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Original Research Article

Comparative Assessment of the Diagnostic Efficacy of Malignancy in Adnexal Masses by International Ovarian Tumor Analysis (Simple Rules) Versus Risk of Malignancy Index

Swati Sinha[1], Hit Narayan Prasad[2]

[1]Senior Resident, Department of Obstetrics & Gynaecology, IGIMS, Patna, Bihar, India
[2]Senior Resident, Department of Radiology, IGIMS, Patna, Bihar, India

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Corresponding author: Dr. Hit Narayan Prasad
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Abstract

Aim: The objective of this study was to compare international ovarian tumor analysis (Simple rules) versus risk of malignancy index for the pre-operative diagnosis of malignancy in adnexal masses.

Methodology: The study was carried out using data prospectively collected from consecutive patients. It evaluated the diagnostic performances of the SRs models and variants of the RMI (I–III) within a population of women who underwent surgery to remove adnexal masses at the Department of Obstetrics and Gynaecology, IGIMS, Patna, Bihar for one year. A total of 200 patients were included in the final analysis.

Results: In the final analysis, 200 patients with 150 (75%) benign and 50 (25%) malignant adnexal masses were included. Endometriomas (20%, 40/200) and serous cystadenomas (14%, 28/200) were the most common benign diagnoses. Among the malignant masses, 7% (14/200) were BOTs. The patients with malignancies were older, were more likely to be post-menopausal and to have a family history of OC, and had higher CA125 levels than those with benign tumors (all $P < 0.05$). Regarding the ultrasound findings, the malignant tumors had significantly greater diameters, more solid tissue, wider solid tissue components, > 10-cyst locules, more papillary projections, and more ascites compared with the benign masses (all $P < 0.001$). None of the patients with malignant tumors had acoustic shadows.

Conclusion: ADNEX and SRs models were excellent at characterising adnexal masses which were superior to the RMI.

Keywords: Adnexal Mass, Tumor, Diagnosis, Ultrasonography, Prediction Model.

Introduction

Ovarian cancer is a common and lethal disease for which early detection and treatment in high-volume centers and by specialized clinicians is known to improve survival [1-4]. According to Globocan 2018, ovarian cancers are the 7th common cancers in females worldwide but have the highest mortality rates among all gynecological cancers [5]. This high mortality is due to late diagnosis in an advanced stage where mortality is high. Infertility, early menarche and late menopause, exogenous hormonal use, high body mass index (BMI), and genetic mutations are considered some of the risk factors for ovarian cancers. Hence,

accurate methods to preoperatively characterize the nature of an ovarian tumor are pivotal.

In 2008 the International Ovarian Tumor Analysis (IOTA) group described the Simple Rules [6]. These are based on a set of 5 ultrasound features indicative of a benign tumor (B-features) and 5 ultrasound features indicative of a malignant tumor (M-features). When using the Simple Rules, tumors are classified as benign if only B-features are observed and as malignant if only M-features are observed. If no features are observed or if conflicting features are present, the Simple Rules cannot classify the tumor as benign or malignant (inconclusive results). Masses in which the Simple Rules yield an inconclusive result can be classified using subjective assessment by an experienced ultrasound operator or, given the high prevalence of malignancy in this group, they can all be classified as malignant to increase the sensitivity for ovarian cancer [7].

Various other classification systems also have been designed, taking USG findings and combining them with other modalities to differentiate adnexal masses. These led to the formation of different types of the scoring system for categorizing adnexal masses into benign and malignant; namely, risk of malignancy index (RMI), Risk of Ovarian Malignancy Algorithm (ROMA), International Ovarian Tumor Analysis (IOTA)-simple rules, IOTA-AdneXa model, Sassone morphology index, etc., RMI, ROMA use CA 125 values along with USG findings and menopausal state, calculation often being complex. The Risk of Malignancy Index (RMI), which accounts for the serum cancer antigen (CA) 125 levels, menopausal status, and the ultrasound findings, is a prediction model that is recommended by many national guidelines [8-10]. However, the procedures used to calculate the RMI are time-consuming, and its diagnostic performance is unsatisfactory.

Majority of ovarian malignancies are epithelial ovarian cancers (EOC), which are rapidly progressing tumors. Timely diagnosis of the nature of the mass ensures appropriate referral to gyneoncologist and treatment [11]. Preoperative diagnosis of adnexal mass as benign or malignant can change the approach to treatment, nonetheless is found to be most challenging. Various diagnostic tests available to date are not very dependable, and the need for a reliable method cannot be ignored. The objective of this study was to compare international ovarian tumor analysis (Simple rules) versus risk of malignancy index for the pre-operative diagnosis of malignancy in adnexal masses.

