Section: Radiodiagnosis

Original Research Article

NEED TO MODIFY THE OPTIMAL CUT OFF FOR BEST DIAGNOSTIC PERFORMANCE OF IOTA ADNEX MODEL FOR MALIGNANT ADENXAL MASSES

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ABSTRACT

Background: Adnexal masses are a common finding on pelvic ultrasound Ultrasonography is used for preoperatively identifying an adnexal mass as benign or malignant and ultimately guiding further management. The IOTA ADNEX model introduces objectivity to facilitate this differentiation. The study aimed at evaluating the performance of IOTA ADNEX model in preoperatively discriminating the nature of adnexal masses and also comparing the performance of the IOTA ADNEX model with subjective radiological assessment in characterising the masses.

Materials and Methods: The study was conducted on women presenting with symptomatic adnexal masses which were evaluated by pelvic ultrasound and characterised as benign or malignant using IOTA ADNEX Model. Simultaneously the same patient was evaluated by a sonologist who also characterised the adnexal mass as benign, indeterminate or malignant based on subjective assessment. The diagnostic performance of IOTA ADNEX model at various cut-offs was compared with sonologist's assessment taking the histopathology of the adnexal mass as reference standard.

Results: The study comprised a total of 49 patients.CA-125 level was found to be a statistically significant predictor (p-value < 0.001) in differentiating between benign and malignant adnexal pathologies. The means of "maximum diameter of lesion" and "maximum diameter of largest solid component" were also significantly higher in groups with malignant ovarian pathologies (p-values of 0.029 and <0.001 respectively).Acoustic shadow was present in 13.79% patients with benign lesions and none in malignant ovarian neoplasms with a significant p value of <0.001.

The diagnostic performance ROC Curve of the IOTA ADNEX model showed an AUC of 0.707 [95% CI (0.560-0.828)] at a standard cut off of 10% and 0.962 [95% CI (0.861-0.995)] at the proposed cut off of 47.1%. At a cutoff of 47.1%, the model demonstrated a sensitivity and specificity of 95% [95% CI (75.1 - 99.9)] and 89.66% [95% CI(72.6-97.8%)] respectively. The AUC of the subjective assessment method was found to be 0.776 [95% CI(0.634 to 0.883)] with a sensitivity of 100% [95% CI (83.2 to 100)] and specificity of 55.17% [95% CI (35.7-75.6)]. When comparing the AUCs between the ADNEX model and subjective assessment method, significant difference was found between the two assessments when using the proposed cut-off of 47.1%, in which case the IOTA ADNEX model was found to be more specific (p-value = 0.002).

Conclusion: IOTA-ADNEX is undoubtedly a promising ultrasound based model which can precisely differentiate adnexal masses as benign or malignant preoperatively and merits clinical application. We found 47.1% as the optimal

cut-off of the model for our tertiary level oncology setup which provided both high sensitivity and specificity as compared to the standard 10% cut-off. Based on our study, we propose higher cut-offs to be used with the IOTA-ADNEX model when being applied in oncological institutes to avoid unnecessary surgeries for benign pathologies.
Keywords: Adnexal Mass; Malignancy; IOTA ADNEX; Radiologist; Subjective assessment.

INTRODUCTION

Adnexal masses are a common finding on pelvic ultrasound. They are diagnosed either in patients presenting with pelvic symptomatology or sometimes incidentally on scans done for other indications. Most of the incidentally detected adnexal lesions are benign and show typical imaging features which are diagnostic eg. hemorrhagic cyst, dermoid cyst and endometriotic cyst. However, ultrasound is also usually the first imaging modality to diagnose or suspect malignant ovarian masses. Ovarian cancer is one of the most common gynecological cancers with the highest mortality rates amongst cancers of the reproductive organs. According to WHO reports, the worldwide annual incidence of ovarian cancer in the year 2020 was 3,13,959 with 207252 deaths. India itself reported 45,701 new cases and 32,077 deaths due to ovarian cancer in the same year.[1] Early detection at a lower stage can significantly improve the 5 year survival rates of patients with ovarian cancers.[2]

Ultrasonography can be utilized for preoperatively identifying an adnexal mass, characterizing it as benign or malignant and ultimately guiding further management.[3] Differentiation of benign and malignant adnexal masses aids the surgeon to decide the plan of action i.e whether the mass requires observation, surgery or additional work up including serum tumor markers or further radiological investigations like CT or MRI.[4] However, precise differentiation between benign and malignant adnexal masses by subjective assessment on ultrasound alone can sometimes be challenging.

