EJGO European Journal of Gynaecological Oncology

Original Research

Preoperative discriminating performance of the IOTA-ADNEX model and comparison with Risk of Malignancy Index: an external validation in a non-gynecologic oncology tertiary center

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Summary

Aim: This study aimed to externally validate the International Ovarian Tumor Analysis-Assessment of Different Neoplasias in the adnexa IOTA-ADNEX model in a tertiary center without a specific gynecologic oncology unit to be used for referral to an oncology center, and to compare its performance with Risk of Malignancy Index (RMI) I-IV. *Materials and Methods:* Data of 285 women who underwent surgery for an adnexal mass with known CA-125 values were prospectively collected and retrospectively analyzed. Preoperative scores of ADNEX model and RMI I-IV were compared with final histopathological diagnosis. Patients were further classified according to their menopausal state. *Results:* Rate of malignancy was 9.1%. Sensitivity and specificity rates of ADNEX model in discriminating malignant tumors were found to be 88.5% and 84.6%, respectively (AUC 0.865 ± 0.039), irrespective of menopausal state at 10% cut-off value as proposed by the original article. Optimal cut-off value of ADNEX model to discriminate malign tumors was found as 14%. ADNEX model exhibited superior sensitivity and specificity compared to all four RMI models. This model was able to discriminate benign lesions from borderline, Stage I ovarian cancer (OC) and Stage II-IV OC, borderline tumors from Stage II-IV OC, and Stage I from Stage II-IV OC (AUC > 0.700) very well. On the other hand, discrimination between borderline with Stage I tumors (AUC 0.576 ± 0.152) was mediocre. *Conclusion:* ADNEX model adds a stratified classification and might be clinically useful for the triage of patients admitted to a non-oncologic center with suspicious adnexal masses to be referred to specialized oncology units.

Key words: Adnexal mass; Decision support techniques; Ovarian neoplasms; Sensitivity and specificity; Ultrasonography.

Introduction

Differential diagnosis of ovarian tumors and identifying adnexal masses remain the most challenging problems in modern gynecology. Although a small fraction of these masses is malignant, a correct preoperative diagnosis is indispensable in the management of adnexal pathology. Treatment and management of these depend on the preoperative differentiation which is essential to optimize care and thereby morbidity, mortality, and survival of the patient [1, 2]. Prevalence of ovarian cancer excluding borderline tumors between 2009 and 2013 in the United States is 11.2/100.000 with a mortality of 7.5 per 100,000 women [3]. The overall survival rates were 78.2% for one-year and 46.2% for five-year of all stages excluding borderline cases [3]. Early diagnosis of malignancy and centralized management in experienced centers are essential to optimize survival [3–5]. Assessment by an ultrasound expert is considered as one of the best ways to differentiate between a benign and malignant adnexal mass prior to surgery [6]. Various ultrasonography-based prediction models and scoring systems have been developed to increase the objectivity and simplicity and to reduce the variation in diagnoses for use by less experienced examiners. It has recently been shown in systematic reviews and meta-analyses that there are only small differences in sensitivity and specificity of ovarian cancer diagnosis between ultrasound operators of varying levels of expertise when using any models and scoring systems [6–8]. One of these scoring systems, The Risk of Malignancy Index (RMI) is an easy, inexpensive, and reliable tool for preoperative assessment. RMI allows accurate planning for management, appropriate preoperative triage of patients to a gynecologist or a gynecological oncologist for expert pattern recognition with combining menopausal state, CA-125, and ultrasonography [9].

