Assessment of Different Neoplasias in the Adnexa Model Versus Risk of Malignancy Index as a Tool for Predicting Ovarian Malignancy in Postmenopausal Ovarian Cysts.

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Abstract

Background: Ovarian cancer is the most lethal gynecologic malignancy and every attempt should be made to develop screening programs to detect it at its early stages in order to improve survival rate. Using the ADNEX model in screening for ovarian cancer will help in triaging patients with adnexal masses before undergoing surgery which will help in optimizing outcomes particularly for those with ovarian malignancy.

Patients & methods: This was a prospective study which included fifty postmenopausal patients with adnexal mass. All the included patients underwent ultrasound assessment of the adnexal mass and measurement of CA 125 level. Then, the data were collected to calculate the RMI, and integrated to IOTA ADNEX calculator. The primary outcome was determining the predictive accuracy of both RMI and ADNEX model for differentiating between benign and malignant ovarian tumors by setting both against the gold standard histopathology.

Results: Out of the included 50 patients, 56% had benign ovarian lesions, 12% had borderline ovarian tumors, and 24% had malignant ovarian tumors. The Area under the receiver operating characteristic curve (AUC) for the RMI was 0.799 and with cutoff value of 115, the sensitivity was 81.8%, the specificity was 60.7% while the AUC was 0.864 for the ADNEX model and at 10% cutoff, the sensitivity was 91.1% and the specificity was 65%. Performance of the ADNEX for the five tumor types was highest when benign histopathology was compared as stage □ - □ malignant cases with AUC of 0.823.

Conclusion: ADNEX model is more sensitive than RMI for differentiating between benign and malignant tumors and it can be used as screening test. However, the application of ADNEX model needs significant experience in ultrasound evaluation of adnexal masses before it can be an integral part in the screening pathway of ovarian malignancy in postmenopausal patients with adnexal masses.

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Keywords: ADNEX model – Risk of malignancy index - Ovarian cancer – Postmenopausal ovarian cysts.

Introduction

Ovarian cancer (OC) is the third most common gynecological malignancy worldwide and is associated with the highest mortality rate. OC has an incidence of 11.7 - 12.1 per 100,000 in the USA and Europe, with slightly lower rates of disease in Asia and the Middle East. About 60% of patients are diagnosed at an advanced stage which contributes to the high mortality rate (1). Stage of ovarian cancer is the most important element influencing prognosis and searching for a tool to detect the disease at an early stage is of paramount importance. At the time being, there is no effective screening strategy for ovarian malignancy (2). In 1990, Jacobs et al. developed a scoring system known as the risk of malignancy index 1 (RMI □) to stratify ovarian masses into benign and malignant before intervention (3). RMI is a combined parameter that is simple, specific, and highly sensitive for the evaluation of adnexal masses. It is a product of ultrasound findings (U), the menopausal status (M), and serum CA-125 levels (RMI = U X M XCA-125). Tingulstad et al., modified the RMI □ to the RMI □ (4) and again to RMI □ (5) with the last modification named RMI □ made by Yamamoto et al., by adding the size of the tumor to the equation (6). A systematic review of diagnostic studies concluded that the RMI I was the most effective for women with suspected ovarian malignancy (7).

Management of ovarian malignancies and borderline ovarian tumors in specialized oncology centers by experienced gyne-oncologists has a favorable impact on prognosis. Different diagnostic models have been developed to help in triaging ovarian masses and predicting the probability of malignancy and based on this prediction, a treatment plan can be implemented (8). The Assessment of Different NEoplasias in the adenXa (ADNEX) model is a model which has been developed by the International Ovarian Tumor Analysis Group (IOTA) that includes a detailed description of the adnexal mass. The model includes six ultrasound parameters and three clinical variables and distinguishes the mass into five subtypes; benign, borderline, stage □ OC, stage □ - □ OC, and metastatic deposits in the ovary (9).

This study aims to determine the diagnostic performance of the ADNEX model in differentiating between benign and malignant ovarian tumors by testing its accuracy against the gold-standard histopathology.

Patients and Methods

This was a prospective diagnostic test accuracy study that was carried out during the period from January 2022 to January 2023 at the Department of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University. Before the initiation of the study, approval of the Ethical Committee of the Faculty of Medicine, Ain Shams University was obtained (MS 585 /2020, FWA 000017585). The sample size was calculated using the PASS program, setting the type-1 error (α) at 0.05 and the power (1-β) at 0.8. Results from a previous study showed that the sensitivity of ADNEX was 96% (2). Data from the RCOG guide showed that the sensitivity of RMI was 78% (10). Calculation according to these values produced a minimal sample size of 50 cases. The study participants were 50 postmenopausal patients who presented to the general gynecology or gynecological oncology outpatient clinic with adnexal mass.

All the included patients were postmenopausal; postmenopausal status was defined as having ≥ 1 year of amenorrhea without using any contraceptive method in women ≥ 45 years while for women < 45 years, two consecutive FSH samples 1 month apart with levels ≥ 30 IU/L were required to confirm menopause. Patients with the accidental discovery of ovarian mass during surgery for other reasons

and patients with known ovarian cancer who were scheduled for interval debulking after neoadjuvant chemotherapy were excluded from the study. Moreover, asymptomatic patients with ovarian cysts with the following criteria; simple, less than 5cm, unilocular, unilateral, and clear were also excluded from the study.

Informed consent was taken from study participants before enrollment and after a thorough explanation of the purpose of the study. After history taking and physical examination to confirm that the patient meets the inclusion / exclusion criteria, both RMI and ADNEX model were evaluated.

