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ORIGINAL ARTICLE

External Validation of a Novel Diagnostic Nomogram for Prediction of Malignancy in Adnexal Masses in Comparison with IOTA-ADNEX Model

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ABSTRACT:

Background: Ovarian cancer is one of the most common and deadliest gynecological malignant tumors. Most individuals receive a diagnosis at an advanced stage since they do not exhibit typical symptoms in the early stages. Therefore, to increase overall survival, early detection measures are needed. To predict malignancy preoperatively in patients with ovarian masses, a unique diagnostic nomogram was developed. It was important to assess this nomogram's ability to predict malignancy in ovarian masses and to compare its results with those of the commonly used IOTA-ADNEX model.

Methods: This prospective cohort study was conducted at the Department of Obstetrics and Gynecology, Zagazig University on patients with ovarian masses. Each woman was subjected to clinical examination, and US examination to detect the presence of M features &features of the ADNEX model and laboratory investigations including the needed serum markers. The risk of malignancy was calculated by applying both the nomogram & IOTA ADNEX model. Results were compared to results of histopathologic examination or the follow-up US for non-operated patients.

Results: There was a good agreement between the nomogram score and the ADNEX risk of malignancy in diagnosing malignant ovarian tumors, with an AUC of 0.933 of at a cut-off value of 128 for the nomogram and an AUC of 0.921 at a cut-off value of 12% for the ADNEX model.

Conclusions: We conclude that this cost-effective and easy-to-use nomogram can effectively predict the risk of malignancy in cases with ovarian masses with results comparable to the most currently used IOTA-ADNEX model.

Keywords: Nomogram; malignancy;adnexal masses; IOTA-ADNEX model.

INTRODUCTION

One of the most prevalent and deadly gynecological malignant tumors is ovarian cancer [1, 2]. Since typical symptoms are missing in the early stages, most patients are discovered late in the disease, usually with widespread peritoneal metastases. As a result, these tumors pose a serious threat to medical professionals and are the main cause of death in ovarian cancer patients [3]. Only 20% to 25% of individuals with late-stage ovarian cancer survive for five years, compared to nearly 90% of those with early-stage disease [4]. Therefore, early identification measures are critically needed to maximize overall survival.

Currently, pelvic examination, tumor markers, primarily serum carbohydrate antigen 125 (CA125), transvaginal ultrasound scanning (TVS), and the developing integrative models are used for diagnosis in patients with ovarian masses. The physician's level of expertise determines the outcome of the pelvic examination with no available standards. Moreover, patients early in the disease or those with uncommon presentations may pass undetected because they don't show the typical symptoms. TVS is a commonly used diagnostic tool for ovarian mass patients. It offers helpful information about the mass's location, size, shape, composition, blood flow, and likelihood of malignancy. Even though TVS sensitivity can reach

90%, there is a concern over using ultrasonography as a reliable tool for differentiating ovarian masses because examiner skill and experience are crucial to the device's functionality. To overcome this, With its four distinct subgroups (borderline, stage I cancer, stage II-IV cancer, and secondary metastatic cancer), the ADNEX (Assessment of Different NEoplasias in the adneXa) risk model was developed in 2014 by the IOTA (International Ovarian Tumor Analysis) group as an objective tool to differentiate benign and malignant ovarian neoplasms [5, 6].

Another parameter which is frequently employed as a blood biomarker for ovarian epithelial carcinoma is CA125. However, when employed as the only diagnostic marker, CA125 has low sensitivity and specificity because it is expressed in only 50% 80% of patients with late ovarian cancers and people with early disease. Additionally, it is raised in a number of benign illnesses[7].

Several coagulation and inflammatory variables, including fibrinogen, D-dimer, albumin (Alb), C-reactive protein (CRP), thrombopoietin, and ratio of monocyte to lymphocyte (MLR), are connected to the initiation, course, and outcome of cancer [8].

Guo et al. have created a novel diagnostic nomogram [9] by including three additional parameters—the fibrinogen/albumin ratio (FAR), age, and CA125— the monocyte/lymphocyte ratio (MLR), and the M features of the IOTA group in the ultrasound examination. This novel nomogram can successfully stratify patients with ovarian masses based on their risk of cancer, including those early in the disease with a good performance [11]. Therefore, the aim of this study was to evaluate the performance of the novel nomogram (Guo-gram) in predicting malignancy in ovarian masses and to compare it to the performance of the IOTA-ADNEX model.