RMI is currently recommended by many national guidelines [10]. Another model with encouraging performance was recently developed by the International Ovarian Tumor Analysis (IOTA) group. Assessment of Different Neoplasias in the adnexa (ADNEX) model consists of three clinical and six ultrasound features to predict the risk of benign ovarian tumor, borderline ovarian tumor (BOT), Stage

Published: 15 April 2020

Eur. J. Gynaecol. Oncol. - ISSN: 0392-2936
XLI , n. 2, 2020
doi: 10.31083/j.ejgo.2020.02.4971

I ovarian cancer (OC), Stage II-IV OC, and ovarian metastasis [11]. This model does not only predict whether a mass is benign or malignant, it also attempts to preoperatively identify various histological types and tumor extension. Gaining insight in specific tumor type makes it possible to optimize treatment which may reduce morbidity and lead to enhanced survival [1, 12]. For example, the effort of distinction between borderline and malignancy is important in the treatment of premenopausal women in order to preserve fertility [11, 12]. The patients at specialized gynecologic oncology centers tend to be clinically and demographically different than others [1, 13].

Most of the recent studies which externally validated the performance of the ADNEX model have been conducted in gynecologic oncology units (GOU) [12-16]. However, it was suggested that their results might not be generalizable due to not including non-gynecologic oncology units, resulting in there being a relatively high prevalence of malignant disease in the study population [14, 17].

Since ADNEX model has the potential to select patients for referral to an oncology center, more evidence to prove the effectiveness of ADNEX model in a non-GOU is needed. The aim of this study was to externally validate the preoperative discriminating performance between benign and malignant adnexal masses of the ADNEX model in a non-GOU and to compare it with another frequently used model (RMI) in the differential diagnosis of an adnexal mass.

Materials and Methods

This study was conducted in a tertiary non-gynecologic oncology center. Medical records of women who underwent surgery due to adnexal mass between January 2013 and September 2016 were analyzed. Indications for surgery were based on individual clinical findings. Women in whom clear evidence of pregnancy, history of malignancy before the surgery, and duration over 120 days between the ultrasonographic evaluation and obtaining pathology were excluded from the study.

Approval from the local Ethics committee was obtained. Collected data were age, reproductive history, ultrasound findings, serum CA-125-II levels, menopausal score, and intraoperative findings. There was no missing data except for serum CA-125-II values in 13 patients which were excluded from the statistical analysis. RMI and ADNEX models were calculated retrospectively by using prospectively collected data. In cases of missing parameters, data were obtained by reassessing the still images. Ultrasonographic examinations were performed prior to the operations by the same team who were Level III skilled in gynecologic sonography and trained in applying the IOTA terms and definitions. Histopathological diagnosis was taken as the gold standard for the calculations and the guideline of the World Health Organization International Classification of Ovarian Tumors was followed for classification [18]. Stage, grade, and histological subtype of the patients were defined according to International Federation of Gynecology and Obstetrics (FIGO) standards. Adnexal masses were described according to IOTA terms and definitions [19].

ADNEX model calculates the risk of ovarian cancer by using software with mathematical algorithms. The model includes three clinical parameters and six ultrasonographic features as described by Van Calster *et al.* [11] RMI was calculated according to ultrasonographic findings, values of CA-125 serum levels, and menopausal state. Scoring system was based on ultrasonographic findings including multilocularity, solid areas, bilaterality, ascites, and intra-abdominal metastases which were scored as one point for each feature. Serum CA-125 values were entered directly into the equations. Preoperative serum CA-125 levels were measured by Architect i2000SR CA-125 II System. Postmenopausal state was defined as more than one year of amenorrhea or age 50 years or older women who had prior hysterectomy. Based on the data obtained RMI-1, RM1-2, RMI -3, and RMI-4 were calculated for all patients: RMI-1 = U × M × CA-125; a total USG score of 0 made U=0, a score of 1 made U=1, and a score of ≥ 2 made U=3. Premenopausal and postmenopausal state made M=1 and M=3, respectively [20]. RMI-2 = U × M × CA-1250; a total USG score of 0 or 1 made U=1, and score ≥ 2 made U=4. Premenopausal and post-menopausal state made M=1 and M=4, respectively [21]. RMI-3 = U × M × CA-125; a total USG score of 0 or 1 made U=1, and a score of ≥ 2 made U=3. Premenopausal and postmenopausal state made M=1 and M=3, respectively [22]. RMI-4 = U × M × S × CA-125; a total USG score 0 or 1 made U=1, and score of ≥ 2 made U=4. Premenopausal and postmenopausal state made M=1 and M=4, respectively. A tumor size (single greatest diameter) of < 7 cm made S=1 and ≥ 7 cm made S=2 [23]. Surgeries of the patients were performed in the present clinic as indicated and the decision to perform frozen section analysis was made by the gynecologist on the basis of the suspicion of ovarian malignancy before or during surgery. ADNEX model and RMI types were correlated with final Histopathological diagnosis. Patients were further classified by their menopausal state.