The **RMI** is measured as follows; **Menopausal status** (score is 3 as all patients were postmenopausal **X Ultrasound score** which is based on assessment of 5 features and with the presence of one feature, the score is 1 while if more than one feature is present, the score is 3; the five ultrasound features are the presence of solid components, multilocularity, bilaterality, ascites, and metastases **X CA – 125 level**. The **ADNEX** model includes nine parameters; Age, CA-125 level, Oncology center (yes/no), and 6 ultrasound features which are the maximal diameter of the lesion, maximal diameter of the largest solid part, more than 10 locules (yes/no), number of papillary projections (0/1/2/3/more than 3), acoustic shadow, and ascites. All data were entered and calculation of the risk of malignancy was done through the ADNEX model calculator available at the website: **iotagroup.org**. All ultrasound evaluations were performed by the same specialist who had more than 10 years of experience in ultrasound evaluation of adnexal masses.

The primary outcome of the study was to assess the predictive accuracy of both the RMI and ADNEX model for differentiating between benign and malignant ovarian tumors by setting both against the gold standard which is histopathology.

Regarding the statistical analysis, Data were analyzed using the Statistical Package for Social Sciences (SPSS version 25). Descriptive analyses were performed to obtain the means, median, standard errors (SE) or SD, IQR, and frequencies. Bivariate analyses were performed using an independent samples t-test and ANOVA test. ROC curves were constructed and the Area under the receiver operator characteristic curves (AUC) with binomial exact 95% confidence intervals were calculated between benign ovarian tumors and malignant ones. The diagnostic performance of the models was also expressed as AUCs. Regarding the comparison between the ADNEX and RMI diagnostic performance AUC, sensitivity, specificity, and positive and negative likelihood ratios were calculated, and MedCalc Software Ltd. Comparison of AUC of independent ROC curves was used to calculate the difference between two AUCs.

Results

A total of 76 patients were recruited. Twenty-six patients were excluded due to the following: 18 patients didn't meet our inclusion criteria; 6 patients had missing data; and 2 patients underwent the operation in another hospital. Fifty patients had their data analyzed.

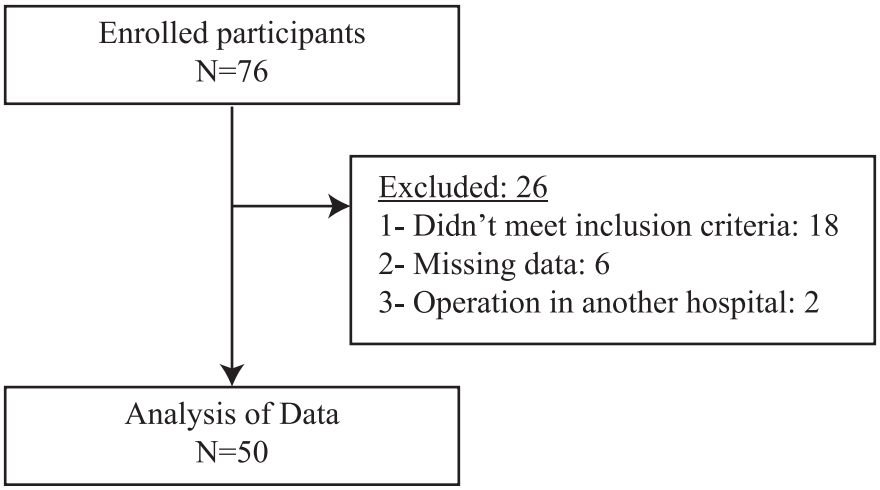

Figure 1: Flow chart of study participants

The sociodemographic data and the relevant data from history are shown in table 1. The presence of each component of the RMI in the study participants is shown in table 2 while table 3 represents the prevalence of each component of the ADNEX model in the study population.

Table 4 describes the different pathologic findings among the study cohort; Among the studied patients; 28 patients (56%) had benign pathology, 16 patients (32%) had malignant pathology, and the histopathologic examination of the specimens of the remaining 12% revealed borderline ovarian tumors. Among the patients with malignant ovarian neoplasms, 11 patients (68.75%) were stage □ - □, 4 patients (25%) had metastatic ovarian deposits while only 1 patient (6.25%) had stage □ ovarian cancer. Among the patients with benign lesions, the two predominant pathologies were serous and mucinous cystadenomas with both representing about 42.8% (21.4% each) while high grade papillary serous carcinoma was the predominant histopathology in patients with malignant OC (63.3%).

Table 5 compares the RMI values among the five histopathologic results with the values being significantly higher in patients with stage □ - □ OC. **Table 6** correlates between the sociodemographic data and the histopathologic subtypes with no significant association between any sociodemographic data and a particular subtype. **Table 7** showed that both ascites and CA-125 level are significantly higher among patients with stage □ - □ OC while the presence of 0-10 locules is significantly associated with benign pathology, there was no significant difference between the histopathologic subtypes regarding the other components of the ADNEX model.

Table 8 shows the AUC set to distinguish adnexal mass as benign or malignant for both ADNEX model and RMI (0.864 and 0.799 respectively). Sensitivity, specificity, positive likehood ratio, and negative likehood ratio for both screening models are shown in the same table; the best cutoff value obtained by this study was 10% for the ADNEX model and 115 for the RMI.

Table 9 shows the AUC when the ADNEX model is used for discrimination the type of the tumor among the five histopathologic subtypes. The highest AUC is 0.864 when the model was used to discriminate between benign and malignant cases and the lowest AUC is 0.722 when the model was used to discriminate between benign and borderline ovarian tumors.