Methodology

The study was carried out using data prospectively collected from consecutive patients. It evaluated the diagnostic performances of the SRs models and variants of the RMI (I–III) within a population of women who underwent surgery to remove adnexal masses at the Department of Obstetrics and Gynaecology, IGIMS, Patna, Bihar India for one year. A total of 200 patients were included in the final analysis. All of the patients underwent pre-operative transvaginal or transrectal ultrasonography examinations according to the IOTA protocol [12] to assess the morphology of the adnexal masses. Clinicians made the final decisions regarding surgery and clinical judgments.

The patients were prospectively and consecutively enrolled, and they presented with ≥ 1 ultrasound-diagnosed adnexal mass. The inclusion criteria were ≥ 1 adnexal mass detected by transvaginal or transrectal ultrasonography that was not a physiological cyst, patients who were prepared to undergo surgery based on a clinician's recommendation, and a time interval of 30 days between ultrasound and surgery. Participants were excluded from the study if they failed to undergo surgery,

they were diagnosed with a recurrence of OC, they had undergone a bilateral adnexectomy previously, they had an ectopic pregnancy, or their clinical data were incomplete.

All patients underwent pre-operative transvaginal or transrectal ultrasonography using ultrasound machines with 5.0–9.0 MHz and 4.0–8.0 MHz transvaginal probes, and 1.0–5.0 MHz transabdominal probes, and the findings were recorded. When a malignancy was suspected or a mass was too large to be evaluated using transvaginal ultrasonography alone, transabdominal ultrasonography was performed. Two expert ultrasonographers with ≥ 10 years of experience in gynaecological ultrasound assessed the tumors' pre-operative sonographic morphologies using the IOTA protocol's nomenclature and methodology [12]. After the ultrasound examinations and before the statistical analysis of the data, we applied three variants of the RMI to calculate the risk of malignancy without knowledge of the histological findings. When multiple adnexal masses were detected, we analyzed the mass with the most complex ultrasonographic morphology, and when masses had similar morphological characteristics, we chose the largest mass [12, 13].

The SRs model comprises a set of rules based on five ultrasound features that indicate benignity (B-features) and five features that indicate malignancy (M-features) [6, 14, 15]. A lesion is classified as benign if ≥ 1 B-feature is present in the absence of any M-features, and malignant if ≥ 1 M-feature is present in the absence of any B-features. If both B-features and M-features are present or if none of the features are present, the model yields an inconclusive result. Three principal variants of the RMI scoring system (RMI-I, RMI-II, and RMI-III) were applied that combined the ultrasound findings, serum CA125 levels, and menopausal status [8-10]. The points attributed to patients' ultrasound findings and menopausal statuses differ for the RMI variants, and these points generate a score; a total score of ≥ 200 points was used as the cut-off for malignancy.

Pathology was the reference standard used for all patients in this study. Tissue specimens obtained during surgery were analyzed by a team of pathologists who specialized in gynaecological pathology and were unaware of the ultrasound findings. The tumors were classified according to the World Health Organization's guidelines for the classification of tumors [16]. The stages of the malignant tumors were defined using the International Federation of Gynecology and Obstetrics 2012 criteria [17].

Statistical Analyses

Basic discrimination between benign and malignant adnexal masses by the ADNEX model with or without the CA125 levels and the three RMI variants was assessed using receiver operating characteristic curves (ROCs) and summarised by calculating the areas under the curves (AUCs). As AUCs could not be calculated for the SRs model, which is based on categorical variables, the McNemar test was used to assess the model's discrimination between benign and malignant adnexal masses. Diagnostic performance measures, including the sensitivities, specificities, positive and negative predictive values, positive and negative likelihood ratios, and the diagnostic odds ratios (DORs), were calculated to evaluate the models' classifications of benign or malignant tumors using cut-off points.