Power of the study was calculated by using PASS 2008 (Power analysis and sample size). Calculated power was found as 71.2% for the lowest area under curve (AUC; 0.723) of RMI and 100% for the AUC (0.950) of malignity index in IOTA-ADNEX model. Statistical analysis was performed by using SPSS 22.0 software. For statistical purposes, borderline tumors were consid-ered as malignant. In women with bilateral tumors only the tumor with the most complex ultrasound morphology was included into the statistical analysis. If both masses had the same morphology, the mass with the largest size was used.

Shapiro-Wilk test was performed if the data fit normal distribution according to the Levene's test for the homogeneity of vari-ance. Mann-Whitney U, Kruskal-Wallis, post hoc Dunn's, Pearson's Chi-Square and Fisher's Exact tests, and polytomous discrimination index were used as appropriate.

Receiver operating characteristics curves (ROC curves), sensitivity, specificity, and accuracy rates were calculated for the ADNEX-model, RMI-1, RMI-2, RMI-3, and RMI-4 and summarized by the AUC with 95% confidence interval (CI) using 3%, 5%, 10%, 15%, and the optimal cut-off values denoting the total risk of malignancy. A $p < 0.05$ was considered as the level of sta-tistical significance.

Results

A total of 298 women who underwent surgery for an adnexal mass were eligible and enrolled in the study. The final cohort consisted of 285 patients; 189 (66.3%) premenopausal and 96 (33.7%) postmenopausal patients.

The median interval between the last preoperative ultra-

Table 1. — *Histologic subtypes of the adnexal masses (n=285).*

Histological subtypes	Total, n (%)	Premenopausal, n (%)	Postmenopausal, n (%)
Benign (90.9%)			
Benign brenner tumours	3 (1.1)	0	3
Cystadenofibromas	16 (6.1)	10	6
Endometriomas	69 (26.6)	64	5
Fibromas	11 (4.2)	0	11
Functional cysts	17 (6.5)	14	3
Mixed	4 (1.5)	4	0
Mucinous cystadenomas	20 (7.7)	15	5
Serous cystadenomas	70 (27)	32	38
Teratomas	40 (15.4)	31	9
Tubal torsion	1 (0.3)	1	0
Tubo-ovarian abscesses	8 (3)	4	4
Total	259 (100)	175 (67.6)	84 (32.4)
Malignant (9.1%)			
Adult granulosa cell tumors	1 (3.8)	0	1
Clear cell carcinomas	1 (3.8)	0	1
Endometrioid/clear cell carcinomas	1 (3.8)	0	2
Serous adenocarcinomas	10 (38.4)	8	1
Serous papillary/clear cell adenocarcinomas	2 (7.7)	1	1
Serous papillary/endometrioid adenocarcinomas	1 (3.8)	0	1
Sertoli Leydig	1 (3.8)	0	1
Endometrioid borderline	1 (3.8)	0	1
Mucinous borderline	3 (11.5)	3	0
Serous borderline	2 (7.7)	0	2
Ovarian metastasis	3 (11.5)	2	1
Total	26 (100)	14 (53.9)	1