Table 1: Sociodemographic data for the studied group (N=50)

Variable		
Age	Mean (SD)	59(6)
	Median (IQR)	59(56-61)
Parity	Mean (SD)	4 (2)
	Median (IQR)	3(2-5)
N (%)		
Education	Illiterate	3 (6)
	Primary	3(6)
	Secondary	5(10)
	Post -secondary	39(78)
PH of cancer	No	49(98)
	Yes	1(2)
FH of cancer	No	42(84)
	Yes	8(16)
	Breast	1(12.5)
	Endometrium	3(37.5)
	Ovary	1(12.5)
	Others	3(37.5)
Degree of relativity	First	6(75)
	Second	2(25)
HRT	No	50(100)
Infertility	No	42 (84)
	Yes	8 (16)
	Primary	5(10)
	Secondary	3(6)
Duration	Mean (SD)	8(2)
	Median (IQR)	9 (6-10)
Treatment	No treatment	3(37.5)
	Induction of ovulation	4(50)
	IVF	3(37.5)

Table 2: Ultrasound components of the RMI among the studied group:

		N (%)
Solid areas	No	25 (50)
	yes	25(50)
Bilaterality	No	38(76)
	yes	12(24)
Multilocularity	No	26(52)
	yes	24(48)
Ascitis	No	41(82)
	yes	9(18)
Metastasis	No	48(96)
	yes	2(4)
RMI value **Mean(SD)** **Min-Max**	**1557.6 (2988.6)** **149 (62- 1431)**	

Table 3: Components of the ADNEX model among the studied group

Age	Mean (SD)	59 (6)
	Median (IQR)	59(56-61)
Max. diameter of lesion(mm)	Mean (SD)	138(67)
	Median (IQR)	130(83-180)
Max. diameter of largest solid part (mm)	Mean (SD)	29(40)
	Median (IQR)	0 (0-39)
CA125	Mean (SD)	216.48(390.1)
	Median (IQR)	44.70 (17.9- 217.5)
	N (%)	
Oncology Center	Yes	50 (100)
Locules	No	1 (2)
	0-10	38 (76)
	>10	11 (22)
No. of papillary projections	0	33 (66)
	1	5(10)
	2	5(10)
	3	4(8)
	>3	3(6)
Acoustic shadow	No	36(72)
	Yes	14(28)
Ascites	No	36 (72)
	Yes	14(28)

Table 4: Pathological findings among the studied group

		N (%)
Pathology (n=50)	**Benign**	**28 (56)**
	Serous cystadenoma	6 (21.4)
	Mucinous cystadenoma	6 (21.4)
	Mature cystic teratoma	3 (10.7)
	Serous cystadenofibroma	3 (10.7)
	Fibroma	5 (17.8)
	Thecoma	1 (3.5)
	Paraovarian simple cyst	2 (7.1)
	Tubo-ovarian abscess	1 (3.5)
	Endometriotic cyst	1 (3.5)
	Borderline	**6 (12)**
	Mucinous	4 (66.7)
	Clear	1 (16.7)
	Serous	1 (16.7)
	Malignant stage I (Mucinous cystadenocarcinoma)	**1(2)**
	Malignant Stages II- IV	**11 (22)**
	HGSC	7 (63.6)
	Low grade serous carcinoma	1 (9.09)
	Endometrioid adenocarcinoma	3 (27.2)
	Metastatic	**4 (8)**
	Breast	1 (25)
	Appendix	1 (25)
	GIT	1 (25)
	Uterus	1 (25)

HGSC: High grade papillary serous carcinoma

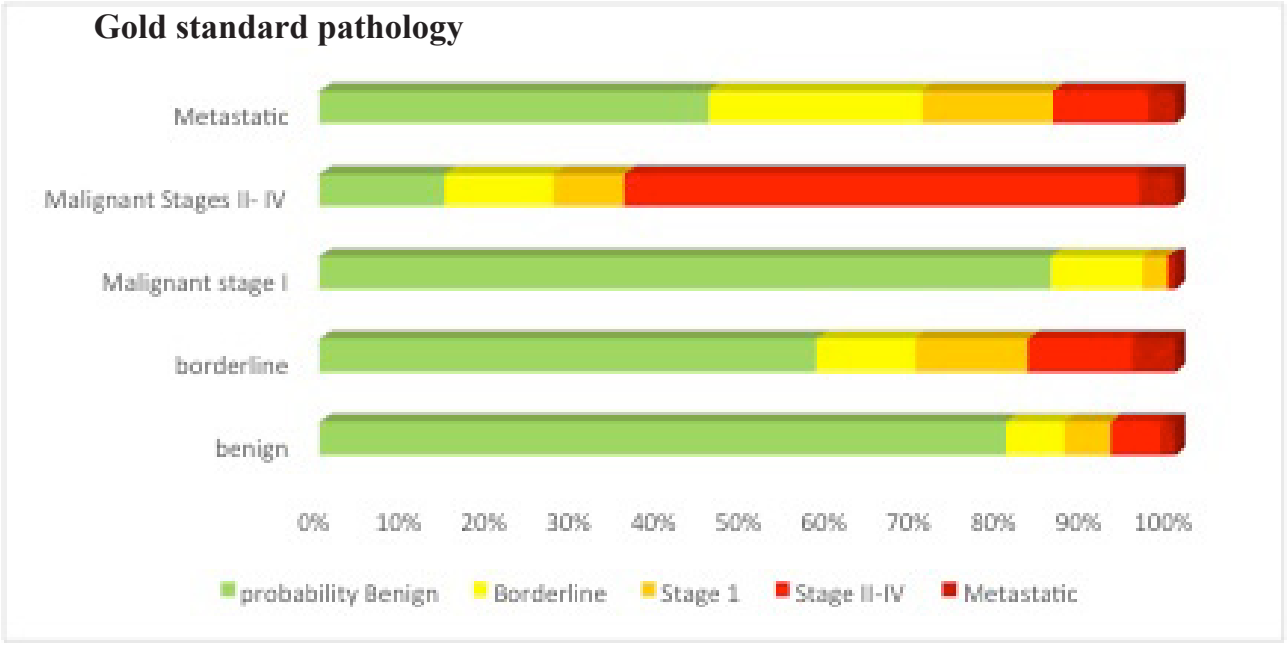

Figure 2: Average predicted risk by ADEX for different pathology results among the studied group

