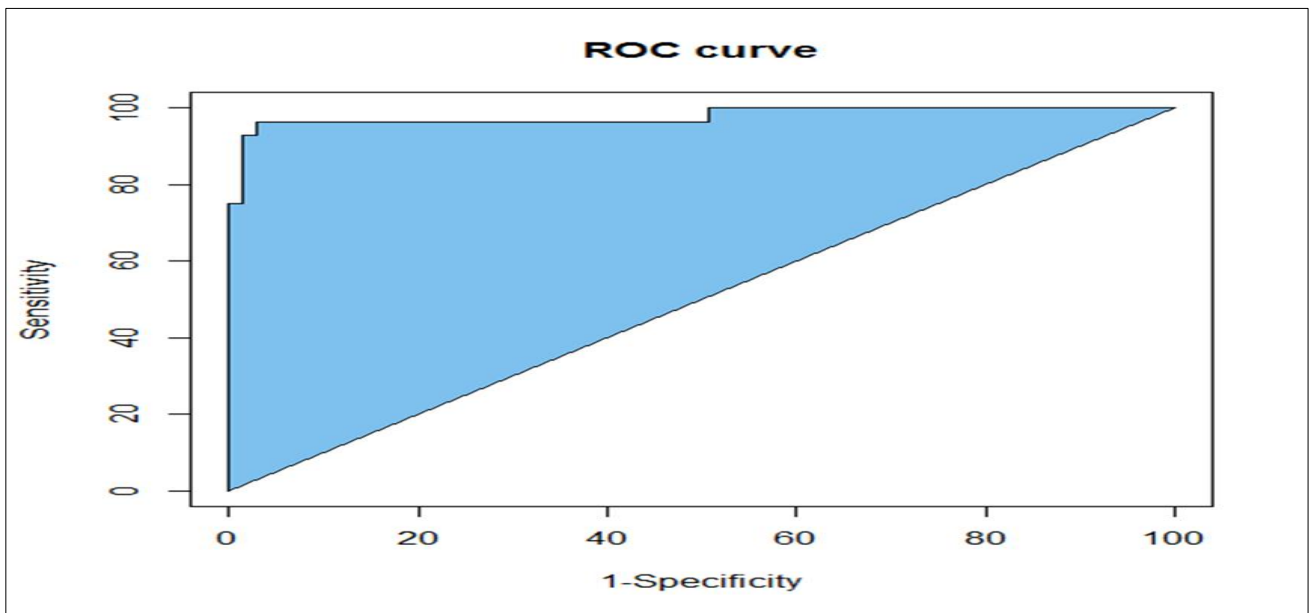
CA-125 (Range 1-30,000 U\mL)

An on line calculator is available at

https://www.iotagroup.org/sites/default/files/adnexmodel/IOTA%20%20ADNEX%20model.htm

Appendix 4: ROC curve and the coordinates of the curve

Test Result Variable(s): IOTA		
IOTA percentage	Sensitivity	1 - Specificity
-.2000	1.000	1.000
.8500	1.000	0.986
1.0000	1.000	0.930
1.1000	1.000	0.915
1.1500	1.000	0.817
1.2500	1.000	0.746
1.4000	1.000	0.690
1.5500	1.000	0.606
1.6500	1.000	0.563
1.7500	1.000	0.507
1.8000	0.964	0.507
1.8500	0.964	0.479
1.9500	0.964	0.408
2.0500	0.964	0.394
2.1500	0.964	0.338
2.2000	0.964	0.282
2.2500	0.964	0.254
2.3500	0.964	0.225
2.4500	0.964	0.197
2.6500	0.964	0.169
2.8500	0.964	0.141
3.0000	0.964	0.127
3.1500	0.964	0.113
3.4000	0.964	0.085
3.6500	0.964	0.070
3.7000	0.964	0.056
3.8000	0.964	0.042
4.1000	0.964	0.028
4.9000	0.929	0.028
5.5500	0.929	0.014
7.5000	0.893	0.014
11.1500	0.857	0.014
15.3000	0.821	0.014
19.4500	0.786	0.014
23.3000	0.750	0.014
29.9500	0.750	0.000
40.3500	0.714	0.000
51.4500	0.679	0.000
57.6500	0.643	0.000
67.1500	0.607	0.000
77.8000	0.571	0.000
81.0500	0.536	0.000
82.7000	0.500	0.000
85.8500	0.464	0.000
88.7000	0.429	0.000
89.7500	0.393	0.000
92.8500	0.357	0.000
95.3000	0.321	0.000
96.7000	0.286	0.000
98.2500	0.250	0.000
98.7500	0.214	0.000
98.9500	0.179	0.000
99.0500	0.143	0.000
99.3500	0.071	0.000
99.7500	0.036	0.000
100.9000	0.000	0.000

Appendix 4: ROC curve and the coordinates of the curve

Appendix 5: STARD guidelines

Present study	STARD guidelines
Tests of diagnostic accuracy	
Sensitivity, Specificity, Likelihood Ratios, Positive and Negative Pred	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)
Abstract	
Abstract given as per STARD Guidelines	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)
Introduction	
Introduction as per STARD Guidelines	Scientific and clinical background, including the intended use and clinical role of the index test
To establish a cut off for the IOTA ADNEX model in our population 2) Compare the ability of RMI1 and ADNEX IOTA Model to differentiate between benign and malignant adnexal masses	Study objectives and hypotheses
Methods	
Study design: Data collection planned before index test (prospective study)	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)
Participants	Eligibility criteria
All women with a diagnosis of an adnexal mass scheduled for surgery	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)
Three centers from 2017-2018	Where and when potentially eligible participants were identified (setting, location and dates)
Consecutive	Whether participants formed a consecutive, random or convenience series
Test methods	
Risk of Malignancy Index RMI (detailed in appendix) IOTA ADNEX Model (detailed in appendix)	Index test, in sufficient detail to allow replication
Reference standard histopathology	Reference standard, in sufficient detail to allow replication
Histopathology golden and final diagnosis alternatives do not exist	Rationale for choosing the reference standard (if alternatives exist)
Cut off for RMI as specified by RCOG is 200 The cut off for the ADNEX IOTA Model was calculated using an ROC	Definition of and rationale for test positivity cut-offs or result categories of the index test
No cut offs in Histopathology it would be either yes for malignancy and no for benign	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory
No	Whether clinical information and reference standard results were available to the performers/readers of the index test
No	Whether clinical information and index test results were available to the assessors of the reference standard
Analysis	
Statistical software for calculation of al the tests specified above	Methods for estimating or comparing measures of diagnostic accuracy
There were no indeterminate tests	How indeterminate index test or reference standard results were handled
There were no missing data	How missing data on the index test and reference standard were handled
No variability	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory
	Intended sample size and how it was determined

Results	
Participants	
Specified in results section	Baseline demographic and clinical characteristics of participants
Not assessed	Distribution of severity of disease in those with the target condition
Endometriosis	Distribution of alternative diagnoses in those without the target condition
Time interval mean 7 days No clinical interventions in between	Time interval and any clinical interventions between index test and reference standard
Test results	
Specified in results section	Cross tabulation of the index test results (or their distribution) by the results of the reference standard
Specified in results section	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)
Nil	Any adverse events from performing the index test or the reference standard
Discussion	
Specified in discussion	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability
Specified in discussion	Implications for practice, including the intended use and clinical role of the index test