METHODS

This prospective cohort study was carried out at Zagazig University's Department of Obstetrics and Gynecology, ultrasound unit starting from July 2023 till July 2024. Written informed consent was taken from all patients. The Institutional Research Board granted approval for the study with approval number 10847-4-6-2023. Every patient underwent a thorough history taking, clinical examination, ultrasound examination, and laboratory testing.

Inclusion criteria:

The study included all patients presenting with ovarian mass(es).

Exclusion criteria:

Those who had a history of pelvic surgery, preoperative chemotherapy, other malignant illnesses, severe pelvic infections in the past, and noticeable pelvic endometriosis were excluded from the study.

Ultrasonographic examination:

According to the IOTA standardized examination procedure and standardized terms and definitions [10], patients with at least one ovarian mass underwent transvaginal grayscale and color Doppler ultrasound examination using the Mindray DC 70 X insight, Sonoscape S50, and Mindray DC 30 ultrasound equipment. For virgin patients, transrectal or transabdominal ultrasonography was employed.

Each ovarian mass was examined for:

- **The presence of M-features:** The IOTA group presented five simple principles to predict malignancy (M-rules): strong Doppler signal (color score 4), ascites, an irregular solid tumor, an irregular multilocular tumor with a maximum diameter of at least 100 mm, and at least four papillary characteristics. M-features were considered to be present if one or more of them were found throughout this inquiry.
- Ultrasound features for the ADNEX model which included (The number of papillary projections, ascites, acoustic shadowing, maximum diameter of the lesion, maximum diameter of the largest solid component, and more than ten cyst locules).

Laboratory investigations:

Preoperative CA125 (IU), fibrinogen level (g/l), serum albumin (g/dl), and complete blood count were obtained. Then, we calculated the fibrinogen/albumin ratio (FAR) and the monocyte/lymphocyte ratio (MLR). All measurements were performed strictly per the manufacturers' requirements and kit instructions.

Calculation of risk of malignancy: by applying the novel diagnostic nomogram issued by ***Guo et al.*** [11], the nomogram calculated for each patient using five different parameters: age, CA125, FAR, MLR, and M characteristics of the IOTA group. On the point scale axis, each parameter is assigned a score based on its predictive value, as follows:

-For CA125 > 35 → 55 points,
-For MLR > 0.249 → 21 points,
-For FAR > 0.070 → 16 points,

-If one M feature is present this gives 57 points,
-Each age has its corresponding point

The total points are obtained by adding the scores for each individual parameter. The total points are then projected to the lower probability axis, as illustrated in Figure, to estimate the chance of malignancy (1).

Calculation of risk malignancy by applying the IOTA-ADNEX model was done for all included patients.

Histopathological examination of adnexal masses was done after surgical management of patients who needed surgery. **Follow-up** of patients who did not undergo operation by ultrasound after three months.

Statistical analysis:

Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 28. Cronbach's alpha coefficient alpha and ROC curve were used.

RESULTS

Sixty-four patients met our inclusion criteria and could therefore be included in the study. Participants in the study ranged in age from 16 to 73, with a mean age of 41.63 (± 12.84) years. The body mass index ranged from 22 to 35 kg/m2 with a mean of 29.09 (± 3.73) kg/m2.

There was a statistically significant relation between the nature of the tumor and the body mass index which was significantly higher among patients with benign lesions (Table 1S).

The median of the maximal diameters of the lesions was 91.5 mm. The median of the maximal diameters of the largest solid parts was 82 mm. About 11% and 17% had >10 cyst locules and acoustic shadows respectively. Ten patients had ascites and about 91% had no papillary projections.(Table 2S)

The mean albumin level was 4.07g/dl, the CA 125 level ranged from 0.6–2951U/ml, and the fibrinogen level ranged from 0.6–11.3g/L. The M/L ratio ranged from 0.016 – 0.88.(Table 3S)

The ADNEX risk of malignant ovarian tumor ranged from 0.2% to 99% with a median of 6.75%.