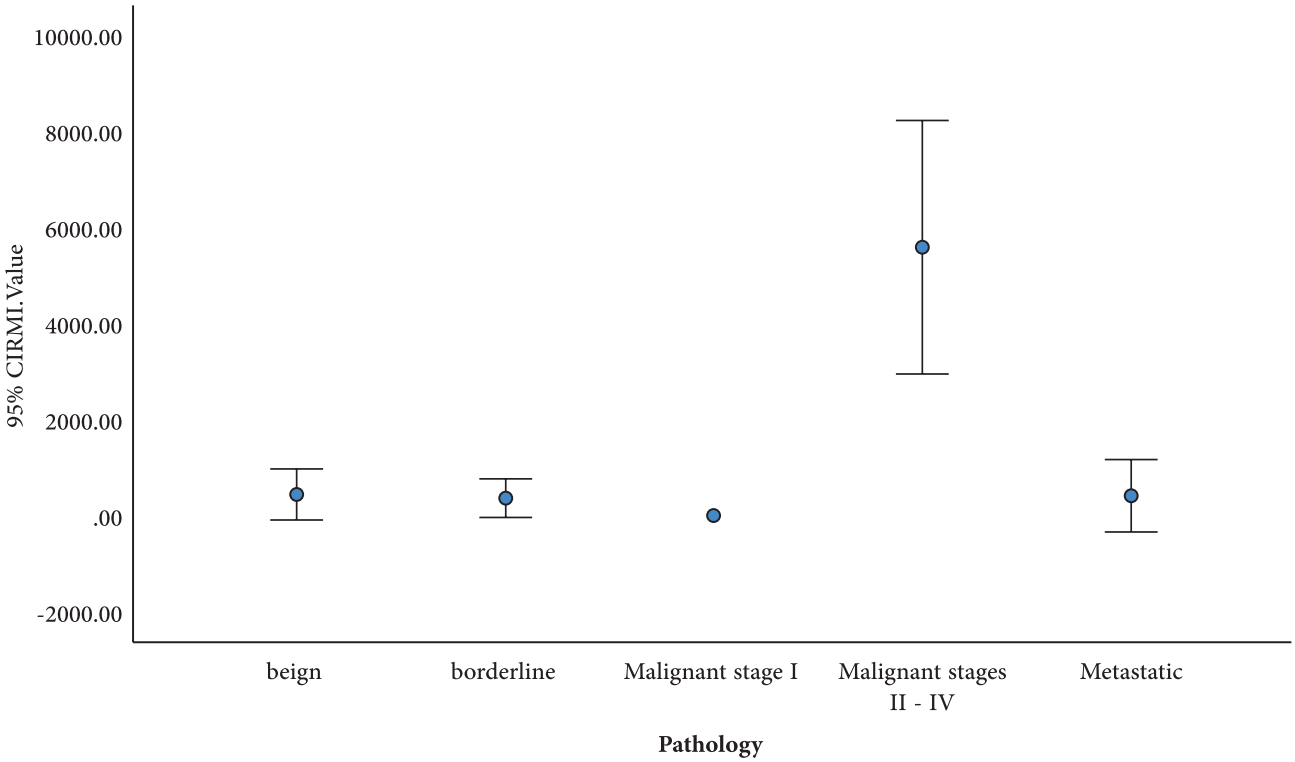

Figure 3: Error bar shows the mean and 95% CI of RMI va lues among different pathology

Table 5: Comparison of different pathology results and RMI value among the studied group (n=50)

			RMI. Value	Test of sig
Pathology	benign	Mean (SD)	439.38 (1348.2)	ANOVA F= 12.68 P value = <0.001*
		Median (IQR)	81.30 (50.3-165.6)	
	borderline	Mean	372.69 (372.69)	
		Standard Deviation	373.52	
		Median	174.58(117-762)	
	Malignant stage I	Mean	6.00 (0)	
		Median	6.00	
	Malignant Stages II- IV	Mean	5611.55 (3941)	
		Median	4599 (2394- 7110)	
	Metastatic	Mean	402.52 (458.2)	
		Median	261.0 (60- 744.3)	

* P value < 0.05: significant

Table 6: Comparison between sociodemographic data and pathology results among the studied group

		Pathology						
		Total (N=50)	Benign (N=28)	Borderline (N=6)	Malignant Stages I (N=1)	Malignant Stages II- IV (N=11)	Metastatic (N=4)	Chi-square p-value
Age cat	<59	30 (60)	18(64.3)	2(33.3)	1(100)	7 (63.6)	2(50)	0.577
	> 59	20(40)	10(35.7)	4(66.7)	0	4(36.4)	2 (50)	
Parity cat	<3	26(52)	13(46.4)	2(33.3)	1(100)	8(72.7)	2(50)	0.408
	> 3	24(48)	15(53.6)	4	0	3(27.3)	2(50)	
Education	literate	3(6)	1(3.6)	0	0	2(18.2)	0(0)	0.604
	primary	3(6)	1(3.6)	0	0	2(18.2)	0(0)	
	Secondary	5(10)	3(10.7)	1	0	0(0)	1(25)	
	University	39(78)	23(82.1)	5	1(100)	7(63.6)	3(75)	
PH of cancer	No	49(98)	28(100)	6	1(100)	11(100)	3(75)	0.019*
	Yes	1(2)	0(0)	0	0	0(0)	1(25)	
FH of cancer	No	42(84)	25(89.3)	4	1(100)	8(72.7)	4(100)	0.418
	Yes	8(16)	3(10.7)	2	0	3(27.3)	0(0)	