In an attempt to introduce objectivity, multiple scoring systems have been developed over the years to facilitate differentiation between benign and malignant adnexal lesions. Early examples of these included the Risk of malignancy index (RMI) and Risk of malignancy algorithm (ROMA) scoring models.[5-7] In 2000, the International Ovarian Tumor Analysis [IOTA] group agreed upon certain terms, definitions and measurements for adnexal masses on ultrasound,[8] and presented logistic regression models for diagnosing ovarian cancers.[9,10] The most recent addition to the scoring systems includes the ADNEX (Assessment of Different NEoplasias in the adneXa) model developed by the IOTA group. The IOTA ADNEX model uses a mathematical algorithm with nine predictors to differentiate between benign or malignant adnexal masses. This model has been externally validated internationally by several centers in their respective populations.[11-15] Few studies are also looking at determining the optimal cut-off to obtain the best performance of the model. However, there are very few validation studies from India and none of these were carried out in a dedicated oncology center.

Our study aimed at evaluating the performance of the IOTA ADNEX model in preoperatively discriminating the nature of adnexal masses in the setting of a tertiary care oncology center in north India and also comparing the performance of the IOTA ADNEX model and subjective radiological assessment in characterizing the masses. We also attempted to find out the most optimal cut-off value to be applied when using the model in our settings in differentiating benign and malignant adnexal masses.

Aims and Objectives

- To assess the accuracy of the ADNEX model in classifying adnexal masses as benign or malignant.
- To compare the performance of the ADNEX model with subjective assessment in differentiating benign and malignant adnexal masses.
- To propose an optimal cut off risk percentage for the ADNEX model to rule out malignancy with acceptable sensitivity and specificity.

MATERIALS AND METHODS

Setting and location of study

This was a single center study performed in a tertiary care referral hospital in north India based on ultrasound data collected prospectively between March 2022 to August 2022 from patients with adnexal masses referred by the gynaecologic oncology department to the Radiology department for IOTA-ADNEX probability scoring and further characterisation. The study was approved by the Institutional ethics committee of Himalayan Institute of Medical Sciences, Jolly Grant, Uttarakhand, India.

Inclusion and exclusion criteria

The inclusion criteria were as follows

1. Presence of at least 1 adnexal mass
2. IOTA ADNEX model assessment requested and images stored in the system.
3. Serum CA-125 level at the initial presentation available
4. Surgery for the adnexal pathology (benign or malignant) in the institute
5. Histopathology report of the adnexal mass available

The exclusion criteria were as follows

1. Pregnancy

2. Previously diagnosed ovarian malignancy
3. Inclusion criteria not met

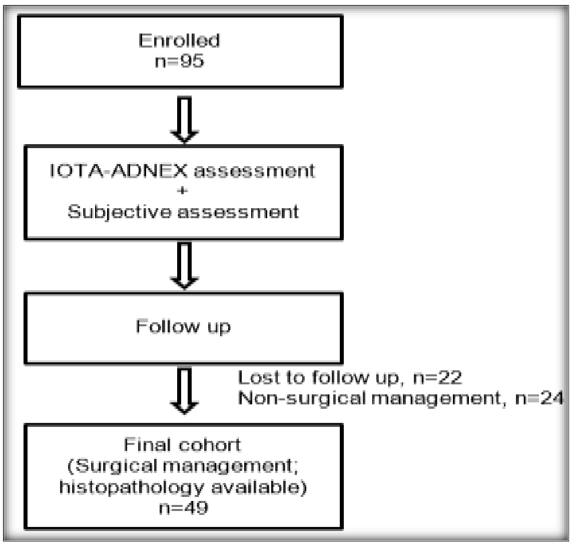
Equipment and methodology

Clinical and demographic parameters as well as the CA-125 levels of patients were recorded at presentation. Philips EPIQ 7G or 5G (Philips Healthcare, Andover, MA, USA) with transvaginal probes of 5.0–9.0 MHz and transabdominal probes of 2–7 MHz were used in the study. Transvaginal ultrasound was preferred except for patients with no prior sexual contact who were subjected to transabdominal ultrasound and those with large masses, in whom, a combination of transvaginal and transabdominal ultrasound was used.

