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COMPARISON OF FOUR MODELS (RMI, IOTA SIMPLE ULTRASOUND BASED RULE, IOTA LR2 MODEL AND ADNEX) TO PREDICT RISK OF MALIGNANCY IN OVARIAN TUMOR

Obstetrics & Gynaecology

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ABSTRACT

Purpose: comparison of 4 different models (RMI, IOTA simple ultrasound, IOTA-LR2 model and ADNEX model) to predict the risk of malignancy in ovarian tumor. **Methods:** This study was prospective observational study,150 patients were recruited in this study **Inclusion criteria-** ovarian tumor >5 centimeter size. **Exclusion criteria-** surgery performed after 120 days of ultrasound and absence of fnac/ biopsy/ histopathology report. Patients with ovarian tumor >5 cms size recruited, history and examination done, serum CA 125 report collected and ultrasound performed for all these patients By using theses risk of malignancy assessed by different methods. After assessment , this report is to be compared with the histopathology report of the tumor and to find out which model is best to predict risk of malignancy in ovarian tumor. **Results:** among these models adnex model have maximum sensitivity (93.44%), npv (76.47%) and auc (0.952). Iota simple ultrasound based method have maximum specificity (96.43%) and ppv (99.08%) and rmi-2 have minimum sensitivity (82.79%), specificity (82.29%), npv (54.35%) and auc (0.952) **Conclusion:** among these 4 models adnex model is best to predict risk of malignancy in ovarian tumor and it also predict borderline nature of the ovarian tumor and tells about the stage of malignancy and metastatic status of the tumor.

KEYWORDS

RMI: Risk of Malignancy Index, IOTA: International Ovarian Tumor Analysis group, LR2: Logistic Regression, ADNEX: Assessment of Different Neoplasia in Adnexa

INTRODUCTION

Ovarian cancer represents the most lethal female reproductive tract malignancy worldwide[1] Despite advances in cytoreductive radical surgery and cytotoxic chemotherapy, only marginal improvement in overall survival of patients with ovarian cancer had seen. Various clinical and ultrasound based methods and models formed. In this study prediction of risk of malignancy calculated by RMI-2, IOTA simple ultrasound based rules, IOTA- LR2 model, and ADNEX model and to compare which model is best to predict risk of malignancy in an ovarian tumor.

Risk Of Malignancy Index (rmi)[2,3]:

"RMI = ultrasound findings × CA125 × menopausal status". scoring system combines the ultrasound features of the mass (U), menopausal status of the patient (M), and serum CA125 level (U/ml) into a risk score (U×M× serum CA125).

Premenopausal score-1, postmenopausal score-4 The ultrasound features are 1.multilocularity, 2.solid areas, 3.bilaterality, 4.ascites and 5. intra abdominal metastasis.

No or 1 feature score-1, >1 feature score-4

Total score of >/ 200 used as a cut–off for malignancy.

The IOTA Simple ultrasoundbased rules[4]:

Its developed by IOTA group, which includes 5 ultrasound features suggestive of benign (B features) and 5 features which suggestive of malignancy(M features).

If one or more B features are present in the absence of M features, the mass is classified as benign, and vice versa.

If both B and M features exist or if none of the 10 features is present, the simple rules yields an inconclusive result.

Table : IOTA simple ultrasound based method (B and M rule)[4]

B- Rule		M-Rule	
B1	Unilocular tumor	M1	Irregular solid tumor
B2	Solid component with largest diameter <7mm	M2	Presence of ascites
B3	Presence of acoustic shadow	M3	>/4 papillary projection
B4	Smooth multilocular tumor with largest diameter <100mm	M4	Irregular multilocular solid tumor with largest diameter >/100 mm
B5	No blood flow(color score 1)	M5	Very strong blood flow (score 4)

The Iota Lr2 Model[5]:

The estimated probability of malignancy for an adnexal tumor is calculated by

LR2 as 1/[1 exp(-z)]

where z= -5.3718+ 0.0354a +1.6159b +1.1768c +0.0697d +0.9586e-2.9486f

(a) Age (years);
(b) Presence of ascites (yes=1, no=0);
(c) Presence of blood flow with in a papillary projection (yes=1, no=0);
(d) Maximum diameter of the solid component (mm; capped at 50 mm);
(e) Irregular internal cyst wall(yes=1, no=0);
(f) Presence of acoustic shadow(yes=1, no=0

A cut-off of (>/10%) was use to predict malignancy.