* P value < 0.05: significant

Table 7: Components of the ADNEX models in different histopathologic subtypes

		Benign (N=28)	Borderline (N=6)	Malignant Stages I (N=1)	Malignant Stages II-IV (N=11)	Metastatic (N=4)	p-value
ADNEX. age	Mean(SD)	58.75(7)	61 (3)	46	60 (5)	63(9)	0.199
Max. diameter of lesion(mm)	Mean(SD)	135.4 (75)	162(37)	180	123(59)	148 (85)	0.790
Max. diameter of the largest solid part (mm)	Mean(SD)	19.5(40)	29(35)	0	50(38)	41(47)	0.262
CA125	Mean(SD)	82.04(174)	57.16(34)	2.30	726.3(543)	47.9(48)	<0.001*
Locules N(%)	No	0 (0)	0(0)	0(0)	1 (9.1)	0(0)	0.031*
	0-10	26(92.9)	5(83.3)	0(0)	5(45.5)	2(50)	
	>10	2 (7.1)	1(16.7)	1 (100)	5(45.5)	2(50)	
No. of papillary projections N(%)	0	22(78.6)	5(83.3)	1 (100)	4(36.4)	1(25)	0.106
	1	2(7.1)	1(16.7)	0(0)	1(9.1)	1(25)	
	2	4(14.3)	0(0)	0(0)	1(9.1)	0(0)	
	3	0 (0)	0(0)	0(0)	3(27.3)	1(25)	
	>3	0(0)	0(0)	0(0)	2(18.2)	1(25)	
Acoustic shadow N(%)	No	22(78.2)	6(100)	1 (100)	5(45.5)	2(50)	0.087
	Yes	6(21.4)	0(0)	0(0)	6(54.5)	2(50)	
Ascites N(%)	No	26(92.9)	5(83.3)	1 (100)	2(18.2)	2(50)	<0.001*
	Yes	2(7.1)	1(16.7)	0(0)	9(81.8)	2(50)	

* P value < 0.05: significant

Table 8: Comparison between RMI value and ADNEX Performance for differentiating benign from malignant tumors

Variable(s)	AUC	Sensitivity	Specificity	LR +	LR -	SE	P value	95% CI	
								Lower	Upper
ADNEX	0.864	91.1%	65%	2.66	0.257	0.057	<0.001*	0.752	0.976
RMI	0.799	81.8%	60.7%	2.06	0.299	0.067	<0.001*	.667	.930
P value	0.460	Difference =0.065		SE of difference=0.088		Z test =0.73			

Cutoff for ADNEX = 10%, and for RMI=115
LR +: positive likehood ratio / LR - : negative likehood ratio

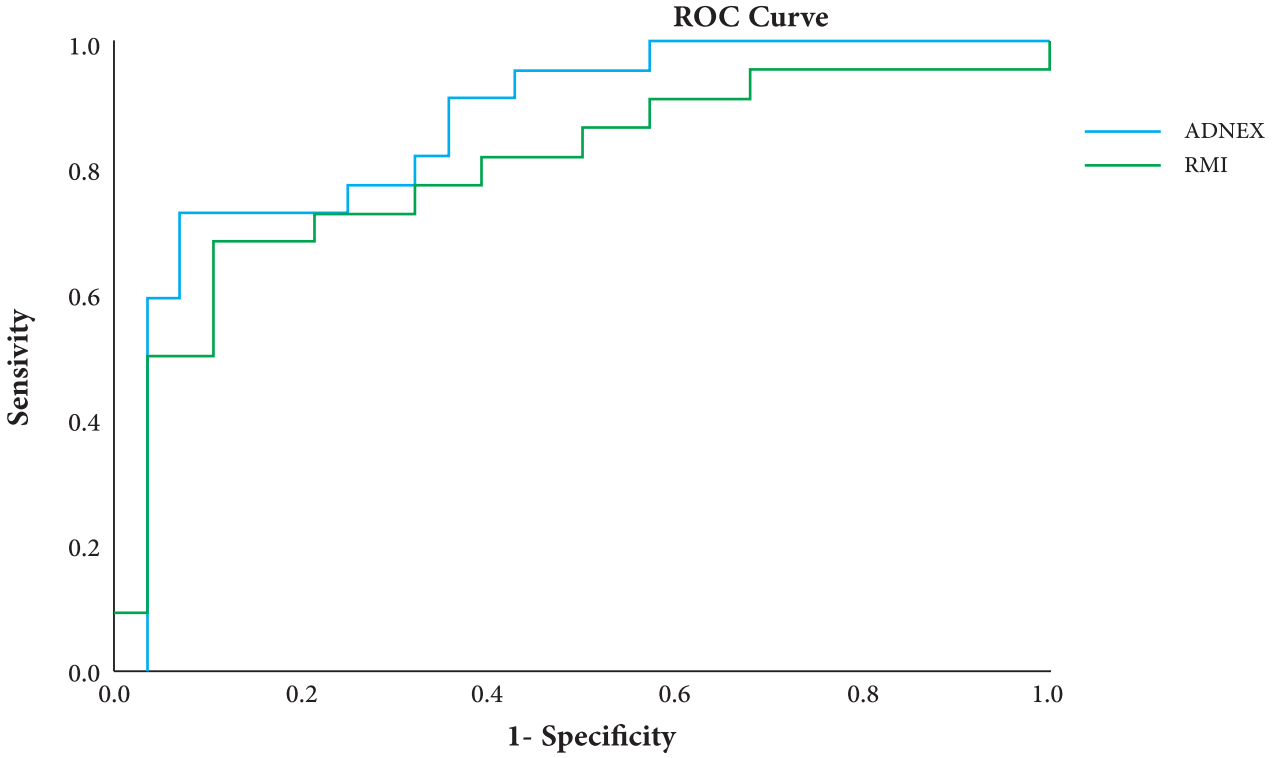

Figure 4: ROC curve for both RMI and ADNEX model

Table 9: Performance of Assessment of Different NEoplasias in the adneXa (ADNEX) model for five tumor types, expressed as area under the receiver–operating characteristics curve (AUC)