The patients were scanned by two radiologists/sonologists, one assessing the masses by the ADNEX model and the other performing the subjective assessment of the lesions and providing a formal standard pelvic ultrasound report, each blinded to the other's result. The ADNEX model provided probability scores of benign v/s malignant masses while the subjective assessment model classified the masses into benign, malignant and indeterminate categories based on the findings. A standard threshold probability level of 10% was used to confirm benignity and rule out malignancy by the IOTA-ADNEX model with all masses with a probability score of more than 10% being considered potentially malignant. A copy of the IOTA-ADNEX model assessment was handed to the patient along with the formal ultrasound report.

Based on the IOTA-ADNEX probability score and subjective assessment, further course of action, either follow up, additional imaging, biopsy, laparoscopy, medical management or surgery, was decided by the referring surgeon.

On follow up, from amongst the 95 patients scanned, 49 patients were subjected to surgery and a final histopathological diagnosis was available for these patients. A retrospective analysis from records of these patients was done including their clinical and demographic parameters, IOTA-ADNEX score and subjective assessment category.



The ADNEX model

In 2014, the IOTA group developed the ADNEX model. The ADNEX model utilizes nine parameters, including patient's age, oncology center referral or not, maximum diameter of the lesion, maximum diameter of the solid part, presence of more than 10 locules, number of papillary projections, presence of acoustic shadows, presence of ascites and serum CA-125 levels, to calculate the probability score of benignity and malignancy. In addition, IOTA-ADNEX model also sub-classifies the malignant lesions into borderline, stage I, stage II-IV and metastatic ovarian cancer with relative probability of each being mentioned in the final analysis. At the time of the study, the IOTA-ADNEX model used was available freely on the internet on iotagroup.org website.

In accordance with the IOTA group's terminology and methods for assessing the morphology of ultrasonographic tumors[8] when a patient presented with multiple adnexal masses, the selection process involved choosing the mass with the most intricate ultrasound morphology. In cases where the masses exhibited similar morphologies, the larger mass was prioritized for analysis.[13]

Statistical Analysis: Statistical tools were employed to assess the performance of both the IOTA-ADNEX model and the subjective assessment method. The reference standard for this evaluation was the final histopathological diagnosis. Softwares used for statistical analysis included SPSS version 22.0 (IBM Corp, Los Angeles, CA, USA) and MedCalc version 15.2.2. For statistical purposes, the masses tagged "indeterminate" by subjective assessment were categorized as "malignant" for analysis.

To validate the IOTA-ADNEX model and the subjective radiological assessment model, we performed Receiver Operating Characteristic (ROC) curve analysis. Subsequently, the areas under the curve (AUCs) were calculated for both models. Comparison of AUCs between the two methods was done by a non-parametric approach, the DeLong method. All nine parameters of the IOTA-ADNEX model were individually assessed to look at the significance of each in diagnosing benign v/s malignant masses. In addition, we calculated the positive and negative likelihood ratios for different cut-off points and a threshold cut-off value with acceptable sensitivity and specificity to rule out malignancy was proposed.

RESULTS

During the time period from March 2022 to August 2022, a total of 95 women underwent US examination and IOTA-ADNEX evaluation for adnexal masses. Of these, 22 patients were lost to follow-up and 24 patients underwent non-surgical management. Hence, the final study group was of 49 patients who underwent surgery and met the inclusion criteria for the study.

