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ORIGINAL ARTICLE

Assessment of Interleukin-22 mRNA as a Diagnostic Marker for Polycystic Ovary Syndrome -Associated Metabolic Dysfunction

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Abstract

Background: Metabolic abnormalities and immune dysregulations are the most common risk factors for polycystic ovary syndrome (PCOS). Interleukin-22 (IL-22) is implicated in the pathogenesis of the immune-inflammatory system in the context of metabolic dysfunction. In the current research, we aimed to investigate IL-22 mRNA in PCOS and explore its correlations with metabolic syndrome (MetS) and reproductive features of PCOS.

Methods: we conducted our research on 60 women as control groups, and 70 patients with PCOS (30 patients without MetS and 40 patients with MetS). We investigated serum IL-22 by ELISA. At the same time, the IL-22 mRNA level was analyzed by RT-qPCR.

Results: Among 70 women with PCOS, 40 (57.1%) had metabolic syndrome. women with PCOS had significantly lower serum and mRNA Expression Levels of IL-22 compared to control. Even more importantly, among PCOS patients, women with MetS had significantly lower serum and mRNA Expression levels of IL-22 compared to women without MetS. serum and mRNA Expression levels of IL-22 were negatively associated with MetS components and inflammatory markers as well as reproductive features of PCOS. The AUC of serum and mRNA levels of IL-22 in the prediction of MetS among PCOS women had a sensitivity of 90%, and 77.5%, respectively, and specificity of 66%, 87.3% and respectively.

Conclusion: PCOS patients had significantly serum and mRNA Expression levels of IL-22 than controls. the lowered IL-22 serum and mRNA levels could be used as diagnostic markers of PCOS patients more specifically women with MetS.

Keywords: Interleukin-22; inflammatory markers ;polycystic ovary syndrome; metabolic syndrome; reproductive phenotypes,

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most frequent female reproductive endocrine disorder, it is prevalence range from 5 to 15% worldwide [1]. Emerging studies demonstrate that it contributes to the prominent cause of

anovulatory infertility. However, the basis for this remains unclear. Furthermore, PCOS aggravates not only reproductive derangements [2], but also metabolic complications such as diabetes mellites, and cardiometabolic diseases [3].

Emerging evidence links insulin resistance (IR) with metabolic syndrome (MS)in PCOS, affecting around 65–70% of all patients [4]. Remarkably, IR and β cell dysfunction have a unique pathogenic role in PCOS susceptibility and they contribute to many metabolic abnormalities [5].

Mounting evidence indicates that the cause of PCOS is complicated. Many factors are associated with PCOS susceptibility and phenotypic features [6]. An interesting study confirmed that visceral obesity is very common in PCOS, and this obesity contributed to IR through chronic low-grade inflammation [7]. Moreover, obesity generally exhibits constantly secreted levels of immunomodulators for example TNF-α, and interleukins (IL) [8].

Many reports detected the pathogenic role of IL in the pathogenesis of endocrine-metabolic disorders such as PCOS. IL-22 is a cytokine produced by T-helper 22 (Th22). In previous reports, it was found that IL-22 was involved in the regulation of the immune-inflammatory system in the context of metabolic dysfunction. [9].

It is well known that PCOS-associated metabolic disease has major adverse effects on women's lives. The purpose of this study was to evaluate serum and mRNA Expression levels of IL-22 in PCOS and to evaluate its association with metabolic dysfunction of PCOS.

Methods

We enrolled 70 PCOS patients;30 patients without MetS 40 patients with MetS and 70 age-matched women. The flowchart of this study is presented in supplementary figure 1. We explained the research aim and technique to all participants and received informed consent before the study began. Investigations were performed according to operating methods in Zagazig University Hospital.

Ethics approval and consent to participate: Written notified consent was obtained from all studied women, and the research was accepted by the research ethical committee of the Faculty of Medicine, Zagazig University, **(IRB≠, 299/23- June 2024).**

Quantitative evaluation of human IL-22 by enzyme-linked immunosorbent assay kit (Catalog No: E-EL-H0106; Elabscience, Wuhan, China) was made according to the manufacturer's instructions.

Analysis of the expression of IL-22 mRNA

Serum RNA was extracted utilizing the miRNeasy Mini Kit (Catalog no. 217004) to profile miRNA expression. The primers are shown in the following table. Results were compared to the housekeeping gene β-actin.

Name (gene)	Sequences
IL-22	F5′-GCTGCCTCCTTCTCTTGG-3′ R5′-GTGCGGTTGGTGATATAGG-3′
β-actin	F 5′-ATGTTTGAGACCTTCAACAC -3′ R5′-CACGTCACACTTCATGATGG-3′

Statistical analysis: to analyze the current study results, we applied SPSS version 26. The normality of variables was verified with the Kolmogorov-Smirnov test. An independent sample t-test and Mann-Whitney-U-tests were performed. Also, we applied the following tests to analysis the results, Pearson correlation, linear regression test and the receiver operating characteristic (ROC) curve analysis. We assumed P-values < 0.05 to be significant.

Results

Participant characteristics

We conducted 140 participants in the current study: 70 PCOS and 70 control women. All participants were premenopausal and matched for age. The mean age of the control group was 28.7±5.94 and the age of PCOS women was 29.02±5.8. The patient's characteristics are shown in Table 1. To investigate the metabolic features of the studied patients, we divided PCOS patients into two groups patients without MetS (n=30, 42.9%) and patients with MetS(n=40, 57.1%). We detected those patients with MetS had statistically significant higher values of metabolic dysfunction parameters such as BMI,

waist/hip ratio, systolic blood pressure, TG, glucose monitoring parameters, and HOMA-IR compared to patients without Mets. Concerning reproductive features of PCOS, patients with MetS had increased values of AFC, hirsutism score, LH, total testosterone, and AMH. Interestingly, inflammatory markers such as ESR and CRP were statistically significantly greater in patients with MetS compared to patients without MetS, $P < 0.001$.