The nomogram score ranged from 8-216. More than 50% of patients had a risk of malignancy between 0.01 and 0.2. (Table 4S)

Regarding distribution of patients according to the nature and stage of the lesion by histopathology or follow-up ultrasound. Thirteen patients (20.3%) had malignant lesions while 51 patients (79.7%) had benign lesions (Figure 4).

With an area under the curve of 0.921, the optimal cutoff of the ADNEX risk of malignancy for the diagnosis of malignant ovarian tumors was ≥12% while the best cutoff of nomogram score in the diagnosis of malignancy was ≥128, with an area under a curve of 0.933. (Table 1)

There was a statistically significant relation between the nature of the tumor and both the ADNEX risk of malignancy and the nomogram score (both were significantly higher among patients with malignant lesions). Figure (5)

When evaluating the agreement between the nomogram score and the ADNEX risk of malignancy in the diagnosis of malignant ovarian tumors, ICC was 0.532, which reflected moderate reliability. Cronbach alpha was 0.82 demonstrating a good agreement. (Table 2)

Table 1: Performance of the ADNEX risk of malignancy and the nomogram score in the diagnosis of malignant ovarian tumor among the studied patients:

Model	Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	+LR	-LR	p
ADNEX	≥12%	0.921	100%	74.5%	50%	100%	79.7%	3.92	0	**<0.001****
Nomogram score	≥128	0.933	92.3%	96.1%	85.7%	98%	95.3%	23.5	0.08	**<0.001****

*AUC, the area under the curve; PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; -LR, negative likelihood ratio; **p≤0.001 is statistically highly significant.*

Table 2: Agreement between the ADNEX risk of malignancy and the nomogram score:

ICC	95% CI		Cronbach's alpha	P
0.532	-0.216	0.823	0.82	**<0.001****

ICC test-retest interclass correlation coefficient CI Confidence interval >0.9 is excellent ¥p for paired sample t-test ∞p for ICC, ICC <0.5 poor reliability, 0.5 to 0.75 moderate reliability, 0.75 to 0.9 good reliability, and any value above 0.9 indicates excellent reliability. Cronbach alpha 0.5 to <0.6 is poor, 0.6 to <0.7 is questionable, 0.7 to <0.8 is good, 0.8 to <0.9 is good, and≥0.9 is excellent agreement.

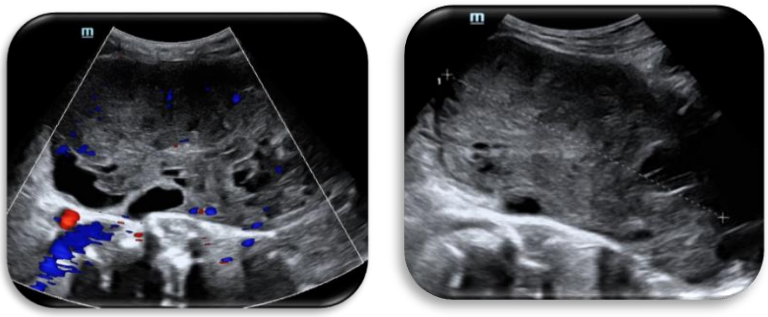

Figure 1: An irregular solid mass with cystic areas, and a color score of 2 in a patient who suffered abdominal pain. The ADNEX risk of malignancy was 98% and the nomogram score was 214 suggesting a high risk of malignancy. HPE showed bilateral high-grade ovarian serous carcinoma.