Table 1: Histopathological diagnosis of adnexal masses

Total (49) N (%)	
Normal	1(2.04)
Benign	1(2.04)
Endometrioma	1(2.04)
Fibroma	6(12.24)
Cyst	3(6.12)
Mature cystic teratoma	8(16.32)
Mucinous cystadenoma	6(12.24)
Serous cystadenoma	2(4.08)
Chronic inflammation and necrosis	1(2.04)
Miliary Koch's	
Malignancy	
Mucinous adenocarcinoma	3(6.12)
Serous adenocarcinoma	10(20.41)
Granulosa cell tumor	1(2.04)
Sex cord stromal tumor	1(2.04)
Moderately differentiated carcinoma	1(2.04)
Poorly differentiated carcinoma	3(6.12)
Ovarian metastasis	1(2.04)

Table 2: IOTA ADNEX features of 49 women with benign and malignant adnexal masses

Characteristics	Benign (59.18) (29)	Malignant (40.82) (20)	P value
Age (in years)	40.83 +/- 17.46	48.65 +/- 13.21	0.127
CA-125	91.42 +/- 218.73	838.21+/- 1857.14	<0.001
Maximum Diameter of Lesion (in mm)	115.72 +/- 64.73	135.05 +/-40.09	0.029
Maximum Diameter of Largest solid component (in mm)	20.14. +/- 29.01	76.80 +/-40.34	<0.001
More than 10 locules	9 (31.03)	4 (20)	0.390
Papillary Projections Present	6(20.69)	10(50.00)	0.076
0	23 (79.31)	12(60.00)	
1	4 (13.79)	0(0.0)	
2	0 (0.0)	2(10.00)	
3	1(3.45)	3(15.00)	
>3	1(3.45)	3(15.00)	
Ascites	2 (6.89)	14(70.00)	0.083
Acoustic Shadow	4(13.79)	0(0.0)	<0.001

Of the total 49 patients who underwent surgery, 40.82% (n=20) had malignant ovarian tumors and 59.18% (n=29) were diagnosed to have benign adnexal lesions. The most prevalent benign masses included mucinous cystadenomas, serous cystadenomas, and simple cysts, while the most frequently encountered malignant tumors comprised serous adenocarcinomas, mucinous adenocarcinomas, and poorly differentiated carcinomas. Table 1 displays the final histopathological diagnoses for adnexal masses, while Table 2 presents the descriptive statistics for IOTA ADNEX ultrasound features related to these masses.

Patients with ovarian malignancies exhibited older age and higher serum CA-125 levels compared to individuals with benign masses. Amongst the two, only CA-125 level was found to be a statistically significant predictor (p-value < 0.001) in differentiating between benign and malignant adnexal pathologies. The means of "maximum lesion diameter" and "maximum diameter of largest solid component" were also significantly higher in groups with malignant ovarian pathologies (p-values of 0.029 and <0.001 respectively).

In our study, we found a greater percentage of benign adnexal pathologies to have more than 10 locules (31.03%) in comparison to ovarian malignancies (20%), the values, however, being statistically insignificant (p-value 0.390). On the other hand, 50% of ovarian malignancies contained papillary projections and 20.69 % of benign lesions showed papillary projections but again with non-significant p-value (p-value 0.076).

Fourteen out of 20 (70 %) women with malignant ovarian masses had ascites while only 2 out of 29 (6.89%) had ascites in the benign adnexal lesion group. Acoustic shadow was present in 13.79% patients with benign lesions. Of note, none of the malignant ovarian neoplasms demonstrated acoustic shadows. Between the two predictors, only acoustic shadow showed a significant p value of <0.001.

The ROC curve illustrated the diagnostic performance of the IOTA ADNEX model. The model's AUC for distinguishing between benign and malignant ovarian masses stood at 0.707 [95% CI (0.560-0.828)] with the standard cutoff of 10% and rose to 0.962 [95% CI (0.861-0.995)] with the proposed cutoff of 47.1%. The sensitivity of the model at cutoffs of 10%, 15%, 20%, 25% and 30% was 100%, 100%, 100%, 95% and 95% while the specificity at the respective cutoffs was 45%, 52%, 62%, 69% and 76%. At a cutoff of 47.1%, the model demonstrated a sensitivity and specificity of 95% [95% CI (75.1 - 99.9)] and 89.66% [95% CI(72.6-97.8%)] respectively. The AUC of the subjective assessment method was found to be 0.776 [95% CI(0.634 to 0.883)] with a sensitivity of 100% [95% CI (83.2 to 100)] and specificity of 55.17% [95% CI (35.7-75.6)]. The reduced specificity of the subjective assessment method could partly be attributed to the fact that the cases tagged "indeterminate" by subjective assessment were included under the "malignant" category for statistical analysis.