sound assessment and obtaining the pathology specimen was 15 days. Pathology results were benign for 259 (90.88%) patients and 26 (9.12%) patients were malignant (Table 1). The most common benign pathologies were cystadenomas (serous and mucinous), endometriomas, and mature teratomas. Mixed benign tumors (with two or more different histological subtypes) were seen in four cases (1.5%) and could therefore not be categorized into a specific subtype. The 49.9% of all malignancies were ovarian serous cystadenocarcinomas (38.4% of which were pure form and 11.5% were mixed form); 23% of all malignant masses were borderline tumors. Three patients had extra-ovarian primaries (two of them were gastrointestinal carcinoma and one was renal cell cancer with metastases to the ovaries). The ages of the patients ranged from 14 to 83 years. The proportion of malignancy increases with age. The mean ages of diagnosis for malignant and benign lesions were 50.5 and 43 years, respectively. Parity and menopausal states did not differ between the patients with benign and malignant tumors and subtypes (Table 2).

The distribution of benign and malignant cases according to age, parity, serum CA-125 level, ultrasonographic features composing ADNEX and RMI 1-4 models, and menopausal states are shown in Table 2. The features able to discriminate between benign and malignant tumors were age, maximal diameter of the lesion, presence, maximal diameter and the proportion of the solid tissue, number of papillations, and presence of ascites ($p \leq 0.01$; Table 2).

Discriminating features of benign and borderline tumors were maximal diameter of the lesion and solid tissue, presence, and the proportion of solid tissue and number of papillations ($p \leq 0.03$). The features able to discriminate between benign and Stage I OC were maximal diameter of the lesion, number of papillations, presence of solid tissue, and presence of ascites ($p < 0.001$). The features able to discriminate between benign and Stage II-IV OC were maximal diameter of the lesion, number of papillations, proportion of solid tissue, laterality, and presence of ascites ($p \leq 0.02$). The presence of acoustic shadow and locules more than ten were not included into the external validation of the items of ADNEX model due to the low numbers (n=3, n=2, respectively). Optimal cut-off values of ADNEX model calculated for all patients was ≥ 14.05 with an AUC for the mere discrimination between benign and malignant tumors was 0.949 (95% CI 224.2-17.8), presenting a sensitivity of 88.5%, specificity of 89.2%, with a 89.1% accuracy rate. Originally proposed cut-off value (10%) had 88.5% sensitivity, 84.6% specificity, and 84.9% accuracy rate with an AUC for the mere discrimination of 0.865 (95% CI 146.4-12) for all patients.

Diagnostic performance of the ADNEX model according to the menopausal state at optimal and progressive cut-