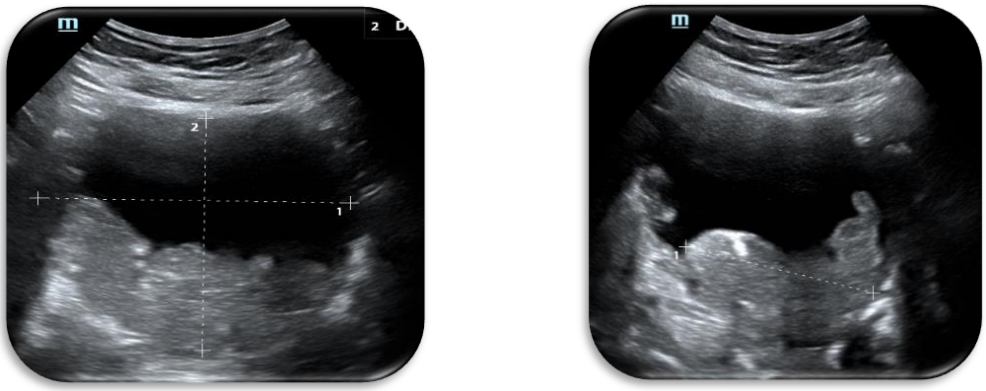

Figure 2: A unilocular cystic solid lesion discovered accidentally during workup for a woman suffering progressive cachexia. ADNEX risk of malignancy was 91.3% and the nomogram score was 205, suggesting high risk of malignancy. HPE showed ovarian low-grade serous carcinoma with positive cytology, tubal & parametrial metastasis.

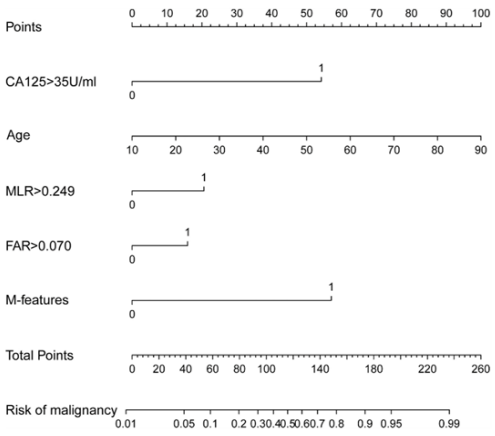

Figure 3: Novel diagnostic nomogram to predict the probability of ovarian cancer for patients with ovarian masses

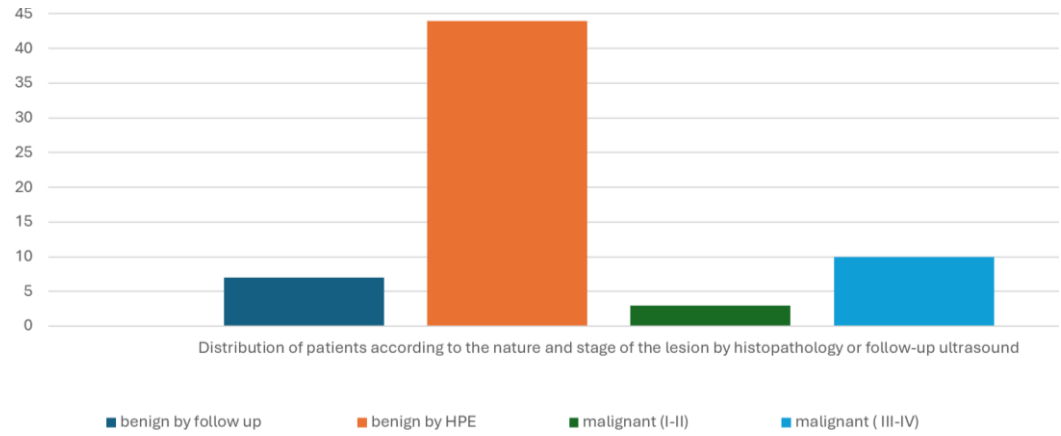

Figure (4): Distribution of patients according to the nature and stage of the lesion by histopathology or follow-up ultrasound.