Types of tumors	AUC	P value	95% CI	
			Lower	Upper
Benign vs malignant	0.864	<0.001*	0.752	0.976
Benign vs Borderline	0.722	0.007*	0.575	0.870
Benign vs Stage 1	0.724	0.007*	0.579	0.869
Benign vs Stage II-IV	0.823	<0.001*	0.694	0.953
Benign vs Metastatic	0.791	<0.001*	0.663	0.918

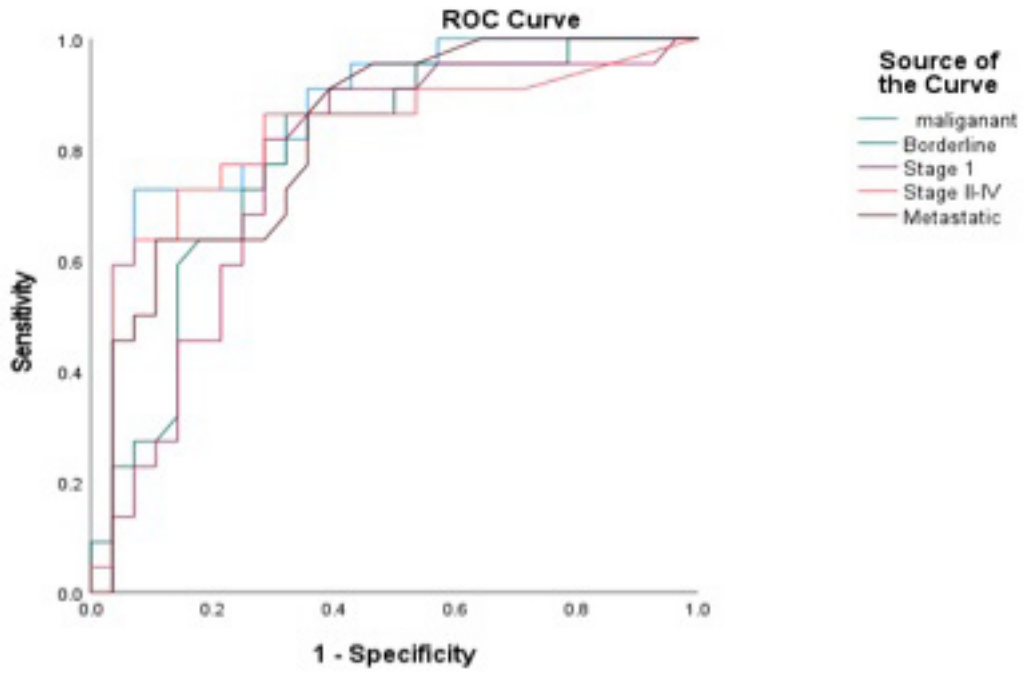

Figure 5: ROC curve shows AUCs for different pathology results

Discussion

Ovarian cancer is predominantly a cancer of postmenopausal women, and it is rare in women below the age of 40 years. Thus, it is classically described as a disease of older women. The median age for women with ovarian cancer ranges from 60 to 65 years in most developed countries. As life expectancy has increased in most countries worldwide, and because the incidence rate of ovarian cancer increases with age, more and more postmenopausal women will have ovarian cancer (11).

Regarding the **sociodemographic data** of the study participants, the overall median age of the study participants was 59 years. All of the included participants were postmenopausal and so, age didn't affect the RMI value as all patients got a score of 3. However, age is a component of the ADNEX model and with increasing age, the probability of malignancy increase. Our study showed no significant difference between those who were older than 59 years and those who were 59 years or younger regarding histopathology results as no certain pathologic entity was significantly higher in either group. Our results were consistent with Huwidi et al., who assessed the diagnostic value of RMI among patients with adnexal mass; there was no significant difference between different age groups regarding either benign or malignant pathology however, the study included different age groups and was not restricted to postmenopausal women (12). Zhang et al., showed no significant age difference between those with benign pathology and those with borderline ovarian tumors in their retrospective study which tested the predictive ability of the RMI among the study patients (13). The performance of ADNEX model for prediction of ovarian cancer was assessed and there was no significant age difference between different pathology groups in the study conducted by Yang et al., however, the study conducted by Lam Huong et al., showed significantly higher median age among patients who were diagnosed with cancer which can be attributed to the much smaller number of patients with cancer (65 VS 396) (14,15). As for parity, the median **parity** in our study was 3 and

there was no remarkable difference at any histopathologic group between patients who were para 3 or less and those who were more than para 3.

The **level of education** of the study participants was assessed in our study. More than 75% of the study cohort reached university level. Alberg et al., evaluated the socioeconomic status of African-American women and their relation to the risk of ovarian cancer, the study revealed an inverse relationship between educational level and ovarian cancer risk after adjustment for ovarian cancer risk factors (16). Such relationship could be explained the cross sectional study which was conducted by Elshami et al., and showed higher level of awareness about risk factors and protective factors of ovarian cancer among those with post-secondary education (17).

Regarding **past history of cancer** among the study participants, only one patient in the study cohort had past history of cancer which was cancer breast and the histopathology revealed that the ovarian mass was already a metastatic deposit. Studies with much larger sample size which targets the relation between past history of gynecological or GIT cancer and present ovarian cancer as its primary outcome and the associated syndromes as BRCA1 or 2 mutation and Lynch syndrome can be of value for better assessment of the relationship between certain malignancy and ovarian cancer

Family history of ovarian or ovarian cancer is well known risk factor for development of OC. At our study, 16% of the study participants had family history of malignancy; only one case had past history of breast cancer but ultimately she had benign pathology and one case with borderline ovarian tumor had family history of ovarian cancer.