ADNEX model[6] : it includes 9 variables

1. Age(years),
2. Serum CA125(u/ml),
3. Type of centre(oncology centre/ other hospital),
4. Maximum diameter of the lesion(mm),
5. Proportion of solid tissue(%),
6. Number of papillary projections (0/1/2/3/>3),
7. More than 10 cyst locules (yes/no),
8. Acoustic shadow (yes/no)
9. Ascites(yes/no)

Implications for clinical practice:

For use in clinical practice, an application is made. www.iotagroup.org/adnexmodel.
IMAGES: Ultrasound features(attached separately)

Methodology:

Study Design: Prospective observational study.

Study Period: 1 year.

Inclusion Crieteria: All ovarian tumor >5 centimeter

Exclusion Crieteria:
1)Surgery performed after 120 days of ultrasound.
2)Absence of Histopathology report.

Sample Size: 150 cases were enrolled.

Patient with ovarian tumor >5 cm size were recruited after taking written and informed consent then assessed by detailed history & clinical examination followed by ultrasound performed and serum CA125 sampling done. By using RMI-2, IOTA simple ultrasound-based rule, IOTA LR2 model and ADNEX model risk of malignancy predicted. To get histopathology report of ovarian tumor either after surgery or biopsy/FNAC in suspected cases of advanced ovarian malignancies with in 120 days from the time when they got enrolled and to compare this histopathology report with these 4 models outcome, and to conclude which model is best to predict risk of malignancy in ovarian tumor.

RESULTS & DISCUSSION

Studies On Rmi And Outcome

TABLE: Different studies on RMI and their outcome:

Studies	sensitivity	specificity	PPV	NPV
J Yazbek et al (2006)9	89	92	50	99.0
Rujuta et al(2014)10	70.5	87.8	70.5	87.8
Zinatossdat et al(2011)11	91.3	96.2	77.7	98.7
Obeidat et al(2004)12	90	89	96	78
Yamamoto et al (2009)13	86.8	89	97.5	63.5
Ulusoy et al (2012)14	76.4	77.9	65.9	79.4
Manjunath et al (2001)15	73	90	93	66
Akker VD et al(2010)16	81	85	48	96
In present study	87.5	82.7	50	97.1

Among these studies, Yazbek et al(2006), Yamamoto et al (2009) and Akker VD has comparable results in view of sensitivity and specificity , irrespective of that Zinatossdat et al(2011), Obeidat et al (2004) had higher sensitivity and specificity of RMI model than present study and study by Rujuta et al(2014), Ulusoy et al (2012), Manjunath et al (2010) had lower sensitivity and specificity than present models.

Yazbek J et al (2006) had done prospective observational study in 106 women. The area under the ROC curve for RMI >200 0.822 (SE 0.081, asymptotic 95% CI 0.662 – 0.981)[70] which is lower than our model which shows at cut-off of 200 at 95% CI area under curve 0.952. Javdekar R et al (2014) had done prospective cohort study on 58 women ROC showed that cut off value of 25 achieved a sensitivity and specificity of 82.35 and 43.9 % respectively, and a cut off value of 1,000 gave a sensitivity and specificity of 58.81 and 97.56 % respectively.[7] In present study if cut off taken as 25 it shows sensitivity 100% which is more than above study and specificity 16.4%which is lesser than above study and if cut off taken as 1000 sensitivity 75% and specificity 99.9%.

Zinatossadat et al (2011) in their study between 2007-2009 in 182 women, RMI with the cut-off point of 265 had a sensitivity of 91.3%, specificity of 96.2 %, PPV of 77.7% and NPV of 98.7% for diagnosis of malignant masses.[72] In our study if cut off is taken as 265 it shows sensitivity 87.5 and specificity 86.1% which is lesser than above study.

IOTA simple ultrasound based rule and their outcome

Table : Different studies on IOTA simple ultrasound based rules and their outcome:

Studies	Sample size	Sensitivity	Specificity
Meys EMJ et al (2016)17	19674	0.93	0.80
Timmerman et al (2010)18	796	0.91	0.96
Sayasnesh et al (2013)19	214	0.87	0.98
Alcazar et al (2013)20	270	0.88	0.97
In present study	150	0.88	0.96

Meys EMJ et al (2016) in their study analysed 47 articles; 13,953 (70.9%) were benign and 5721 (29.1%) were malignant. Simple rules (classifying inconclusives as malignant) shows sensitivity 0.93 [95% CI 0.91 e0.95] and specificity 0.80 [95% CI 0.77e0.82]).[22] that is more in respect to present study, reason may be better ultrasound facility or interobserver variability to interpret the findings.