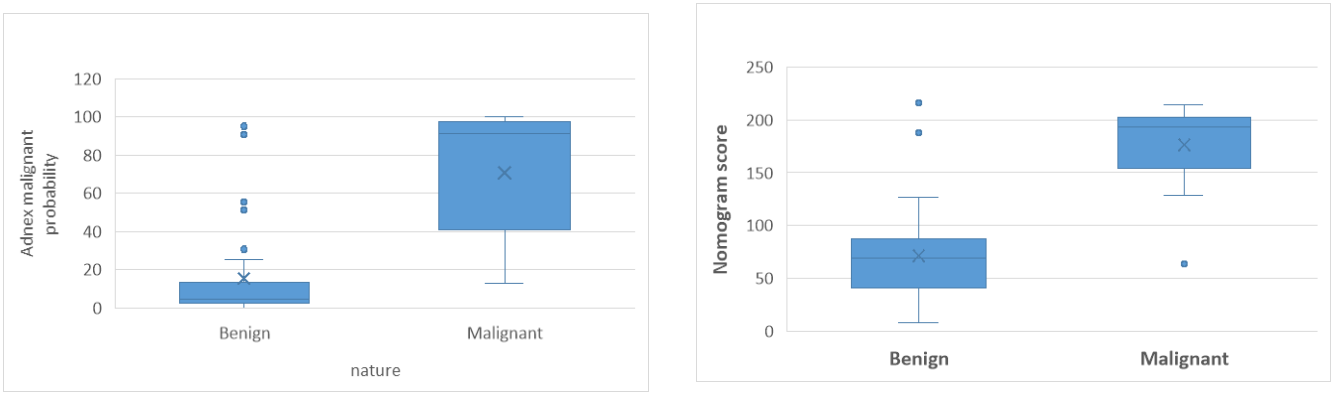

Figure 5: Boxplot showing the relation between the nature of the lesion, the ADNEX risk of malignancy (*on the left)*, and the nomogram score (*on the right)*.

DISCUSSION

It can be challenging to distinguish between benign and malignant ovarian masses before surgery, and there is no better test or algorithm. Thus, the fundamental goal of management is to differentiate between benign and potentially malignant masses in order to optimize morbidity and outcomes through appropriate triaging for conservative management or laparoscopic procedures, thereby avoiding laparotomy whenever feasible, or referral to a gynecological oncologist at a gynecological oncology center when necessary [12].

Many efforts have been undertaken to develop reliable strategies for predicting malignancy in patients with ovarian masses, including tumor markers, imaging, and evolving integrative models. Many biomarkers have been created to track the progression of ovarian cancer; the most well-researched and therapeutically applied of these is CA125. Less than 35 U/mL of CA125 is now considered normal. Just 50% of women with stage I ovarian cancer had elevated levels, compared to almost 90% of those with advanced-stage disease. Additionally, serous tumors—as opposed to mucinous tumors—are more strongly linked to increased levels of CA125. During follow-up, doubling serum CA 125 levels is frequently used to identify illness recurrence [13].

Owing to the poor performance of single indicators to accurately predict the risk of malignancy, integrative models have been increasingly used to classify patients with ovarian tumors according to their risk of malignancy. The IOTA ADNEX model is the most popular model.

In clinical practice, ultrasound is frequently used to detect and diagnose ovarian cancer. However, sonographer experience has a major impact on diagnosis accuracy. In order to lessen subjective differences and increase the diagnostic accuracy of ovarian cancer, the IOTA group proposed the ADNEX model in 2014. This new multiple risk prediction model is composed of three clinical parameters (age, serum CA-125 level, and type of center) and six ultrasonographic parameters. The primary benefit is that the ADNEX model, which categorizes ovarian cancer into four subtypes (borderline, stage I, stages II–IV, and metastasis), is the first multi-classification model for ovarian cancers. One can assess both the overall risk of ovarian cancer and the risk of each subtype at the same time [6].

The nomogram issued by *Guo et al* [9] is an integrative model using ultrasound findings, tumor markers, and inflammatory markers. It is based on age, CA125, the ratio of monocyte to lymphocyte, the ratio of fibrinogen to albumin, and ultrasonography (M characteristics) to classify people with ovarian masses based on their possible risk of cancer, incorporating those early in the disease. It has been found that various cancers have been linked to increased monocytes and decreased lymphocytes, reflecting the host's immunological state. High MLR enhances tumor angiogenesis, proliferation, migration, and invasion. plasma fibrinogen levels are connected to angiogenesis, metastasis, tumor growth, and prognosis in ovarian cancer patients. Patients with low serum Alb levels are malnourished, and this can compromise their immune system's ability to fight cancer and give them a poor prognosis [14]. Therefore, it made sense to forecast the prognosis and likelihood of malignancy in patients with ovarian cancer using variables that reflected their systemic condition [9].