Studies that have thoroughly adjusted for the effects of factors like duration of oral contraceptive use and number of full-term pregnancies, have not noted a strong association between difficulty in conceiving and the risk of ovarian cancer among parous women. However, an increased risk among infertile women who remain childless despite long periods of unprotected intercourse has been reported in two large, pooled analyses. It remains to be understood whether such women are at risk due to the primary basis for their infertility, some correlate of infertility such as exposure to ovulation-inducing drugs, a shared genetic susceptibility to ovarian cancer and infertility, or some other reason (18). Previous studies have debated whether OI could increase the risk of invasive ovarian cancer (IOC) and borderline ovarian tumors (BOT). Although most studies have concluded that OI does not contribute to the risk of IOC and BOT, some scholars still proposed that OI may be associated with them (19). Infertility, its duration and the management which was adopted to deal with it was assessed in our study; 8 patients representing 16% of the study participants had history of infertility and out of those 8 patients, 3 received induction of ovulation for treatment of their fertility problems with only one patient developing ovarian cancer. Retrospective cohort studies with much larger sample size is more suitable for evaluating the relationship between infertility and ovarian cancer.

The RMI was evaluated in different histopathologic subtypes and it was shown to be significantly higher among those with malignant pathology stages □ - □ and in those with metastatic ovarian cancer. Our results were similar to those obtained by Lycke et al., who showed significantly higher mean RMI among patients with FIGO stage □, □ ovarian cancer compared with those with benign or borderline ovarian tumors whether the patients were premenopausal or postmenopausal (20). Similar results were also achieved by Dora et al., who showed significantly higher RMI among patients with malignant ovarian masses (21). Only one patient among our study cohort was diagnosed with stage □ ovarian cancer and so a comparison with

benign cases regarding the RMI value needs further studies with more cases ultimately diagnosed with stage □ ovarian cancer.

The components of the ADNEX model were evaluated in the five histopathological categories; the three components which were significantly different between the were the CA-125 level, the presence of ascites, and the number of locules. The first 2 were associated with malignant cases while from 1-10 locules were predominant in the benign cases. Lam Huong et al., showed that ascites was more prevalent in the cancer group however, there was significant difference regarding all other components; this difference can be attributed to the fact that the study wasn't limited to postmenopausal women. Moreover, the histopathological results were either benign or malignant i.e the analysis was not based on the five histopathological groups which can be predicted by the ADNEX model (15). The results obtained by Yang et al., showed significant difference between benign and malignant cases regarding all ultrasound components of the ADNEX model however, the authors included the patients with borderline ovarian tumors into the malignant category despite being completely different entity and this could affect the reliability of the findings (14). In daily practice, the two most prevalent histological subtypes are the benign and the stage □ - □ OC and so, for prospective assessment, comparison between these two subtypes in particular would be more reliable in identifying which ultrasound feature correlate better with a given subtype. The other 3 histological subtypes are relatively rare and so, multicentric and retrospective studies would be more suitable for evaluation of the ultrasound features of these 3 subtypes.

The **diagnostic performance** of both RMI and ADNEX model for differentiating benign from malignant ovarian tumors was assessed; the ROC curve showed a bigger area under the curve (AUC) for the ADNEX model. Regarding the RMI, a cutoff of 115 was associated with 81.8% sensitivity, 60.7% specificity, positive likehood ratio of 2.06 and negative likehood ratio of 0.299 while the ADNEX model at a cutoff level of 10 was associated with 91.1% sensitivity, 65% specificity, 2.66 positive likehood ratio and 0.257 negative likehood ratio. By using the ADNEX model, Yoeli-Bik et al., achieved a sensitivity of 91%, specificity of 86%, LR+ of 6.7, and LR- of 0.7 and these results were obtained at 10% cutoff; such higher specificity could be attributed to the fact that 33% of the study cohort didn't undergo surgical intervention and were included in the study if they had adequate clinical or imaging follow-up which can point to a tendency towards operating on cases with high probability of malignancy which shall decrease the incidence of false positive results (22). Another muticenter cohort study by Van Calster et al., which included 4905 patients from 36 oncology centers assessed the predictive ability of the ADNEX model and the RMI for detecting ovarian cancer; regarding the ADNEX model, the overall sensitivity was 91% and the overall specificity was 85% and this was achieved with 10% risk threshold and 0.94 AUC. The higher AUC compared to our study can be attributed to the much larger sample size and the fact that 2151 patients (44%) of the study cohort were postmenopausal women which would increase the probability of ovarian malignancy in the cohort. Regarding the RMI, at a cutoff of 200, the overall sensitivity was 60% and the specificity was 95%, such lower sensitivity and higher specificity compared to our study is attributed to the lower cutoff value which was set (115 vs 200) (23). Another study by Pelayo et al., which assessed the predictive accuracy of the ADNEX model yielded 94% sensitivity and 82% specificity with 0.92 AUC; the lower false positive cases compared to our study can be attributed to the fact that 39% of the study participants suffer from digestive symptoms which should increase the probability of malignancy in contrast to our study participants who were asymptomatic besides the fact that 16 % of the

study participants underwent sonography by non-expert sonographers and 8 % came from the emergency room; such diversity could affect the reliability the interpretation of the ultrasound findings (24). Results obtained by Poonyakanok et al., showed 98% sensitivity and 87% specificity when using 10% threshold of malignancy probability; the higher sensitivity and specificity compared to our study can be attributed to the fact that the authors excluded 13 patients from those who were recruited as they were ultimately diagnosed with uterine or abscess lesions which would indirectly raise the accuracy of the ultrasound which is integral part of the ADNEX model (25). Results were also similar to those obtained by Peng et al., who achieved with the same cutoff value a 94% sensitivity, 74% specificity, 3.06 LR+ and 0.08 LR-; both studies were conducted at a tertiary oncology centers and the incidence of benign and malignant pathology were also similar (26). Yang et al., achieved 93% sensitivity, 73% specificity, 3.39 LR+ and 0.1 LR- using 10% malignant probability; the authors excluded masses which didn't originate from the ovary on the histopathology specimen; this exclusion will raise the predictive ability of the ultrasound and will decrease the false positive results (14).