Table 2. — *Patients' clinical and sonographic features.*

	Benign (n=259)	Malignant (n=26)	Malignant				p^a	p^b
			Borderline (n=6)	Stage I (n=11)	Stage II-IV (n=6)	Metastasis (n=3)		
	Median (min-max)	Median (min-max)	Median (min-max)	Median (min-max)	Median (min-max)	Median (min-max)		
Age	43 (14-83)	50.5 (22 -73)	38.5 (22-73)	47 (34-65)	57.5 (41-69)	51 (50-51)	0.01*	0.06
Parity	2 (0-10)	2.0 (0-5)	1 (0-4)	2 (0-5)	2 (1-3)	2 (0-4)	0.77	0.69
CA-125	20.7 (3-951)	22.8 (7.5-827)	13.3 (8-211)	21.4 (9-570)	248.7 (11-828)	9.2 (8-34)	0.43	0.05
Max lesion size (mm)	70 (22-255)[1]	84.5 (50-210)	107 (60-210)	85 (50-150)	85 (61-120)	84 (80-85)	0.003*	0.03*
Max solid tissue size (mm)	0 (0-60)[1,2,3]	45.5 (0-130)	44.25 (0-130)	43 (0-130)	45.45 (38.5-60)	55.8 (41-64)	< 0.001*	< 0.001*
Proportion of solid tissue	0 (0-1)[1,3]	0.54 (0-0.95)	0.58 (0-0.95)	0.45 (0-0.91)	0.55 (0.43-0.68)	0.66 (0.51-0.75)	< 0.001*	< 0.001*
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	< 0.001*	< 0.001*
Number of papillas								
0	246 (95)	15 (57)	4 (67)	5 (45)	4 (67)	2 (67)		
1	11 (4)	3 (11)	1 (17)	2 (18)	0 (0)	0 (0)		
2	1 (0)	4 (15)	1 (17)	0 (0)	2 (67)	1 (33)		
3	1 (0)	3 (11)	0 (0)	3 (27)	0 (0)	0 (0)		
> 3	0 (0)	1 (4)	0 (0)	1 (1)	0 (0)	0 (0)		
Menopausal state								
Postmen.	84 (32.4)	12 (46.2)	3 (50.0)	5 (45.5)	3 (50.0)	1 (33.3)	0.19	0.49
Premen.	175 (67.6)	14 (53.8)	3 (50.0)	6 (54.5)	3 (50.0)	2 (66.7)		
Laterality								
Bilat.	43 (16.6)	6 (23.1)	0 (0.0)	2 (18.2)	4 (66.7)	0 (0.0)	0.27	0.02*
Unilat.	216 (83.4)[3]	20 (76.9)	6 (100.0)	9 (81.8)	2 (33.3)	3 (100.0)		
Solid tissue								
No	205 (79.2)	3 (11.5)	1 (16.7)	1 (9.1)	0 (0.0)	1 (33.3)	< 0.001*	< 0.001
Yes	54 (20.8)[1,2]	23 (88.5)	5 (83.3)	10 (90.9)	6 (100.0)	2 (66.7)		
> 10 locules								
No	257 (99.2)	26 (100.0)	6 (100.0)	11 (100.0)	6 (100.0)	3 (100.0)	-	-
Yes	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Acoustic shadow								
No	256 (98.8)	26 (100.0)	6 (100.0)	11 (100.0)	6 (100.0)	3 (100.0)	-	-
Yes	3 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Ascites								
No	258 (99.6)	19 (73.1)	6 (100.0)	8 (72.7)	3 (50.0)	2 (66.7)	< 0.001*	< 0.001*
Yes	1 (0.4)[2,3]	7 (26.9)	0 (0.0)	3 (27.3)	3 (50.0)	1 (33.3)		
Frozen section								
No	116 (44.8)	3 (11.5)	1 (16.7)	1 (9.1)	1 (16.7)	0 (0.0)	0.001	0.026*
Yes	143 (55.2)[2]	23 (88.5)	5 (83.3)	10 (90.9)	5 (83.3)	3 (100.0)		

*Mann Whitney U test (Monte Carlo) / Pearson Chi Square Test(Monte Carlo) / Fisher Exact test (Monte Carlo) / Kruskal Wallis Test(Monte Carlo) - Post Hoc Test: Dunn's Test / Min.: Min. - Max. Max. a: Benign and malignant comparison b: Benign an subtypes of malignancies comparison excluding metastasis. 1: Significant compared to borderline tumours. 2: Significant compared to Stages I / 3. Significant compared to Stages II-IV. *p < 0.05.*

off points are presented in Table 3. The sensitivity, specificity, and the AUC values discriminating benign and malignant tumors of the RMI 1, 2, 3, and 4 and frozen section are shown in Table 3. AUC values for the polytomous discrimination performance of the ADNEX model and post hoc tests are shown in Table 4.

The model was able to discriminate between benign lesions from borderline (AUC 0.905 ± 0.049), Stage I ovarian cancer (AUC 0.934 ± 0.034), Stage II-IV ovarian cancers (AUC 0.997 ± 0.003), and borderline tumors from Stage II-IV OC (AUC 0.861 ± 0.110), and Stage I compared with Stage II-IV OC (AUC 0.742 ± 0.125). On the other hand, discrimination between borderline compared with Stage I tumors (AUC 0.576 ± 0.152) was mediocre. Metastatic tumors were not included into the polytomous discrimination due to the relatively very low numbers (n=3).

