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A prospective study on the evaluation of adnexal masses by the ADNEX model

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Abstract
Background: Pre-operative discrimination of malignant from benign adnexal masses is crucial for planning additional imaging, preparation, surgery and postoperative care. This study aimed to define key ultrasound and clinical variables and develop a predictive model for calculating preoperative ovarian tumor malignancy risk in a gynecologic oncology referral center. We compared our model to a subjective ultrasound assessment (SUA) method and previously described models.
Objective: This study aims at the evaluation of adnexal masses using the ADNEX model thereby predicting the risk of benign and malignant tumours.
Methodology: This prospective study was done at Government RSRM lying in hospital, Chennai from December 2017 to September 2018. A total of 60 non pregnant females admitted with complaints of lower abdominal pain and abdominal distension were studied. If ultrasound suggest any adnexal mass, then the 3 clinical criteria and 6 ultrasound predictors of ADNEX model was applied and these patients were evaluated.
Results: Among the 60 patients, 52 patients had benign masses and 8 patients had malignant masses. The presence of ascites was an independent risk factor for all malignant masses. With a cut off ≥ 10%, this model had high sensitivity and low specificity. It predicted the risk estimates for borderline, stage I, stage II-IV, metastatic ovarian tumours and their mean score was statistically higher in malignant patients as compared to malignant patients. (p <0.05)

Keywords: Ascites, ADNEX model, adnexal masses

Introduction
Adnexal masses are very common in the women and the morbidity and mortality of the patients depends on the corrective pre-operative differentiation. The ultrasound examination having advantage of being more specific and the gives the better way to differentiate malignant from benign adnexal masses prior to surgery.
An improvement in the accuracy of current triaging and referral pathways whether using new imaging tests or biomarkers would therefore be of the value in order to optimize the appropriate selection of patients for such care. The IOTA's promising tests include LR2, Ultra sound base simple rules (SR). They offers more accuracy triage compared to the existing risk of malignancy Index (RMI). ADNEX is a novel test that enables the more specific sub typing of adnexal cancers like borderline, stage I invasive, Stage II-IV Invasive and secondary metastatic malignant tumors. The IOTA which is the largest diagnostic accuracy with group running more than 15 years ago with goal to develop evidence based algorithms for the classification and management of all types of adnexal masses.
Timmerman *et al.* (2000) [1] and Kaijser *et al.* (2012) [2] developed the unified possible ultrasound variables and it forms a base for further analysis and unique model for the ADNEX masses finding with accuracy to predict the correct diagnosis and testing procedures.
OVARIAN cancers are the second most common gynaecological malignancies worldwide. They represent the greatest clinical challenge because they have a high mortality. Surgical management is also difficult and optimal therapy includes optimal debulking followed by platinum based combination chemotherapy.
It has the highest case fatality ratio of all gynaecological malignancies. A womens risk at birth of having ovarian cancer at some point in her lifetime is 1 to 1.5% and that of dying from ovarian cancer is almost 0.5%. The annual incidence of ovarian cancers is 5.6 per 1,00,000 and

death rate is 2.6 per 1,00,000. Over the past two decades there has been an increase in the incidence as well as survival rates amongst women with ovarian cancer. The risk of a women developing cancer of the ovary is 1:70 to 1: 100. Women of low parity, decreased fertility and delayed childbearing appear to be more predisposed.

There appears to be familial predisposition to the disease. Association between ovarian cancer, colon &breast cancer and endometrial adenocarcinoma has also been recognized. In such families, cancers tend to occur at a younger age.

Five to ten percent malignant tumours are genetic, BRCA1 & BRCA2 gene mutations are implicated in its genetic predisposition. Pattern of Inheritance is autosomal dominant and ovarian tumour occurs at a younger age below 50 years in these population.

The preoperative evaluation of these masses is of utmost importance in selecting the optimal management strategy. Accurate differentiation between the benign & malignant lesions can lead to referral to oncology centers for further diagnosis, staging & this positively influences the diagnosis.

Objective

This study aims at the evaluation of adnexal masses using the ADNEX model thereby predicting the risk of benign and malignant tumours.

Methodology

This prospective study was done at Government RSRM lying in hospital, Chennai from December 2017 to September 2018. A total of 60 non pregnant females admitted with complaints of lower abdominal pain and abdominal distension were studied. If ultrasound suggest any adnexal mass, then the 3 clinical criteria and 6 ultrasound predictors of ADNEX model was applied and these patients were evaluated.

Inclusion criteria

1. All NON pregnant women with adnexal masses diagnosed clinically.
2. Hemodynamic ally stable patients.
3. Palpable pelvic masses.