The ADNEX model discriminates ovarian tumors into five subtypes; benign, borderline, malignant stage □, malignant stage □-□, and metastatic ovarian deposits. At our study, the model performed best at discriminating between benign and malignant ovarian tumors with AUC of 0.864 while the least performance was observed with differentiating between benign and borderline and stage I OC with AUC of 0.722 and 0.724 respectively. Results achieved by Sayasneh et al., showed the highest performance when discriminating between benign and stage □- □ OC with AUC of 0.99; the higher AUC compared to our study in particular when the model discriminated between benign and stage □ OC is attributed to the much higher sample size in the that multicenter study which led to higher percentage of patients with stage □ OC compared to our study (8% vs 2%) and the fact that the percentage of cases diagnosed with stage □ - □ OC in our study was the double (22% vs 11%) had led to the lesser AUC in our study when ADNEX model was used to discriminate between benign and malignant cases (0.864 vs 0.99) (27). Meys et al., assessed the performance of the ADNEX model for the five tumor subtypes and the highest AUC was obtained when the model was used to discriminate between benign and stage □ - □ OC (0.97) which is higher compared to our study (0.823) which could be related to the fact that the percentage of benign cases was lower in our study (56 % vs 64%) (28). These results are in agreement with the results obtained by Van Calster et al., which also showed in their multicentric study that the highest AUC obtained when benign lesions are compared against stage □ - □ OC; the comparison of power of discrimination between benign and all other four histological subtypes showed excellent performance by ADNEX model with all AUCs higher than 0.9; the high percentage of benign lesions among the studied cohort (67%) in comparison with other histological subtypes can contribute to this performance (29).

The ADNEX model can change the future management of ovarian cancer by prediction of the staging of ovarian cancer which is particularly important as it largely improves the prognosis when the cancer is detected at stage □. It has better sensitivity and specificity for differentiating between benign and malignant tumors when compared with RMI; however, it needs more experience in the ultrasound evaluation of adnexal masses so it can be implemented in screening programs on a large scale. Moreover, the discrimination between the five histopathologic subtypes is of a great value as it can lead to proper triaging of the patients; when the model predicts that the mass is benign, the patient can be managed by in a general gynecology hospital while if

it predicts a malignant nature of the mass, the patient must be referred to a gynecological oncology for multidisciplinary team (MDT) consultation as this will largely influence the management and prognosis. Such MDT consultation will guide the management to achieve the best possible results; when the model predicts borderline or stage □ OC, the patient should have optimum surgical staging by an experienced gyne-oncologist while patients with high probability of stage □ - □ can have further imaging as Computed Tomography (CT) scan abdomen and pelvis for better detection of advanced disease and then receive neoadjuvant chemotherapy first followed by interval debulking. Finally, if the model predicts that the mass is metastatic, other investigations can be ordered to find out the primary origin such as mammogram, upper and lower GIT endoscopy or even Positron Emission Tomography (PET)-Scan and the patient can avoid surgery and its potential complications.

The major drawback of the ADNEX model is the fact that it needs significant experience in the field of ultrasound so as to be fruitful and of value. Training programs must be adopted in order to upgrade the skills needed for precise evaluation of adnexal masses by ultrasound which is extremely important before using the ADNEX model for screening purposes.

Our study was not without limitations; data were collected from single tertiary center and this can negatively impact the representation of different regions of the country in this study. Further studies from different centers are needed so as to produce a larger sample size which will be a better representative of the predictive ability of the ADNEX model particularly for rare findings such as borderline and stage □ OC

Conclusion

ADNEX model is more sensitive than RMI for differentiating between benign and malignant tumors and it can be used as screening test. However, the application of ADNEX model needs significant experience in ultrasound evaluation of adnexal masses before it can be an integral part in the screening pathway of ovarian malignancy in postmenopausal patients with adnexal masses.

Declarations of interest

a) Ethical approval and informed consent:

Informed consent was obtained from study participants. The study was registered in Clinicaltrials.gov, ID: NCT05755841 , and was approved by the Research Ethics Committee, Faculty of Medicine, Ain Shams University (MS 585 /2020, FWA 000017585). All methods were carried according to the relevant guidelines and regulations in the Declaration of Helsinki

b) Authors' contribution:

Elmaraghy AM: Protocol development Manuscript writing - Data analysis

El-shalakany AH: Protocol development Manuscript editing - Data analysis

Dwedar AMM: Data collection

Ahmed ME: Data analysis

Morsi H: Data collection

Labib K: Protocol development

c) Publication statements:

The authors declare that this work described has not been published before; that it is not under consideration for publication anywhere else; that its publication has been approved by all co-authors, if any, as well as by the responsible authorities.

d) Funding:

The study was based on investigators' self-funding

e) Conflicts of interest:

The authors declare that there are neither fi-

nancial nor non-financial conflicts of interest concerned with the manuscript of the study

f) Consent to participate:

Informed consent was obtained from all individual participants included in the study.

g) Consent to publish:

Study participants consented to publish their data prior to submitting this paper to the journal.

h) Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

i) Acknowledgments:

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