Table 3. — *Diagnostic performance of IOTA ADNEX model at different cut-offs for total probability of malignancy depending on menopausal state.*

	Cut-off*	Sensitivity	Specificity	Accuracy rate	AUC ± SE	*p*	OR (95% CI)
Postmenopausal							
ADNEX							
	3%	91.7%	66.7%	69.8%		0.001	22,0 (179.1 - 2.7)
	5%	91.7%	75.0%	77.1%		< 0.001	33.0 (271.1 - 4.0)
	10%	91.7%	77.4%	79.2%		< 0.001	37.6 (310.4 - 4.6)
	15%	91.7%	81.0%	82.3%		< 0.001	46.8 (388.8 - 5.6)
	Optimal (332)	83.3%	97.6%	95.8%	0.950 ± 0.035	< 0.001	205.0 (1.619.7 - 25.9)
RMI type							
(Standard cut-off)							
	1 (200)	25.0%	89.3%	81.3%	0.571 ± 0.095	0.425	2.8 (12.2 - 0.6)
	2 (200)	50.0%	78.6%	75.0%	0.643 ± 0.091	0.111	3.7 (12.7 - 1.1)
	3 (200)	25.0%	86.9%	79.2%	0.560 ± 0.094	0.506	2.2 (9.5 - 0.5)
	4 (450)	33.3%	88.1%	81.3%	0.607 ± 0.095	0.232	3.7 (14.6 - 0.9)
	Frozen section	81.8%	98.4%	95.9%	0.901 ± 0.070	< 0.001	274.5 (22.5 - 3.345.4)
Premenopausal							
ADNEX							
	3%	92.9%	69.1%	70.9%		< 0.005	29.1 (228.3 - 3.7)
	5%	92.9%	80.0%	81.0%		< 0.006	52.0 (411.0 - 6.6)
	10%	85.7%	88.0%	87.8%		< 0.007	44.0 (210.4 - 9.2)
	15%	78.6%	94.3%	93.1%		< 0.008	60.5 (252.1 - 14.5)
	Optimal (13.3)	85.7%	93.1%	92.6%	0.951 ± 0.025	< 0.001	81.5 (406.8 - 16.3)
RMI type							
(Standard cut-off)							
	1 (200)	28.6%	89.7%	85.2%	0.591 ± 0.086	0.255	3.5 (12.3 - 1.0)
	2 (200)	35.7%	86.9%	83.1%	0.613 ± 0.086	0.160	3.7 (11.9 - 1.1)
	3 (200)	28.6%	87.4%	83.1%	0.580 ± 0.086	0.320	2.8 (9.6 - 0.8)
	4 (450)	35.7%	92.0%	87.8%	0.639 ± 0.088	0.085	6.4 (21.7 - 1.9)
	Frozen section	83.3%	100.0%	97.8%	0.917 ± 0.064	< 0.001	-
Total							
ADNEX							
	3%	92.3%	68.3%	70.5%		< 0.001	25.9 (112.2 - 6.0)
	5%	92.3%	78.4%	79.6%		< 0.001	43.5 (189.7 - 10.0)
	10%	88.5%	84.6%	84.9%		< 0.001	42.0 (146.4 - 12.0)
	15%	84.6%	90.0%	89.5%		< 0.001	49.3 (154.1 - 15.8)
	Optimal (14.05)	88.5%	89.2%	89.1%	0.949 ± 0.020	< 0.001	63.3 (224.2 - 17.8)
RMI type							
(Standard cut-off)							
	1 (200)	26.9%	89.6%	83.9%	0.582 ± 0.064	0.166	3.2 (8.2 - 1.2)
	2 (200)	42.3%	84.2%	80.4%	0.632 ± 0.063	0.026	3.9 (9.1 - 1.7)
	3 (200)	26.9%	87.3%	81.8%	0.571 ± 0.063	0.233	2.5 (6.5 - 1.0)
	4 (450)	34.6%	90.7%	85.6%	0.627 ± 0.064	0.033	5.2 (12.9 - 2.1)
	Frozen section	82.6%	99.3%	97.0%	0.910 ± 0.047	< 0.001	674.5 (71.6 / 6.354.8)

AUC: Area under the curve — SE: Standart error — OR: Odds ratio — CI: Confidence interval.