Exclusion criteria

1. Pregnant females.
2. Physiological cyst such as corpus luteal cyst
3. Refusal of transvaginal ultrasound examination
4. Family history of ovarian cancer

1. Result histopathology

The study population consists of 60 patients admitted in our hospital with adnexal masses. Based on the histopathological analysis, 52 patients had benign pathology constituting 86.6% and 8 were malignant which constituted 13.4%. (Table 1)

Table 1: Histopathology

Histopathological result	Number of patients	Percentage
Benign	52	86.6
Malignant	8	13.4

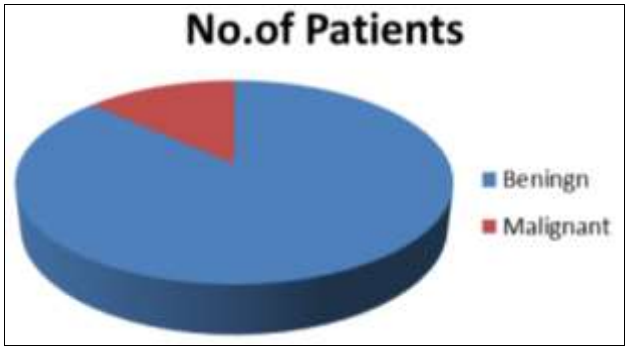

Fig 1: Histopathology

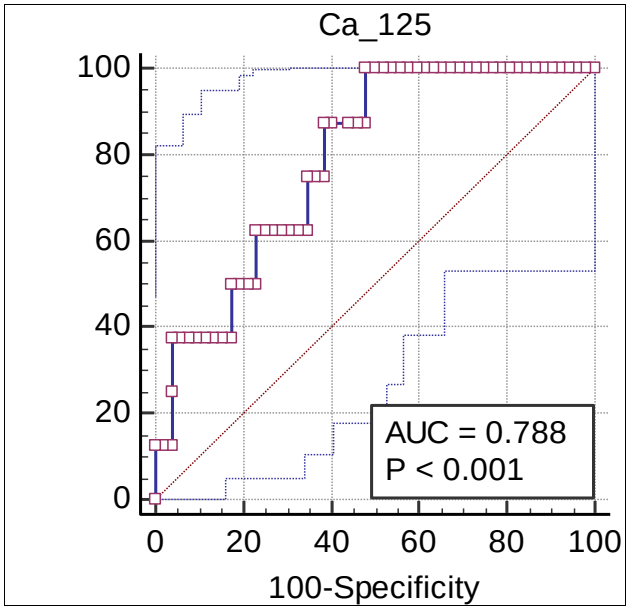

Fig 2a: ROC curves CA 125

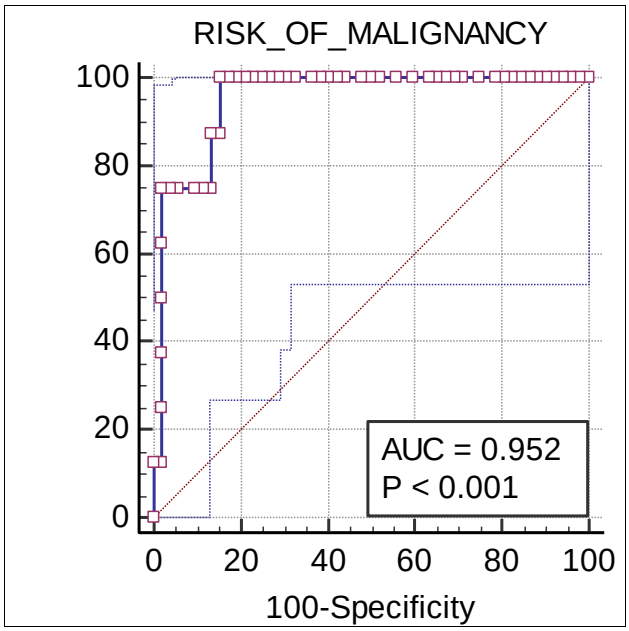

Fig 2b: Predicted risk of malignancy

Table 2: ROC curve CA 125

Variable	Ca_125
Classification variable	HPE
Sample size	**60**
Positive group [a]	8 (13.33%)
Negative group [b]	52 (86.67%)
[a] HPE = 1	
[b] HPE = 0	
Disease prevalence (%)	unknown

Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.788
Standard Error [a]	0.0739
95% Confidence interval [b]	0.664 to 0.883
z statistic	3.903
Significance level P (Area=0.5)	0.0001

Youden index

Youden index J	0.5192
Associated criterion	>22.9
Sensitivity	100.00
Specificity	51.92

Criterion values and coordinates of the ROC curve [Hide]