Timmerman (2010) in their study on 796 patients this rules was applicable, at 95% confidence interval sensitivity was 0.91 (0.86 – 0.95) and specificity was 0.96 (0.94 – 0.98)[18] more than present study, reason may be better ultrasound facility or interobserver variability to interpret the findings.

Sayasneh et al (2013)) in their study on 214 patients rules was applicable, 24.8, at 95% CI sensitivity was 0.87 (0.75 – 0.95) and specificity was 0.98 (0.95 – 1.00)[19] that is comparable to our study.

Alcazar et al (2013) in their study on 270 cases rules was applicable, at 95% CI sensitivity was 0.88 (0.72 – 0.97) and specificity was 0.97 (0.95 – 0.99)[20] that is comparable to our study.

Studies On Iota Lr2 Model And Outcome:

Advantage: based on both clinical and ultrasound based parameters has better sensitivity and specificity than RMI and IOTA simple ultrasound based rule.

Disadvantages: not able to differentiate borderline tumor, score calculation needed complicated calculations or need web software applications which freely available on IOTA site.

No recommendation till date to use in clinical practice.

In this study, after analyzing 150 cases IOTA LR2 model diagnose 114 cases as benign, 36 cases as malignant. After comparing with gold standard (in which borderline considered as malignant for statistics purpose), it shows at 95% Confidence Interval.

Sensitivity= 91.8% (85.44-96.0)
Specificity= 92.86% (76.50-99.12)
Positive predictive value= 98.25% (93.64-99.53)
Negative predictive value= 72.22% (58.73-82.61)
Positive Likelihood ratio=12.85
Negative likelihood ratio= 0.09
Accuracy=92.0% (86.44-95.80)
Prevalence= 81.33% (74.16-87.22)
Area under curve= 0.953 at 95% CI (0.918-0.988)

Coordinates of the Curve :

if cut-off is taken as
0.010 sensitivity=100%, specificity=27.9
if ,0.015 sensitivity 100%, specificity=47.5
if, 0.029 sensitivity= 100%, specificity=71.8%
Studies on IOTA LR2 model and their outcome:
Timmerman et al(2005) in their prospective multicentric study 1,066 patient recruited 800 patients had benign tumors and 266 had malignant tumors. 312 patients was assessed on 6 variable shows results AUC 0.94, and a probablity cutoff value of 0.10 gave sensitivity 0.93 and specificity 0.76.[14] at same cut off present model shows sensitivity 91.8% and specificity 92.86%

Timmerman et al(2010) in their study they had found out of 1938 cases, On external validation (997 patients from 12 centers), the area under the receiver–operating characteristics curve (AUC) LR2 was 0.949.[73] In present study at same cut off it shows AUC 0.952 that is comparable.

E.M.J.Meys et al(2016) in their study shows IOTA LR2 model sensitivity 0.93, specificity 0.79, PPV 0.71, NPV 0.95, LR+ 4.46, LR-0.09.[22] In present study sensitivity 0.91, specificity 0.92, PPV 0.98, NPV 0.72, LR+ 12.85, LR-0.09 Among these only sensitivity and LR- is comparable.

Studies On Adnex Model And Outcome:

developed by IOTA group in 2014.
Advantage: based on both clinical, tumor marker and ultrasound parameters. Differentiate benign and malignant ovarian tumor also tell about borderline tumor and stage of the disease like stage 1, stage 2-4 and metastatic ovarian tumor.

Disadvantage: difficult to use, we need online application to calculate risk of malignancy, need better ultrasound facility to assess the ultrasound parameters.

No recommendation till now for use in clinical practice.

After analyzing 150 cases using ADNEX model, shows 116 cases as benign, 10 cases as borderline and 24 cases as stage 2-4, for statistics

purpose borderline and stage 2-4 cases considered as malignant. After comparing with gold standard (in which borderline considered as malignant for statistics purpose) .