Results

Table 1: Distributions of histology outcomes of 200 adnexal masses

Histological type of masses	N (%)
Benign n=150 (75%)	
Endometrioma	40 (20)
Serous cystadenoma	28 (14)
Teratoma	20 (10)
Mucinous cystadenoma	14 (7)
Hydrosalpinx	12 (6)
Fibrothecoma	8 (4)
Mesosalpinx cyst	7 (3.5)
Parovarian cyst	6 (3)
Cystadenofibroma	3 (1.5)
Fibroma	2 (1)
Adenofibroma	1 (0.5)
Brenner tumor	1 (0.5)
Peritoneal mesothelioma	1 (0.5)
Sertoli-Leydig cell tumor	1 (0.5)
Sclerosing stromal tumor	1 (0.5)
Tuberculosis	1 (0.5)
Other ovarian benign lesion	4 (2)
Borderline n=14 (7)	
Serous	8 (4)
Mucinous	5 (2.5)
Endometrioid	1 (0.5)
Primary ovarian malignant N=28 (14)	
Serous adenocarcinoma	13 (6.5)
Clear cell carcinoma	4 (2)
Endometrioid adenocarcinoma	3 (1.5)
Mucinous adenocarcinoma	1 (0.5)
Sertoli-Leydig cell tumor	1 (0.5)
Carcinosarcoma	1 (0.5)
Granulosa cell tumor	1 (0.5)
Seromucinous adenocarcinoma	1 (0.5)
Diffuse large B cell lymphoma of ovary	1 (0.5)
Small cell neuroendocrine carcinoma	1 (0.5)
Strumal carcinoid of ovary	1 (0.5)
Metastasis 8 (4)	
Gastric cancer	4 (2)
Appendiceal adenocarcinoma	1 (0.5)
Cholangiocarcinoma	1 (0.5)
Breast cancer	1 (0.5)
Pancreatic cancer	1 (0.5)

In the final analysis, 200 patients with 150 (75%) benign and 50 (25%) malignant adnexal masses were included. Endometriomas (20%, 40/200) and serous cystadenomas (14%, 28/200) were the most common benign diagnoses. Among the malignant masses, 7% (14/200) were BOTs.

Table 2: Results regarding clinical characteristics and ultrasound features for 200 patients with adnexal mass

Characteristic	Benign (n = 150)	Malignant (n = 50)	P
Age (years)	41 (31-51)	54 (42-63)	<0.001
Menopausal status			
Premenopausal	114 (76)	22 (44)	<0.001
Postmenopausal	36 (24)	28 (56)	
CA125 (U/mL)	10 (11-38)	54 (18-517)	<0.001
Family history of OC	0 (0.0)	2 (1)	0.012
Maximal diameter of lesion (mm)	56 (44-72)	78 (50-126)	<0.001
Presence of solid tissue	36 (30)	45 (90)	<0.001
Proportion solid tissue if present (mm)	31 (17-46)	44 (20-65)	<0.001
Presence of papillary projections	12 (10)	19 (38)	<0.001
0	135 (90)	30 (60)	<0.001
1	8 (5.34)	5 (10)	
2	2 (1.34)	2 (4)	
3	2 (1.34)	3 (6)	
>3	3 (2)	10 (20)	
>10-cyst locules	5 (3.34)	9 (18)	<0.001
Acoustic shadows	15 (10)	0 (0.0)	<0.001
Ascites	1 (0.66)	15 (30)	<0.001

The patients with malignancies were older, were more likely to be post-menopausal and to have a family history of OC, and had higher CA125 levels than those with benign tumors (all $P < 0.05$). Regarding the ultrasound findings, the malignant tumors had significantly greater diameters, more solid tissue, wider solid tissue components, > 10-cyst locules, more papillary projections, and more ascites compared with the benign masses (all $P < 0.001$). None of the patients with malignant tumors had acoustic shadows.

Table 3: Diagnostic performance of the prediction models for discrimination between benign and malignant adnexal masses

Assessment method	AUC	Sensitivity	Specificity	PPV	NPV	LR+	LR-	DOR
ADNEX[125]	0.94 (0.92-0.96)	0.93 (0.87-0.97)	0.76 (0.72-0.81)	0.80 (0.75-0.84)	0.92 (0.87-0.95)	3.93 (3.20-4.72)	0.09 (0.04-0.22)	43.67
ADNEXN[125]	0.94 (0.91-0.96)	0.93 (0.87-0.97)	0.74 (0.69-0.79)	0.78 (0.73-0.83)	0.92 (0.87-0.95)	3.60 (3.00-4.31)	0.09 (0.05-0.20)	40.00
SRs+BE	NA	0.69 (0.60-0.77)	0.96 (0.93-0.97)	0.94 (0.90-0.97)	0.76 (0.70-0.80)	15.82 (9.66-25.93)	0.32 (0.25-0.42)	49.44
SRs+MAL	NA	0.93 (0.86-0.97)	0.86 (0.82-0.89)	0.87 (0.82-0.91)	0.92 (0.88-0.95)	6.51 (5.04-8.42)	0.09 (0.05-0.16)	72.33
RMI-I	0.87 (0.83-0.90)	0.55 (0.46-0.64)	0.93 (0.90-0.96)	0.89 (0.83-0.94)	0.67 (0.62-0.72)	8.05 (5.33-12.19)	0.48 (0.43-0.59)	16.77