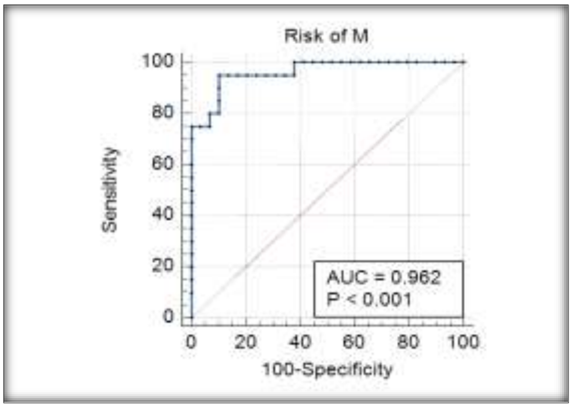


Figure 1: ROC curve of IOTA ADNEX model using proposed cut-off percentage of 47.1% in discriminating between benign and malignant adnexal masses using HPE diagnosis as reference

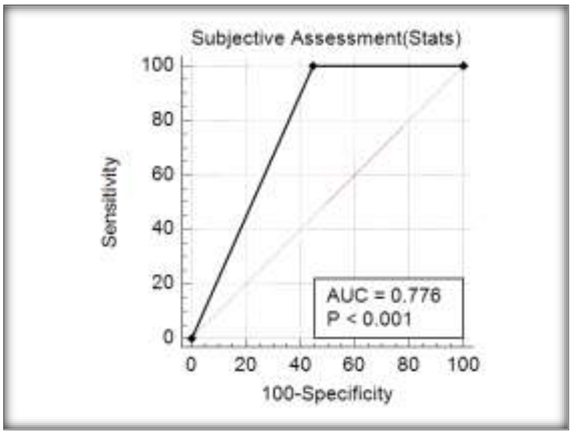


Figure 2: ROC of radiologist's subjective assessment in discriminating between benign and malignant adnexal masses using HPE diagnosis as reference

When comparing the AUCs between the ADNEX model at the standard 10% cutoff and the subjective assessment method using a nonparametric approach, no statistically significant difference was observed (p-value = 0.149). However, a significant difference was identified between the two assessments when employing the proposed cutoff of 47.1%. In this scenario, the IOTA ADNEX model demonstrated higher specificity (p-value = 0.002).

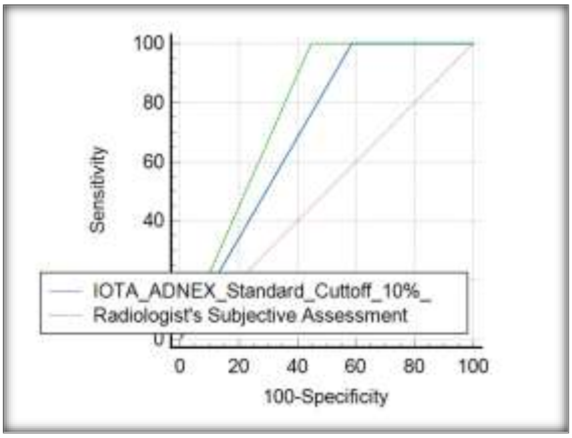


Figure 3: Comparison of ROCs of IOTA-ADNEX Model (standard cut off i.e 10%) and Radiologist's Subjective Assessment

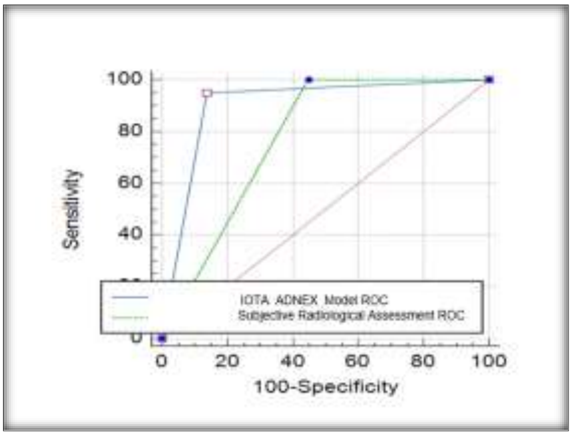


Figure 4: Comparison of ROCs of IOTA-ADNEX Model (proposed cut- off i.e 47.1%) and Radiologist's Subjective Assessment