In this study shows @ 95 % CI After analyzing data(N= 150) which shows 122 were benign and 28 cases were malignant At 95% confidence interval it shows,

Sensitivity = 93.44% (87.49-97.13)
Specificity 92.86% (76.50-99.12)
PPV = 98.28 % (93.74-99.54)
NPV =76.47% (62.27-86.49)
Positive likelihood ratio = 13.08
Negative likelihood ratio =0.07
Accuracy= 93.33% (88.08-96.76)
Prevalence 81.3

Meys EMJ et al(2016)[17] in their study included 326 cases shows, ADNEX model shows sensitivity (0.98), NPV (0.98) that is more than our model and specificity 0.62, PPV 0.58 that is less than our model. Interpretation of ultrasound findings, interobserver variation may be ther reason for differences in outcome of the study.

Table: comparison of different models (RMI-2, IOTA simple ultrasound based rule, IOTA LR2 model and ADNEX and related studies:

	RMI Model	IOTA SIMPLE ULTRASOUND BASED MODEL	IOTA LR2 MODEL	ADNEX MODEL
SENSITIVITY	82.79	88.52	91.8	93.44
SPECIFICITY	89.29	96.43	92.86	92.86
PPV	97.12	99.08	98.25	98.28
NPV	54.35	65.85	72.22	76.47
POSITIVE LR	7.73	24.79	12.85	13.08
NEGATIVE LR	0.19	0.12	0.09	0.07
ACCURACY	84	90.0	92.0	93.33

150 cases based on inclusion criteria were taken to predict the risk of malignancy in ovarian tumor.

For comparison sample size taken as 146(for statistics purpose) as RMI-2, IOTA simple ultrasound method, IOTA LR2 model not able to predict borderline ovarian tumor.

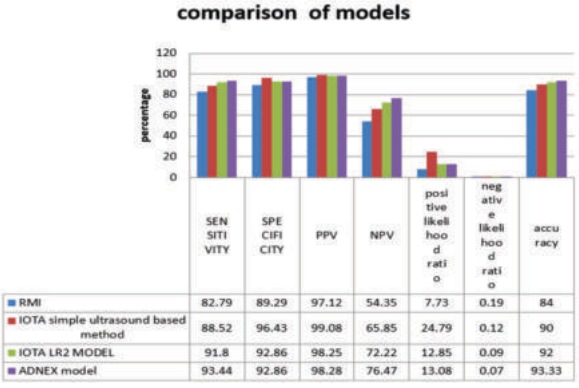
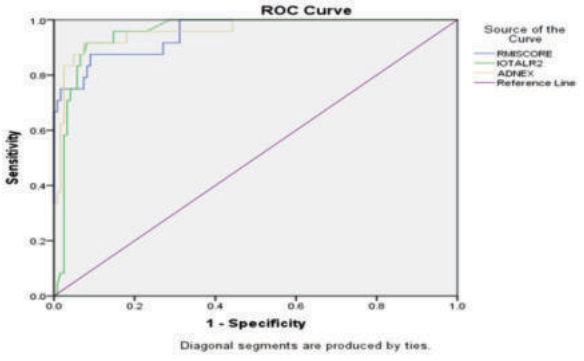


Image 5: attached

Prediction model	sensitivity		specificity		PPV		NPV		LR+		LR -	
	E.M.J.Meys et al(2016)17	In our study	E.M.J.Meys et al (2016)	In our study	E.M.J.Meys et al	In our study	E.M.J.Meys et al	In our study	e.m.j. meys et al study	In this study	E.M.J. Meys ET AL STUDY	In this study
ADNEX model	0.98	0.93	0.62	0.92	0.58	0.98	0.98	0.76	2.56	13.08	0.03	0.07
Simple ultrasound based rules	0.90	0.88	0.91	0.96	0.83	0.99	0.95	0.65		24.79		0.12
IOTA LR2 model	0.93	0.91	0.79	0.92	0.71	0.98	0.95	0.72	4.46	28.13	0.09	0.10
RMI-2 model	0.74	0.82	0.73	0.89	0.60	0.97	0.84	0.54	2.74	7.73	0.36	0.19