Guo et al [9] 383 patients were examined in a validation cohort and 894 patients in a training cohort. Additionally, a validation cohort including 781 patients with benign tumors and 246 patients with early-stage ovarian cancer (FIGO stages I and II) was used to examine how well the nomogram model performed in identifying early-stage ovarian cancer. After internal validation, they discovered that the nomogram model functioned effectively and had an AUC of 0.897, which was higher than the AUC of 0.792 for CA125. This suggests that the nomogram model has potential uses in the prediction of malignancy. in contrast to models that are currently on the market, like ROMA, CPH-I, and RMI. This nomogram has the ability to detect ovarian cancer in its early stages and demonstrated a greater efficacy in predicting malignancy.

Our study aimed to validate the performance of the nomogram issued by Guo et al. [9] in comparison with the IOTA ADNEX model being the most common model used currently.

This prospective cohort study was carried out at the Zagazig University ultrasonography facility in the Department of Obstetrics and Gynecology between July 2023 and July 2024. In this study, sixty-four women with ovarian masses were included. Each woman was subjected to history taking, clinical examination, and US examination to detect the presence of M features &features of the ADNEX model and laboratory investigations including the needed serum markers. The risk of malignancy was calculated by applying both the nomogram & IOTA ADNEX model. Results were compared to results of histopathologic examination of the ovarian tumor or the follow-up US for patients who did not undergo surgery.

The ages of the studied participants ranged from 16 to 73 years. The body mass index ranged from 22 to 35 kg/m2. There was a statistically significant relation between the nature of the tumor and body mass index which was significantly higher among patients with benign lesions. This was expected, as malignant ovarian tumors usually present with anorexia, gastrointestinal complaints, and loss of weight.

In our study, the median of the maximal diameters of the lesions was 91.5 mm. Ten patients had ascites, about 91% had no papillary projections and 25% of patients had at least one of the M features. In *Guo et al*. [9] study, the median of the maximal diameters of the lesions was 78 mm. Thirteen percent of patients had ascites, about 94.9% had no papillary projections and 41.6% of patients had at least one of the M features.

Regarding laboratory investigations, the mean albumin level was 4.07 ± 0.44 g/dl. The CA 125 level ranged from 0.6 – 2951 with a median of 19.35. The fibrinogen level ranged from 0.6 – 11.3 (g/L) with a median of 3.8 and the M/L ratio ranged from 0.016 – 0.88 with a median of 0.26. In *Guo et al.* (2021) study, albumin levels ranged from 3.7 - 4.3 (g/dl) with a median of 4.2. The CA 125 level ranged from 13.3 – 125.6 with a median of 23.5. The fibrinogen level ranged from 2.19 – 3.33 (g/L) with a median of 2.59 and the M/L ratio ranged from 0.16 – 0.30 with a median of 0.21.

In our study, thirteen patients (20.3%) had malignant lesions; ten of them had advanced malignancy, while 51 patients (79.7%) had benign lesions. The nomogram score ranged from 8 to 216. Twelve patients were agreed upon as having malignant ovarian tumors by both nomogram and histopathology and 49 patients were agreed upon as having benign lesions, with almost perfect agreement. The nomogram yielded an AUC of 0.933, with 92.3% sensitivity, 96.1% specificity, 85.7% 96.3 percent positive predictive value, 98% negative predictive value, and a 95.3% total accuracy at a cut-off of 128 (equivalent to a 0.5 cancer risk) (table 7). In *Guo et al.* [9] study, the nomogram exhibited an AUC of 0.937, with 87.9% sensitivity, 85.7% specificity, 79.6% positive predictive value, 91.8% negative predictive value at a cut-off of 100 (corresponding to the risk of malignancy of 0.298). Our study showed similar AUC but at a higher score cut-off, with higher values for sensitivity, specificity, and positive and negative predictive values. This is mostly due to the different distribution of lesion nature between our group of studied patients and theirs. Most of our patients with malignant ovarian masses were in advanced stages, while all patients with malignant masses in the original study were in early stages. The performance of the nomogram is better in the extremes of ovarian pathology; the benign nature, and the advanced stage malignant nature.