DISCUSSION

Our study implemented the IOTA-ADNEX model within the context of a tertiary-level oncology hospital in North India. We included patients with adnexal masses who were operated on in our institute. The patients were pre-operatively assessed by both subjective radiological assessment and the IOTA-ADNEX model. Data analysis was then done using the final histopathological diagnosis as reference standard.

Application of the Youden index method in our study suggested 47.1% as the optimal cut off percentage with a sensitivity and specificity of 95% (95 % CI (75.1 - 99.9) and 89.66%(95% CI(72.6-97.8%) respectively. This cut off percentage provides the model both high sensitivity and specificity for ruling out or ruling in an ovarian malignancy. At this proposed cut-off, the model performed better than subjective assessment in terms of specificity and was comparable to subjective assessment in terms of sensitivity and diagnostic accuracy. S Y Jeong et al. proposed a similar cut-off value of 47.3% in their study done in the Korean population with a specificity of 97.7-98%.[16] This value offers a significant improvement in specificity of the model compared to the standard 10% cut-off which is important in pre-operatively identifying benign masses.

Other studies suggested different optimal cut-off values depending on their findings. A recent study published by Le Lam Huong et al. in 2022 proposed a cut-off value of 13.5% instead of the standard 10%.[16] In their article offering practical recommendations for implementing the ADNEX model, B Van Caster et al. argued that the cutoff percentage is flexible and can vary depending on the types and requirements of a center.[17] In certain centers, prioritizing a high sensitivity might be crucial, achieved by opting for a low cutoff (5-15%) for malignancy. This facilitates appropriate referrals to specialized gynecologic oncology institutes. In a different medical facility, the emphasis might be on reducing the number of false positives. This can be achieved by selecting a substantially higher cutoff value (30-45%) for malignancy, with the objective of preventing unnecessary surgeries for patients diagnosed with benign pathologies. Diverse strategies could be employed across countries, each characterized by unique health systems and referral protocols. In the Indian scenario, our high proposed cut-off of 47.1% may be appropriate for tertiary level oncology referral centers.

In our study, 17 out of 49 patients were false positive for malignancy by the IOTA-ADNEX model using the standard 10% cut-off. This number would be reduced to 4 when the optimal proposed cut-off of 47.1% is applied. Out of the 17 false positive patients, 12 had presence of a solid component, 8 had a maximum lesion diameter of more than 10 cm, 8 had more than 10 locules, 7 had abnormal CA-125 levels, 5 had presence of papillary projections, 3 had presence of ascitis and 1 showed acoustic shadowing. Although the statistical significance of each of the individual characteristics has been discussed earlier, it is a combination of these that determines the final risk score in any individual patient. In our study, amongst the various parameters, we found that only CA-125 levels, maximum diameter of solid component and presence of acoustic shadows individually showed statistically significant levels.

Determining the presence or absence of a solid component, in particular, can sometimes be challenging. Adherent organized clot or contents and fat can be confused for solid components by a relatively less experienced operator. Hence, adequate training is essential before using this model to reduce the number of false positives.

We did not encounter any false negatives in our study with the standard cut-off of 10%, accounting for the 100% sensitivity. If we use the proposed cut-off of 47.1%, however, we would have missed one malignancy which turned out to be serous adenocarcinoma by the final histopathological evaluation. This particular post-menopausal patient had a lesion size of 154 mm, showed more than 10 locules, had no solid component, papillary projections, acoustic shadow or ascites and a CA-125 of less than 4 U/ml with risk of malignancy by IOTA-ADNEX model of 21.6%. This was tagged "Indeterminate" by subjective radiological assessment and was grouped under the "Malignant" category for statistical purposes in our study.