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR
≥8.6	100.00	63.1 - 100.0	0.00	0.0 - 6.8	1.00	
>22.9	100.00	63.1 - 100.0	51.92	37.6 - 66.0	2.08	0.00
>23.4	87.50	47.3 - 99.7	51.92	37.6 - 66.0	1.82	0.24
>27.97	87.50	47.3 - 99.7	61.54	47.0 - 74.7	2.28	0.20
>28.4	75.00	34.9 - 96.8	61.54	47.0 - 74.7	1.95	0.41
>30.07	75.00	34.9 - 96.8	65.38	50.9 - 78.0	2.17	0.38
>30.1	62.50	24.5 - 91.5	65.38	50.9 - 78.0	1.81	0.57
>35.9	62.50	24.5 - 91.5	76.92	63.2 - 87.5	2.71	0.49
>45	50.00	15.7 - 84.3	76.92	63.2 - 87.5	2.17	0.65
>61.84	50.00	15.7 - 84.3	82.69	69.7 - 91.8	2.89	0.60
>66.8	37.50	8.5 - 75.5	82.69	69.7 - 91.8	2.17	0.76
>120	37.50	8.5 - 75.5	96.15	86.8 - 99.5	9.75	0.65
>127.6	12.50	0.3 - 52.7	96.15	86.8 - 99.5	3.25	0.91
>943.4	12.50	0.3 - 52.7	100.00	93.2 - 100.0		0.88
>1844	0.00	0.0 - 36.9	100.00	93.2 - 100.0		1.00

Table 3: ROC curve

Variable	Risk of malignancy
Classification variable	HPE
Sample size	60
Positive group [a]	8 (13.33%)
Negative group [b]	52 (86.67%)
[a] HPE = 1	
[b] HPE = 0	
Disease prevalence (%)	unknown

Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.952
Standard Error [a]	0.0290
95% Confidence interval [b]	0.863 to 0.990
z statistic	15.595
Significance level P (Area=0.5)	<0.0001

[a] DeLong *et al.*, 1988
[b] Binomial exact

Youden index

Youden index J	0.8462
Associated criterion	>14.7
Sensitivity	100.00
Specificity	84.62

Criterion values and coordinates of the ROC curve [Hide]

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR
≥0.3	100.00	63.1 - 100.0	0.00	0.0 - 6.8	1.00	
>14.7	100.00	63.1 - 100.0	84.62	71.9 - 93.1	6.50	0.00
>14.8	87.50	47.3 - 99.7	84.62	71.9 - 93.1	5.69	0.15
>18.3	87.50	47.3 - 99.7	86.54	74.2 - 94.4	6.50	0.14
>20.1	75.00	34.9 - 96.8	86.54	74.2 - 94.4	5.57	0.29
>37.5	75.00	34.9 - 96.8	98.08	89.7 - 100.0	39.00	0.25
>85.6	12.50	0.3 - 52.7	98.08	89.7 - 100.0	6.50	0.89
>86.3	12.50	0.3 - 52.7	100.00	93.2 - 100.0		0.88
>99	0.00	0.0 - 36.9	100.00	93.2 - 100.0		1.00

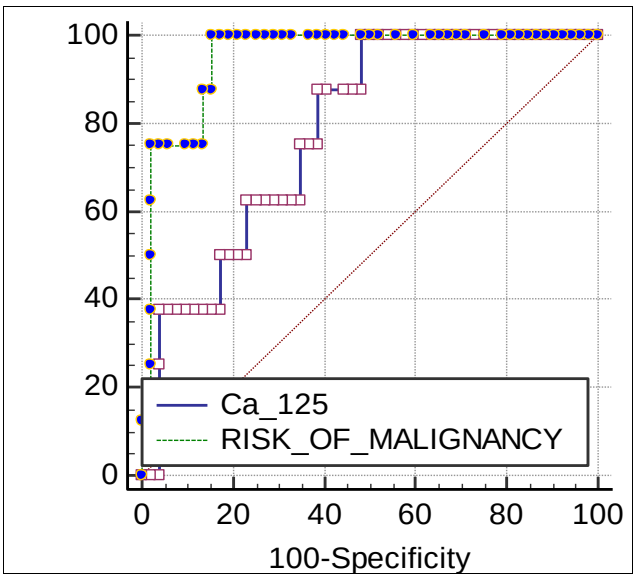

Fig 3: Comparison of ROC curves Ca125 and predicted Risk of malignancy

Table 4: Comparison of ROC curves

Variable 1	**CA 125**
Variable 2	Risk of malignancy
Classification variable	HPE
Sample size	60
Positive group [a]	8 (13.33%)
Negative group [b]	52 (86.67%)
[a] HPE = 1	
[b] HPE = 0	

Variable	AUC	SE [a]	95% CI [b]
Ca_125	0.784	0.0730	0.658 to 0.880
RISK_OF_MALIGNANCY	0.952	0.0290	0.863 to 0.990

[a] DeLong *et al.*, 1988
[b] Binomial exact

Pairwise comparison of ROC curves

CA 125 risk of malignancy	
Difference between areas	0.168
Standard Error [a]	0.0613
95% Confidence Interval	0.0480 to 0.288
z statistic	2.743
Significance level	P = 0.0061

Discussion

This prospective observational study conducted in our hospital with 60 patients admitted with the diagnosis of adnexal tumours. Out of these 52 patients had benign tumours and 8 patients had malignant tumours? About 25% of the malignancy was reported in age < 40 years and 75% of malignancy was reported in age >

40 years. According to this malignancy risk increased in age group > 40 years, risk increases with increase in age.

