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ROLE OF OIARSS IN RISK STRATIFICATION OF PCOS

Radio-Diagnosis

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ABSTRACT

Background: Polycystic ovarian syndrome (PCOS) is the most common endocrine abnormality in women of reproductive age. Outlining clearly defined diagnostic criteria for PCOS holds great significance as early diagnosis is warranted due to the considerable evidence that women with PCOS are at an increased risk for infertility, dysfunctional uterine bleeding, metabolic syndrome, type II diabetes and cardiovascular disease. There is no universally accepted ultrasound protocol currently while categorizing a case of PCO into either of polycystic ovarian morphology (PCOM) or polycystic ovarian syndrome (PCOS). This study intends to minimize this deficiency and help in edging towards a clearer consensus among the clinical radiologists while interpreting PCO on ultrasound. **Results:** Out of a total of 1500 patients comprising the training set, 242 patients who had no clinical symptoms of polycystic ovarian syndrome (PCOS) as well as had no polycystic ovaries (PCO) on ultrasound were classified under 'Category A'. Out of the remaining 1258 patients in the training set, there were 522 patients who had no clinical symptoms of PCOS but showed PCO on ultrasound. This group of patients was classified under 'Category B'. There were 736 patients who had one or more clinical symptoms of PCOS in addition to the visualization of PCO on ultrasound. This group of patients was grouped as 'Category C'. On multiple regression analysis, follicle number per ovary (FNPO) > 20, ovarian volume (OV) > 10.0 cc, stromal volume (SV) > 8.0 cc, ratio of stromal volume to total ovarian volume (SV/OV) > 0.8, ratio of stromal area to total ovarian area (SA/TA) > 0.4, peripheral follicular distribution and irregular outline were the ultrasound features showing statistical significance for the probability of PCOS (Category C). **Conclusions:** We found that there was excellent agreement among the different observers, thus implying that this Ovary imaging reporting and scoring system (OIRASS) shows comparable and reproducible results in the analysis of the ultrasound features of an ovary by different radiologists

KEYWORDS

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is the most common endocrine abnormality in women of reproductive age with a prevalence of 7-8%.[1] It is a multifactorial disease with a wide spectrum of clinical presentation mainly characterized by ovulatory dysfunction and hyperandrogenism.

Outlining clearly defined diagnostic criteria for PCOS holds great significance as early diagnosis and intervention is warranted due to the considerable evidence that women with PCOS are at an increased risk for infertility, dysfunctional uterine bleeding, metabolic syndrome, type II diabetes and cardiovascular disease.[2] The two most recent sets of consensus criteria proposed by the Rotterdam ESHRE/ASRM (European Society of Human Reproduction and Embryology/ American Society for Reproductive Medicine) sponsored PCOS consensus workshop group (2003) as well as the Androgen excess and PCOS society (2009) have established the ultrasound finding of polycystic ovaries (PCO) as part of the diagnostic criteria for PCOS.[3] It has to be noted that the definition of biochemical hyperandrogenism is still unresolved. Also, the criteria used to define oligo- or anovulation is insufficient.[4]

MATERIALS AND METHODS

Study preparation

We obtained the institutional review board approval for this prospective study. On 1st December 2022, five radiologists from our institution held a meeting to discuss and develop a consensus on the study design and population. While many ultrasound features of polycystic ovaries were considered by the participating radiologists, this meeting was mainly convened to develop an 'Ovary imaging reporting and scoring system' (OIRASS) to stratify the risk of PCOS in a particular ovary. Firstly, for the purpose of our study, we categorized ovaries into a normal ovary (Category I- Normal), polycystic ovarian morphology (Category II- PCOM) and polycystic ovarian syndrome (Category III- PCOS). All participants acknowledged the importance of developing the OIRASS.