**Probability equal to or more than cut-off indicates malignancy for Adnexa model.*

Discussion

This study showed that ADNEX model had a good overall discriminating performance between benign and malignant adnexal masses with an AUC of 0.865 ± 0.039 at 10% cut-off value. ADNEX model exhibited superior sensitivity and specificity compared to all four RMI models. Sensitivity values above 85% were found at cut-off points of 10% and 15% in all patients irrespective of menopausal state. This value was 91.7% and 85.7% in post- and premenopausal patients, respectively. In the prospective multicentre diagnostic study first investigating the efficacy of ADNEX model in discriminating benign and malignant lesions by Ben Van Calster *et al.,* 5,909 patients in 12 non-GOU and 13 GOU centers were assessed. Rates of malignant lesions were 17% and 42% in the non-GOU and GOU centers respectively. Odds ratios for predictors in ADNEX model of these centers for borderline vs. benign, primary ovarian cancer *vs.* benign and metastatic cancers

vs. benign lesions were between 1.57-2.59. Sensitivity and specificity of ADNEX model was calculated as 96.4% and 73.2% at 10% cut-off value, respectively. However, in this study, efficacy of the ADNEX model according to the type of clinics (*i.e.* GOU or non-GOU) was not calculated. All other studies in the literature were conducted in GOU centers and these values were reported between 94.1%-98% and 55.5%-75.3, respectively, at the proposed 10% cut-off value [11, 12, 14–16]. To the best of the present authors' knowledge, no study was found in addressing the efficacy of ADNEX model in a non-GOU center. The present study was performed in a non-GOU center and the rate of malignancy was found as 9.1%. Sensitivity and specificity rates of the ADNEX model in discriminating malignant tumors were found as 88.5% and 84.6% respectively, regardless of the menopausal state at the proposed 10% cut-off value.

The higher sensitivity rate in the abovementioned studies might be due to possible referred patients because of suspected malignancies might increase the ovarian cancer rate. Ben Van Calster *et al.* suggested that different countries with different health systems should determine their own center-specific cut-off values for the ADNEX model in order to achieve optimal clinical management strategies [17]. In the present study population, an optimal cut-off value of 14.05% exhibited more balanced results for sensitivity and specificity for all patients. Optimal cut-off values were found 13.3% and 33.2% for premenopausal and postmenopausal patients, respectively. Overall malignancy rate was found at 35.3% in a study conducted in a GOU center with 326 patients by Meys *et al*. They found a sensitivity of 98% and a specificity of 62% for ADNEXA model at 10% cut-off value in their study [14]. Similar trends in high sensitivity and low specificity were maintained in also postmenopausal and premenopausal patients [14]. This slight difference might be explained by the type of the center (GOU) that might limit the number of false positive results. In the study of Meys *et al.*, in accordance with the present results, AUC values for the subgroups of the ADNEX model were efficacious except borderline *vs.* Stage I ovarian cancer unlike the original study of Ben Van Calster *et al.* Arajuo *et al.* also found similar results with the present [16]. The other studies in the literature, ADNEX model was found as efficacious in discriminating borderline *vs.* Stage I ovarian cancer [12]. The failure of ADNEX model in discrimination of borderline and Stage I cancers could be due to the similarity of these diseases in ultrasonographic features in the present population. For example, presence of solid tissue between borderline and Stage I ovarian cancer were close to each other in the current study (83.3% *vs.* 90.9%), however that rate was slightly different from each other in the original study (78.8% *vs.* 92.1%), and the study conducted by Sayasneh *et al.* (71% *vs.* 98%) [11, 12].