In our study, the ADNEX model risk of malignancy was also calculated for all cases before surgery, which ranged from 0.2% to 0.99%. Comparing results with histopathology, thirteen patients were agreed upon as having malignant ovarian tumors by both the ADNEX score and histopathology and 38 patients were agreed upon as having benign lesions by both with moderate agreement. At a cut-off value of 12%, it demonstrated an overall accuracy of 79.7% with an AUC of 0.921, 100% sensitivity, 74.5% specificity, 50% positive predictive value, and 100% negative predictive value (table 8).

There was a statistically significant relation between the nature of the tumor and both the ADNEX risk of malignancy and the nomogram score. Both were significantly higher among patients with malignant lesions. Moreover, there was a good agreement between the nomogram score and the ADNEX risk of malignancy in diagnosing malignant ovarian tumors. Fourteen patients were agreed upon as having malignant ovarian tumors by both the ADNEX score and the nomogram and 38 patients were agreed upon as having benign lesions by both. So, both models can be used alternatively in the preoperative prediction of ovarian malignancy, giving the same outcome.

Conclusions

We conclude that this cost-effective and easy-to-use nomogram can effectively predict the risk of malignancy in cases with ovarian masses with results comparable to the most currently used IOTA-ADNEX model.

Conflict of interest statement: The authors declared that there were NO conflicts of Interest.

Disclosure: The authors have no financial interest to declare in relation to the content of this article.

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Table 1S: Relation between the tumor nature and the demographic data of the studied patients:

	Benign	**Malignant**	**t**	**p**
	Mean ± SD	**Mean ± SD**		
Age (year)	40.41 ± 12.86	46.38 ± 12.07	-1.513	0.135
BMI (kg/m^2)	30.0 ± 3.12	25.54 ± 3.91	4.371	<0.001**
	Median (IQR)	**Median (IQR)**	Z	
Parity	2.5 (2 – 3)	2 (1.25 – 3)	-1.185	0.236

*t independent sample t test Z Mann Whitney test *p<0.05 is statistically significant **p≤0.001 is statistically highly significant. Parameters are described as Mean ± SD and Median (IQR)*

Table 2S: The ultrasonographic data of the studied group:

	Median (IQR)	**Range**
Maximal diameter of the lesion (mm)	91.5 (58.5 – 138)	9 – 992
Maximal diameter of the largest solid part (mm)	82 (47.5 – 119.5)	8 – 160
	No.	**%**
>10 cyst locules	**7**	10.9%
Acoustic shadow present	11	17.2%
Ascites present	10	15.6%
The number of papillary projections: **0** **1** **≥4**	 58 1 5	 90.6% 7.8% 16%
M features (present)	16	25%

IQR interquartile range

Table 3S: The laboratory investigation of the studied group:

	Median (IQR)	**Range**
CA-125 (U/ml)	19.35 (9.25 – 72.8)	0.6 – 2951
Monocytes (X10^3/uL)	0.6 (0.4 – 0.7)	0.2 – 2.4
Lymphocytes (X10^3/uL)	2.2 (1.73 – 2.78)	0.7 – 5.1
M/L ratio	0.26 (0.18 – 0.33)	0.016 – 0.88
Fibrinogen (g/L)	3.8 (2.83 – 4.8)	0.6 – 11.3
F/(AX10)	0.09 (0.06 – 0.1)	0.01 – 0.3
	Mean ±SD	
Albumin (g/dl)	4.07 ± 0.44	2.4 – 5.01

IQR interquartile range

Table 4S: The ADNEX and the nomogram score and its risk of malignancy among the studied group:

	Median (IQR)	**Range**
ADNEX risk of malignancy	6.75 (3.13 – 41.13%)	0.2 – 99%
Nomogram score	76 (51 – 125.75)	8 – 216
Nomogram risk of malignancy:	**No.**	**%**
[0.01 - 0.05]	12	18.8%
[0.05 - 0.1]	9	14.1%
[0.1 - 0.2]	16	25%
[0.2 - 0.4]	6	9.4%
[0.4 - 0.5]	2	3.1%
0.5	1	1.6%
]0.5-0.6]	2	3.1%
[0.6 – 0.7]	3	4.7%
0.7	1	1.6%
[0.9 - 0.95]	4	6.3%
>0.95	8	12.5%

IQR interquartile range

Citation

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