Study population

Since our diagnostic prediction model needs validation, our study was split into two phases. In the first phase during the period from 1st September 2021 to 10th April 2022, our study group comprised of 1500 consecutive female patients aged between 18years and 45years referred to the Department of Radio-diagnosis for pelvic ultrasound scans for symptoms like oligomenorrhea, pelvic pain, infertility, hirsutism, acne, obesity, diabetes, obstructive sleep apnea and mood disorders as well as routine health check up.

After an ultrasound scan was performed, each patient in this training set was classified into one of the following three categories: Category 1:- No clinical symptoms and no polycystic ovaries (PCO) on ultrasound; Category 2:- No clinical symptoms but presence of PCO on ultrasound; Category 3:- Presence of one or more clinical symptoms as well as PCO on ultrasound. The objective of differentiating the ovaries into these three categories was to study the preponderance and association of each suspicious ultrasound feature in these three categories separately.

In the second phase during the period from 3rd May 2022 to 3rd July 2022, our study group comprised of 800 consecutive female patients. This group of patients represented a test set for validation of the diagnostic prediction model.

Ultrasound technique and image evaluation

Ultrasound was performed by five radiologists with 1 to 10 years of experience in pelvic ultrasound. The scanning protocol in all cases included both transverse and longitudinal real-time imaging of both the ovaries. All sonograms obtained were saved in a picture archiving and communication system.

Data and statistical analysis

The statistical analysis of this study consisted mainly of 2 steps. The first step was to determine the risk score of independent sonological features to quantify how strongly the presence or absence of a particular ultrasound feature in a polycystic ovary was associated with either of PCOS (Category C) or PCOM (Category B). The second step was to validate this prediction model from the training set using the test set.

DISCUSSION:

In 1935, Stein and Leventhal first described a medical condition comprising of amenorrhea, obesity and masculinizing symptoms that is now termed as the polycystic ovarian syndrome (PCOS).[3] PCOS is now recognized as the most common endocrine abnormality in women of reproductive age group and it is worrisome that even after these many years since this condition was first described, there is no clear consensus on the diagnostic criteria and its aetiology remains incompletely understood.

The diagnostic criteria of PCOS have been proposed and grouped in numerous classifications that have been conflicting for many years.[4] The two most recent and widely followed sets of consensus criteria proposed by the Rotterdam ESHRE/ASRM (European Society of Human Reproduction and Embryology/ American Society for Reproductive Medicine) sponsored PCOS consensus workshop group (2003) as well as the Androgen excess and PCOS society (2009) are becoming fast obsolete with the frequent upgradation of the software and the resolution of ultrasound machines. The Rotterdam ESHRE/ASRM criteria defined the polycystic ovary as having 12 or more follicles, measuring between 2 and 9 mm (Follicle number per ovary/ FNPO), and/or an ovarian volume (OV) >10 cm^3 but does not take into account the distribution pattern of follicles and the description of the ovarian stroma for the diagnosis of PCOS.[5] In our study, we tried to differentiate PCOS from PCOM solely on the basis of ultrasound features and develop and validate a simple diagnostic prediction model. We found that ultrasound cutoff of FNPO > 20 with a risk score of 6 was the most sensitive sonological feature in confirming PCOS and differentiating it from PCOM which had preponderance to have a FNPO of 12 – 20 per ovary. Normal ovaries were categorized as those ovaries with a FNPO < 12 in our study. The reason for the high number of cases in our study with a FNPO > 20 compared to various other previous studies could be partly due to the ultrasound machine equipped with a superior resolution. There are presently many conflicting studies which have recommended various cutoff values for the FNPO. The Androgen excess and PCOS society Task Force recommended a relatively higher threshold of FNPO =/> 25 when using newer technology that affords maximal resolution of ovarian follicles (i.e. transducer frequency ≥8 MHz).[6,7] Lujan.M.E, et al observed that an FNPO threshold of 26 follicles had the best compromise between sensitivity (85%) and specificity (94%) when discriminating between controls and PCOS.[8] However, there have been other authors who observed that at least one ovary with 12 or more follicles measuring 2–9 mm was sensitive enough in predicting polycystic ovarian syndrome.[9,10] Conway, et al also recommended the maintenance of the broad diagnostic criteria of Rotterdam, but focused on the need for specific identification of the each of the four phenotypes of PCOS.[11] FNPO > 22 was highly sensitive in all phenotypes, and was the single best criterion assessed for all subjects, suggesting the important role of ultrasound.[12] A programmable grid system over the viewing window to estimate the total follicle number per ovary. They observed that the mean FNPO was as high as 44.6 +/- 2.3.[13] While this may offer good reliability and interobserver agreement (interobserver agreement of 0.82) in its the ability to obtain reproducible follicle counts, we have observed that careful real time imaging by uninterrupted scanning of the entire ovary, from the inner to the outer margins in a longitudinal cross-section using an endovaginal transducer of high resolution will also be equally effective in the diagnosis of PCOS. We observed a higher interobserver agreement of 0.94 (95% CI: 0.93-0.95) for calculation of FNPO on real time imaging without using the grid analysis. Based on the derived risk score in our study, we believe that a cutoff value of FNPO > 20 is a highly sensitive (sensitivity = 93.71%) sonological feature in differentiation of PCOS from PCOM in any ultrasound machine with a fair degree of resolution.