Serum CA125 has been widely utilized as a screening test for epithelial ovarian tumors.[18] Nevertheless, this tumor marker lacks specificity as it also rises in various benign conditions such as endometriosis, pelvic inflammatory disease, peritonitis, cirrhosis, and others. Furthermore, up to 20% of ovarian cancers lack expression of the CA125 antigen which leads to low levels of serum CA125. Research is on to look for other antigens expressed in such CA125 deficient cancers.[19]

Multiple models and tools have been devised and tested over the years to predict the nature of adnexal masses. The RMI (Risk of Malignancy Index) was introduced in the UK national guidelines for management of women with suspected ovarian masses by the Royal College of Obstetricians and Gynaecologists (RCOG). It took into consideration the ultrasound features, menopausal status and CA-125 levels of patients to generate a score. Despite its utilization, the RMI has proven to be less effective than subjective radiological assessment in discerning ovarian tumors. Moreover, it has exhibited poor diagnostic performance when compared to alternative models such as logistic regression or other ultrasound based models.[13,20-23]

In 2008, the IOTA group formulated the "Simple Rules," encompassing five characteristics indicative of benign tumors (B-features) and five characteristics indicative of malignant tumors (M-features). These rules serve as the basis for categorizing tumors as Benign, Malignant, or Inconclusive.[10] The B-features included unilocularity, presence of solid components of largest diameter <7 mm, presence of acoustic shadows, smooth multilocular tumor with largest diameter <100mm and no blood flow on color doppler. The M-features included presence of an irregular solid tumor, presence of ascites, presence of at least 4 papillary structures and a color score of 4 on doppler. As the Simple Rules did not give a predicted risk, they were used to develop a risk calculator tool (SR Risk Calculator) using a logistic regression model.

The IOTA group introduced the ADNEX model in 2014, a tool that not only distinguishes between benign and malignant masses but also offers the relative risk probability for borderline tumors, stage-I cancer, stage II-IV cancer, and secondary metastatic cancer.[11-13] Numerous external validation studies have been performed worldwide to test the performance of the ADNEX model in various settings and to compare it with previously used tools.[11-14] The IOTA-ADNEX model has consistently shown better performance compared to all previously used risk predictors and has been comparable to subjective expert radiological assessment. Our study also revealed similar results with the proposed cut-off of 47.1% although the model showed poor specificity with the standard 10% cut-off. We have not studied the diagnostic performance of the model to sub-classify the malignant masses into borderline, stage-I, stage II-IV and secondary metastatic cancer due to the relatively small sample size. Recent studies are concentrating particularly on studying the diagnostic accuracy of the model in differentiating borderline tumors from benign and stage-1 ovarian cancers which can be challenging.[24,25]

This study had certain limitations. Firstly, the study's strength to draw a reliable conclusion regarding the diagnostic performance of the model may have been impacted by the small size of the study population. Secondly, it was a single centre based research which could potentially introduce bias due to sample distribution. Thirdly, the investigators did not have any prior formal training in using the model which could have affected the results. Notably, quite a few patients had to undergo assessment using transabdominal ultrasound due to large size of lesions and/or no history of prior sexual contact. Our study did not look into the diagnostic performance of the model in sub-classifying the malignant masses into borderline, stage I-IV and metastatic categories which is being studied by other researchers worldwide.

CONCLUSION

IOTA-ADNEX is undoubtedly a promising ultrasound based model which can precisely differentiate adnexal masses as benign or malignant preoperatively and merits clinical application.

With a properly selected and validated cut-off, the IOTA-ADNEX model performs comparably or even better than subjective radiological assessment for discriminating between benign and malignant adnexal pathologies. Particularly high sensitivity of this model is desirable and reduces the chances of missing ovarian malignancies. High specificity is possible with a suitably selected cut-off for any particular setting and will contribute to the correct identification of benign counterparts.

In our tertiary-level oncology setup, we identified 47.1% as the optimal IOTA-ADNEX model cut-off. This threshold demonstrated acceptable sensitivity and superior specificity compared to the standard 10% cut-off. Based on our study, we propose higher cut-offs to be used with the IOTA-ADNEX model when being applied in oncological institutes where the surgical workload of ovarian malignancy is high to avoid unnecessary surgeries for benign pathologies.

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