RMI-II	0.83 (0.80-0.86)	0.61 (0.52-0.70)	0.92 (0.89-0.95)	0.89 (0.83-0.93)	0.70 (0.65-0.75)	7.95 (5.42-11.75)	0.42 (0.33-0.52)	18.93
RMI-III	0.82 (0.78-0.86)	0.53 (0.44-0.63)	0.94 (0.91-0.96)	0.90 (0.84-0.95)	0.67 (0.62-0.72)	9.30 (5.91-14.49)	0.50 (0.45-0.63)	18.60

The AUCs for the ADNEX models for differentiating malignant tumors from benign tumors that did and did not account for the CA125 level were 0.94 (95% CI: 0.92–0.96) and 0.94 (95% CI: 0.91–0.96), respectively. At a cut-off of 10%, the performance of the prediction model that included CA125 was excellent, with a sensitivity of 0.93 (95% CI: 0.87–0.97), a specificity of 0.76 (95% CI: 0.72–0.81), and a DOR of 43.67, and the performance of the prediction model that did not include CA125 had a sensitivity of 0.93 (95% CI: 0.87–0.97), a specificity of 0.74 (95% CI: 0.69–0.79), and a DOR of 40.00. The SRs model was applicable to 422 (86.8%) patients with adnexal tumors. Of the tumors with inconclusive diagnoses, 56.3% (36/64) were benign tumors, 20.3% (13/64) were BOTs, 14.1% (9/64) were stage I OCs, 4.7% (3/64) were stages I–IV OCs, 4.7% (3/64) were metastases, approximately 43.8% were malignant histologically, and most of the benign masses (75.0%, 27/36) presented with a solid component.

Discussion

Correctly discriminating between benign and malignant adnexal masses is a crucial starting point for optimal treatment. We compared the diagnostic performances of the ADNEX and SRs models, and the RMI. The RMI was the first prediction model used clinically, and it is the most widely used model in many regions [18-20]. However, our study's findings showed that the ADNEX model was superior to the three RMI variants at distinguishing between benign and malignant adnexal masses. The ADNEX model with and without CA125 had higher AUCs (both 0.94) than the AUCs generated for the RMI variants that ranged from 0.82 to 0.87. Pre-operative evaluations using the SRs model were robust, with a sensitivity of 0.93 (95% CI: 0.86–0.97) and a specificity of 0.86 (95% CI: 0.82–0.89) for adnexal masses with inconclusive diagnoses that were classified as malignant; these findings are similar to the results from previous studies [21, 22].

The SRs model is easy to apply in clinical practice, and it can be used for approximately 76-89% of adnexal masses [23, 24]. The SRs model was applicable to about 86.8% of the patients in our study. When specialists in gynaecological ultrasonography are not available, classifying tumors as malignant is reasonable following inconclusive diagnoses using the SRs model [23,24]. However, this approach could be biased by the prevalence of malignant tumors within the population, and approximately half of the patients with benign diagnoses might undergo unnecessary interventions [23,24]. Our analyses determined that patients had tumors with inconclusive diagnoses following the application of the SRs protocol to the ADNEX model with or without CA125 and the three RMI variants. Compared with the three RMI variants, the AUC for the ADNEX model was higher (0.59 vs 0.73), the sensitivity was greater (0.29–0.36 vs 0.89), and the specificities were lower (0.86–0.89 vs 0.33–0.39). Regarding the tumors with inconclusive diagnoses, the prediction models' AUCs did not differ, which may be attributable to the limited sample size. Nevertheless, regarding the identification of malignant tumors among the masses with inconclusive diagnoses, the ADNEX

model yielded slightly higher AUCs and DORs than the three RMI variants. [25]

Additionally, we prospectively and consecutively enrolled unselected patients, and only patients whose data were complete were included. Moreover, our results were validated within a relatively large total study population between benign and malignant patients, however the sample size in particular subtypes was still limited. The study's weakness, namely, its single-centre design, may have caused a sampling bias and limited the applicability of the results to other regions. Moreover, the ultrasound examinations were not performed by those with different levels of training experience in our study. More studies in different diagnostic centres with different levels of ultrasound expertise are needed to further evaluate the prediction models.

Conclusion

In conclusion, our study's findings showed that the ADNEX and SRs models performed well in relation to discriminating between benign and malignant adnexal masses, and that both models were superior to the RMI.

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