In a retrospective multicenter study conducted by Van den Akker *et al.* [24], RMI was investigated for triage of patients with high risk of malignancy to centers where frozen section analysis was available. They advocated in patients with RMI scores < 20 frozen section analysis was not required. In the present study, performing frozen section examination was decided clinically and showed sensitivity (82.6%) and specificity (99.3%) rates in concordance with the results of an extensive meta-analysis conducted by Geomini *et al.* [25].

Table 4. — *Polytomous discrimination performance of IOTA ADNEX model.*

Types of discrimination	AUC ± SE.
Benign *vs.* Malignant	0.941 ± 0.042
Benign *vs.* BOT	0.905 ± 0.049
Benign *vs.* Stage I OC	0.934 ± 0.034
Benign *vs.* Stage II-IV OC	0.997 ± 0.003
BOT *vs.* Stage I OC	0.576 ± 0.152
BOT *vs.* Stage II-IV OC	0.861 ± 0.110
Stage I *vs.* Stage II-IV OC	0.742 ± 0.125

SE.: Standard error — BOT: Borderline ovarian tumour — OC: ovarian cancer.

Further studies might address the usefulness of ADNEXA for the decision of performing frozen section analysis. In this study, all four types of RMI exhibited poor sensitivity and specificity in predicting malignancy at their proposed cut-off values (200, 200, 200, 450), but RMI 2 and 4 were found superior than RMI 1 and 3 ($p = 0.026$, $p = 0.033$, respectively) with a sensitivity of 42.3% and 34.6%, and specificity of 84.2 and 90.7% respectively. However, in the original study Yamamoto *et al*. found only RMI 4 as more accurate than the remaining RMI 1, 2, and 3 [26]. In an extensive meta-analysis, besides other scoring systems, Dodge *et al.* investigated the accuracy of RMI 1 and 2 [27]. They found the sensitivity and the specificity values of RMI 1 to be 79.2% and 91.7%, and those of RMI 2 to be 79% and 81%, respectively. In the present study, these values were found to be 26.9% and 89.6% for RMI 1 and 42.3% and 84.2% for RMI 2, respectively.

The present far below sensitivity levels of RMI 1 and 2 compared to those of the aforementioned meta-analysis might be due to the low number of advanced stage cancers in the study population. Most of the malignancies in this study group were Stage I and borderline tumors whose RMI scores were expected to have lower than those of the higher stage cancers. On the other hand, the sensitivity values of the ADNEXA in the present study were comparable with those of the literature [11, 12, 14–16].

The main advantage of the present study is its performance in a non-GOU clinic which allows the validation of the ADNEX model for patients of general gynecology clinics. Inclusion of the GOU clinic patients might distort the data and change the sensitivity and the specificity values, so one could suggest that the results from the other external validation studies conducted in a GOU centers as less generalizable. The present study still did not validate the item of "type of center" since the answer was "no" for all patients in the ADNEXA model.

Validation of the remaining items of the ADNEX model were analyzed individually. Two-step approach for the clinical use of ADNEX model to benefit from the polytomous discrimination ability in gynecologic oncologic referral centers was proposed by original authors [17]. The present authors recommend to test if the first step of this approach would be enriched with specific clinical signs of benign tumors such as cyclic pelvic pain for endometrioma. Further research might focus on calculating their center-specific own cut-off values as the potential advantages were stated [17]. Further analysis of the accuracy of the ADNEX model for subgroups of benign lesions such as endometriomas, dermoid tumors or abscesses might be investigated in future studies.

Conclusion

In this study conducted in a non-GOU center, it was found that ADNEX model by adding a stratified classification was found superior to RMI 1, 2, 3, and 4 in discriminating benign adnexal masses from malignant ones. The optimal cut-off value of ADNEX model to discriminate benign and malign tumors was found to be 14%.

Acknowledgements

The authors acknowledge that only the authors and their institutions made significant contributions to the study.

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