Meys EMJ et al (2016) in their retrospective diagnostic accuracy study, between 2011 to 2015, total of 851 patients was taken.The final cohort consisted of 326 patients involving 128(39.3%) premenopausal and 198 (60.7%) postmenopausal women. The area under the receiver-operating characteristics curve (AUC) of the ADNEX model for discrimination between benign and malignant tumors was 0.93(95% CL, 0.89-0.95). AUCs for the subtypes of malignancy (i.e. borderline, stage 1-4 and metastatic adnexal tumors) ranged between 0.60 and 0.90. Only subjective assessment (AUC, 0.96(95% CL, 0.93-0.98) was superior to the ADNEX model (P=0.01) in differentiating malignant from benign tumors. AUCs for the other models were 0.9 (95%CL, 0.89-0.95) for LR2, 0.85(95%CL, 0.81-0.89) for RMI1, 0.82 (95%cl, 0.77-0.86) for RMI 2 and 0.84 (95%CL, 0.80-0.88 for RMI3. At the proposed cut-off of>/10%, the ADNEX model has the highest sensitivity (0.98 (95%CL, 0.93-1.00) but the lowest specificity (0.62(95%CL, 0.55-0.68)) compared with the other models. Both subjective assessment (sensitivity, 0.90(95%CL, 0.83-0.95); specificity 0.91 (95%, 0.86-0.94)) and the simple rules model with inconclusive cases classified by subjective assessment (sensitivity, 0.89(95%CL, 0.81-0.94); specificity, 0.90 (95%CL, 0.85-0.94)) had lower sensitivity, but their sensitivity and specificity were better balanced.[17]

A Sayasneh et al (2016) in their multicentric cross sectional cohort study data from 610 women were analyzed. The overall prevalence of malignancy was 30%. The area under the receiver operator curve (AUC) for the ADNEX diagnostic performance to differentiate between benign and malignant masses was 0.937 (95% CI: 0.915–0.954) when CA125 was included, and 0.925 (95% CI: 0.902–0.943) when CA125 was excluded. The calibration plots suggest good correspondence between the total predicted risk of malignancy and the observed proportion of malignancies. The model showed good discrimination between the different subtypes.[21]

In comparison to Meys EMJ(2016) study in present study RMI has better sensitivity and specificity, IOTA simple ultrasound based rule has lesser sensitivity but high specificity, IOTA LR2 model sensitivity is comparable but in present study has higher specificity than study by Meys EMJ, ADNEX model sensitivity is less in our study than respective study but high specificity.

But Meys EMJ and present study both have maximum sensitivity of ADNEX model, maximum specificity of IOTA simple ultrasound based rule and minimum sensitivity and specificity of RMI model.

CONCLUSION

In this study, among all these 4 model ADNEX model have maximum area under curve AUC 0.958, max sensitivity (93.44) and max NPV (76.47),

- IOTA simple ultrasound based method have max PPV (99.08) and specificity (96.43)
- RMI-2 have minimum AUC 0.952 and minimum sensitivity, specificity and NPV among these 4 model.
- Among these 4 model ADNEX model is best to predict risk of malignancy in ovarian tumor and it also tells about the stage of disease.

Limitation Of Study : Expertise in ultrasound is must.

Clinical Relevance: By using these methods we can predict risk of malignany and furthur management can be planned accordingly.

Declaration:-
We have no conflict of interest.

Images:1 Septa And Multilocularity

Image2: Solid Area In Tumor

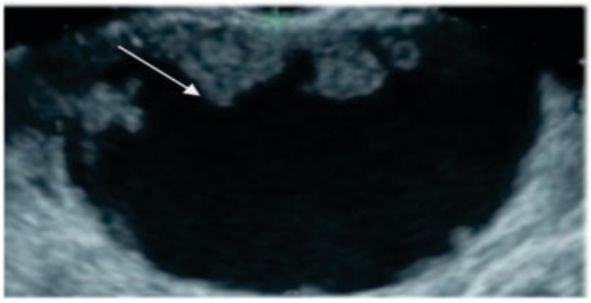


Image:3 Papillary Projection In Ovarian Tumor

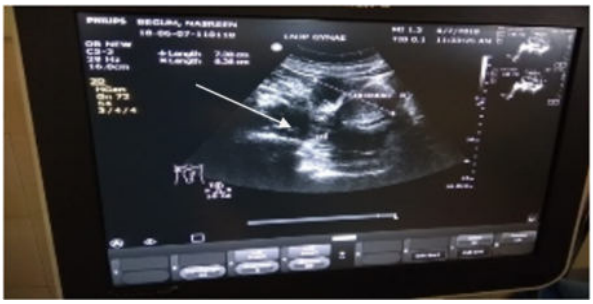


Image:4 Acoustic Shadow

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