RESULTS

This study comprised a total of 2300 patients. The average age of the patients was 25.1 years (Range: 18–45 years). In our study, we observed a rather higher incidence of PCOS (Category C) in the age groups of 18 – 20 years (362/498 patients; 72.6%) as well as 21 – 25 years (356/509 patients; 69.9%) compared to the age groups of 26 – 30 years (99/286 patients; 34.6%), 31 – 35 years (109/340 patients; 32.0%), 36 – 40 years (81/275 patients; 29.4%) and 41 – 45 years (104/392 patients; 26.5%). But then, our study was not a multicentric study and only represented the values obtained from a single hospital. This significant relationship between the age and PCOS could be attributed to the fact that the ovarian follicle number and volume decreases naturally with age.

Construction of the diagnostic prediction model using training data set

Out of a total of 1500 patients comprising the training set, 242 patients who had no clinical symptoms of polycystic ovarian syndrome (PCOS) as well as had no polycystic ovaries (PCO) on ultrasound were classified under 'Category A'. Out of the remaining 1258 patients in the training set, there were 522 patients who had no clinical symptoms of PCOS but showed PCO on ultrasound. This group of patients was classified under 'Category B'. There were 736 patients who had one or more clinical symptoms of PCOS in addition to the visualization of PCO on ultrasound. This group of patients was grouped as 'Category C'.

The association between PCOM (Category B), PCOS (Category C) and various sonographic features of the training data set is summarized in Table 1.

Table 1. Association between PCOM, PCOS and various ultrasound features of training data set on multiple logistic regression and risk score analysis

Training data set			Validation (Test) data set		
Total score *	n	Rate of PCOS (%)	Total score *	n	Rate of PCOS (%)
0	242	0	0	200	0
1	29	7.2	1	11	6.1
2	21	11.5	2	19	9.4
3	30	17.6	3	24	19.2
4	70	30.0	4	29	28.6
5	30	35.4	5	37	30.1
6	130	41.1	6	40	39.4
7	128	47.1	7	31	44.5
8	71	59.4	8	20	62.3
9	10	68.4	9	24	69.4
10	18	77.9	10	19	76.1
11	55	84.8	11	25	83.1
12	28	89.2	12	54	92.9
13	43	94.1	13	39	95.9
14	322	96.5	14	79	97.5
15	65	97.2	15	63	97.8
16	49	97.9	16	26	98.1
17	35	98.5	17	36	99.4
18	124	100.0	18	24	100.0

Table 2: Rate of PCOS by Total Score on Multiple Logistic Regression Model in Training and Validation Data Sets