By comparing the menstrual pattern, 89.7% patients with benign tumours had regular cycles.10.3% of patients with malignant tumours had regular cycles and 25% patients belong to postmenopausal and 20% patients belonged to perimenopausal age group.

Among the 8 patients with malignant tumours, 1 patient was nulligravida and 7 patients belonged to multiparous group. Of the 52 patients with benign tumours, 14 patients were nulligravida and 38 are of multiparous group. Most of the tumours in multiparous group are benign.

The risk of ascites was present in 22 patients evaluated for adnexal mass. In patients with malignant tumours, 7 patient's ascites was present. Among the 52 patients with benign tumours, ascites was present in 15 patients. Presence of ascites increases the risk of malignancy.

The levels of CA125 were increased in patients with malignant tumours. Most of the patients with malignant tumours had CA125 levels greater than the cut off value> 35 u/ml. Among the patients with benign tumours, 25% patients had ca125 greater than 35 u/ml.

According to our study the sensitivity and specificity of CA125 was 100% and 52% respectively. In our study, the range of CA 125 levels was 8.6 – 1844 U/Ml. Ca125 levels were high in high grade serous carcinomas. Using the 3 clinical predictors and 6 ultrasound predictors of ADNEX model, the % predicted risk of malignancy was a very good marker to detect the malignancy in the study population.. It is wise to use ADNEX model to distinguish between a benign and malignant lesion (based on >10% cut off level). When the risk exceeds 10% and a malignant tumour is suspected, the model provides absolute risk estimates for each ovarian malignancy based on the patient and tumour features. Thus the sensitivity of this model is high.

All the 8 adnexal masses which were confirmed as malignant, had risk of malignancy >10%.Hence the model was able to predict the risk estimate with high sensitivity. The risk of malignancy for these malignant masses were 49.8%,85.6%,99%,74.6%,14.8%,65.5%,20.1%,52.2%,which were all > 10%.

The model was good at differentiating benign from Stage II-IV or secondary metastatic tumours and borderline from secondary metastatic tumours.

Summary

About 60 patients of all age groups admitted in our hospital were included in this study by satisfying the inclusion and exclusion criteria. In our study patients during admission, proper history elicitation, general examination and pelvic examination were done.

During the study CA125 levels were tested in all the patients' pre operatively. The ADNEX model application was downloaded from IOTA official website. Transvaginal ultrasound was done and the 6 ultrasound predictors of ADNEX model were measured. Using the 3 clinical predictors and 6 ultrasound parameters the patients were evaluated. Risk > 10% was considered to be malignant. After surgery the histopathological results of the excised specimen was the reference standard.

The model differentiated the masses into benign, borderline tumours, stage I invasive, Stage II-IV invasive ovarian cancer and secondary metastatic cancer. The median time interval between ultrasound examination and obtaining the pathology results was 25 days. Results were benign for 52(86.6) masses and malignant for 8 (13.4) masses.

The most common benign pathologies were simple serous cyst, cyst adenoma, cystadenofibroma, mature cystic teratoma and simple mucinous cyst. The risk of malignancy was predicted for all malignant tumours pre operatively and were all >10%.

In our study, the mean age of 38.8±12.2 years and age range of 14-62 years. The risk of malignancy increases with advancing age. The presence of ascites was an independent risk factor for all malignant masses. Ca125 levels with a cut off > 35 U/ML was increased in all malignant tumours. The other variables (CA 125,risk of metastatic cancer to the adnexa, risk of stage II-IV ovarian cancer, risk of stage I ovarian cancer, risk of borderline tumour, risk of malignancy) mean score was statistically higher in malignant patients as compared to benign patients.($p < 0.05$)

This model can be used as the first line approach in the estimation of the risk of malignancy of adnexal masses.

Conclusion

During the pre-operative evaluation of the patients with adnexal masses, the ADNEX model can be considered a useful method in the differentiation of benign and malignant tumours. Pathology was the clinical reference standard.

The ADNEX model at a cut off > 10% had high Sensitivity and high specificity. The model was able to predict the risk estimates for borderline, stage I, stage II-IV ovarian cancers. It can be used for the evaluation of adnexal masses for selecting optimal management strategy like conservative or laparoscopic method or laparotomy.

It can improve and fine tune management decisions and so reduce the morbidity and mortality associated with adnexal pathology.

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