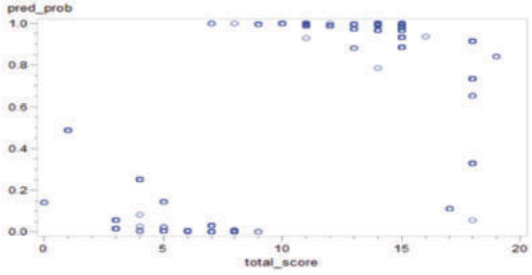
Suspicious Ultrasound feature	PCOM (n = 522)	PCOS (n = 736)	P (By chi-square test)	Odds Ratio (95% CI)	Sig. p (By multiple logistic regression analysis)	Risk Score
Number of follicles			<0.05			
>20	47	701		7.11(1.5,0)	0.047	6
12-20	475	35		1.00 (reference)		0
Ovarian volume			<0.05			
>10	133	602		2.3(1.2,0)	0.046	2
<=10	389	134		1.00 (reference)		0
Stromal volume			<0.05			
>10	22	358		3.04(0.005,0.486)	0.026	2
8.1- 10	95	240		1.60(0.01,0.451)	0.006	1

</=8	405	138		1.00 (reference)		0
SV/TV			<0.05			
>0.8	17	383		3.98(0,.c)	0.009	4
.71-.8	239	246		2.75(0.008,47.843)	0.033	2
.61-.7	249	98		2.004(0.982,5.121)	0.045	1
<=.6	17	9		1.00 (reference)		0
SA/TA			<0.05			
>0.4	37	195		2.42(7.2,6)	0.083	2
0.31-.4	206	368		1.99(0,.c)	0.093	1
.21-.3	183	121		1.92(11.955,8.9)	0	1
<=.2	96	52		1.00 (reference)		0
Stromal echogenicity			0.448			
Increased	40	63		0.981(0.309,3.12)	0.053	0
Normal	482	673		1.00 (reference)		0
Follicular distribution			<0.05			
Peripheral	448	641		1.889(0.938,4.804)	0.038	1
Even	74	95		1.00 (reference)		0

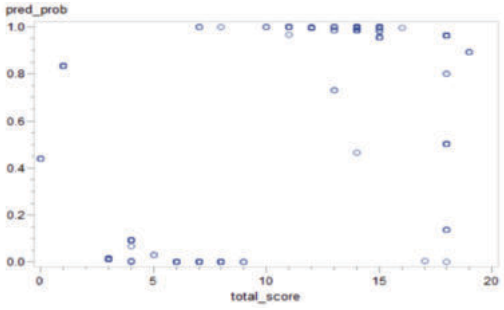
Note: '*' denotes the sum of all scores of individual ultrasound features.

The predicted probability of PCOS tended to rise along with the total risk score (Figure 1A). Area under the ROC curve (Receiver operating characteristic) was 0.9815 (95% CI, 0.9813-1.000) at training data set (Figure 2A).

Fig. 1. Scatter plots of predicted probability by total score. Predicted probability of PCOS tended to increase as risk score increased in both data sets. **A.** Training data set. **B.** Validation data set.



(1A) Training Dataset



1B) Validation Dataset

Validation of the diagnostic prediction model

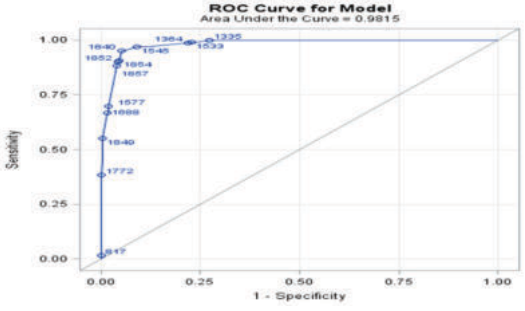
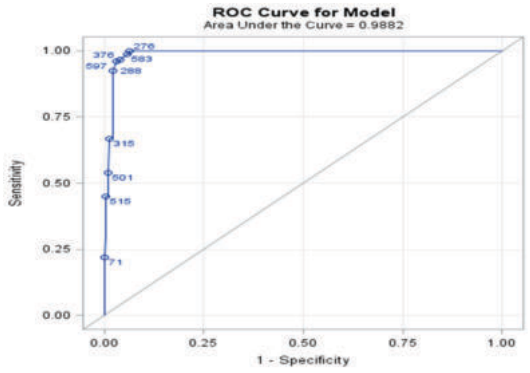


Fig. 2. Receiver operating characteristic (ROC) curves for training and validation data set based on risk scores from logistic regression model.

Training Dataset



Validation Dataset

A. Area under curve is 0.9815 at training data set. **B.** Area under curve is 0.9882 at validation data set.

Table 3: OIRASS risk score comparison with LH/FSH ratio

OIRASS Total risk score	Number of cases (n)	Rate of PCOS (%)	Average LH (mIU/ml)	Average FSH (mIU/ml)	Average LH/FSH
0	200	0	3.79 +/- 0.213	6.76 +/- 0.235	0.56 +/- 0.14
1	11	6.1	3.95 +/- 0.222	5.41 +/- 0.188	0.73 +/- 0.18
2	19	9.4	3.90 +/- 0.219	5.49 +/- 0.191	0.71 +/- 0.17
3	24	19.2	4.12 +/- 0.232	5.21 +/- 0.181	0.79 +/- 0.19
4	29	28.6	4.44 +/- 0.250	5.16 +/- 0.179	0.86 +/- 0.21
5	37	30.1	5.54 +/- 0.312	6.22 +/- 0.216	0.89 +/- 0.22
6	40	39.4	6.15 +/- 0.346	6.47 +/- 0.225	0.95 +/- 0.23
7	31	44.5	6.84 +/- 0.385	6.27 +/- 0.218	1.09 +/- 0.27
8	20	62.3	7.16 +/- 0.403	5.82 +/- 0.202	1.23 +/- 0.30
9	24	69.4	7.70 +/- 0.434	4.58 +/- 0.159	1.68 +/- 0.42
10	19	76.1	9.14 +/- 0.515	5.34 +/- 0.186	1.71 +/- 0.42
11	25	83.1	9.85 +/- 0.555	4.80 +/- 0.167	2.05 +/- 0.51
12	54	92.9	10.35 +/- 0.583	4.64 +/- 0.161	2.23 +/- 0.55
13	39	95.9	12.97 + /- 0.731	5.33 +/- 0.185	2.43 +/- 0.60
14	79	97.5	14.16 +/- 0.798	5.46 +/- 0.190	2.59 +/- 0.64
15	63	97.8	14.98 +/- 0.844	5.38 +/- 0.187	2.78 +/- 0.69
16	26	98.1	15.48 +/- 0.872	5.37 +/- 0.186	2.88 +/- 0.71
17	36	99.4	16.19 +/- 0.912	5.36 +/- 0.186	3.02 +/- 0.75
18	24	100.0	18.47 +/- 1.041	5.86 +/- 0.204	3.15 +/- 0.78

Ovary imaging reporting and scoring system (OIRASS) risk score comparison with hormonal assays

The Luteinizing hormone/ Follicle stimulating hormone ratio (LH/FSH) of all the 800 patients in the validation set in this study were documented. The average LH levels, FSH levels and the ratio of LH to FSH for an OIRASS total risk score of 0 were 3.79 +/- 0.213 mIU/ml, 6.76 +/- 0.235 mIU/ml and 0.56 +/- 0.14 respectively (Table 3).

CONCLUSION:

We found that there was excellent agreement among the different

observers, thus implying that this Ovary imaging reporting and scoring system (OIRASS) shows comparable and reproducible results in the analysis of the ultrasound features of an ovary by different radiologists

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