To assess the serum level of IL-22 (Pg/ml) in studied groups, we applied ANOVA tests and we found that patients with MetS had statistically significant lower values of serum IL-22(0.82±0.158) compared to patients without MetS (0.91±0.12) and control group (1.92±0.131), $P < 0.001$ figure 1a.To elucidate IL-22 mRNA levels in studied groups we used RT-qPCR.We detected that patients with MetS had statistically significantly lower values of IL-22 mRNA (0.47±0.24) compared to patients without MetS (.51±0.316) and control group (0.91±0.09), $P < 0.001$ Figure 1b.

Prevalence of various components of metabolic syndrome by NCEP among PCOS women is shown in supplementary figure 2

Among PCOS women without MetS (n=30,42.9%), 3 women (4.3%) had no component, 10 women (14.3%) had one component and 17 women (24.3%) had two components**, (supplementary figure 2).**

Regards PCOS women with MetS (n=40,57.1%), 12 women (17.1%) had three components,18 women (25.7%) had four components, and 10 women (14.3%) had five components, supplementary figure 2.

The correlations of IL-22 serum and mRNA with phenotype characteristics of the PCOS group are in Table 2.

To further evaluate the associations between IL-22 serum and mRNA with metabolic risk factors, inflammatory markers, and phenotype characteristics of PCOS, we applied the Pearson correlation coefficient and the results illustrated in Table 2. There were statistically significant negative associations between serum IL-22 and metabolic parameters such as BMI, waist/hip ratio, TG, fasting serum insulin, HbA1c, and HOMA-IR, $P < 0.001$. Regarding PCOS reproductive features, there were statistically significant negative associations between serum IL-22 and hirsutism score as well as total testosterone, $P < 0.001$. Interestingly, the inflammatory markers; ESR and CRP were significantly negatively correlated with serum IL-22, $P < 0.001$.

To elucidate the associations of IL-22 mRNA, we used the Pearson correlation coefficient and we detected that it was negatively associated with BMI, waist/hip ratio, TG, fasting serum insulin, HbA1c, and HOMA-IR, $P < 0.001$. Regarding PCOS reproductive features, there were statistically significant negative correlations between IL-22 mRNA and hirsutism score as well as total testosterone, $P < 0.001$. Remarkably, the inflammatory markers; ESR and CRP were significantly negatively correlated with IL-22 mRNA, $P < 0.001$.

To confirm the previous findings, we applied linear regression analysis among women with PCOS. the results confirmed that serum IL-22 was best predicted by HbA1c, HOMA-IR, BMI, ESR, and hirsutism score ($P < 0.01$). To interpret the independent associations of IL-22 mRNA, we used linear regression analysis among women with PCOS and we detected that among the studied parameters, only HbA1c, HOMA-IR, Waist/hip ratio, BMI, TG, and hirsutism score were independently associated with IL-22 mRNA, $P < 0.01$), table 3.

The Accuracy of IL-22 Serum and mRNA for Prediction of PCOS

To investigate serum IL-22's ability to predict PCOS we performed ROC analysis. The AUC was 0.986(95% CI = 0.959–1.000) with sensitivity = 98.6%, specificity = 91.3%, and the cutoff values (1.73), (Figure 2a). Concerning IL-22 mRNA level, The AUC was 0.958 (95% CI = 0.922–0.993) with sensitivity = 90.1%, specificity = 99%, and cutoff values (0.72), (Figure 2a).

The Precision of IL-22 serum and mRNA for differentiation between MetS between PCOS women

serum IL-22 ability to predict PCOS had AUC of 0.900 (95% CI = 0.832–0.968) with sensitivity = 90%, specificity = 66%, and the cutoff values (0.863), (Figure 2a).

Concerning IL-22 mRNA level, The AUC was 0.837 (95% CI = 0.715–0.959) with sensitivity = 77.5%, specificity = 87.3%, and the cutoff values (0.463), (Figure 2b).

Table 1: Characteristics of PCOS groups

Variable	PCOS with MetS (mean ± SD), (n=30)	PCOS with MetS (mean ± SD), (n=40)	P
Age (years)	28.10±5.94	29.22±5.7	0.816
Body mass index (kg/m2)	24.55±5.51	35.32±8.16	<0.001*
Waist/hip ratio	0.93±0.22	1.44±0.358	<0.001*
Systolic blood pressure (mm Hg)	121.6±2.48	128.6±6.67	<0.001*
Diastolic blood pressure (mm Hg)	87.7±4.54	88.7±510	0.433
Hirsutism score	11.4±0.981	16.8±4.12	<0.001*
Ovarian volume (cm^3)	9.5±389	10.8±4.96	0.221
AFC (number)	19.1±6.42	24.6±6.52	<0.001*
Triglycerides (mg/dL)	138.6±24.15	190.5±35.7	<0.001*
HDL cholesterol (mg/dL)	44.26±7.4	41.76±5.1	0.09
Fasting plasma glucose (mg/dL)	92.12±8.95	119.11±26.8	<0.001*
Fasting serum insulin (lU/mL)	9.85±3.45	33.1±7.41	<0.001*
HbA1c (%)	5.12±0.32	6.4±0.12	<0.001*
HOMA-IR	1.9±0.25	9.63±3.12	<0.001*
FSH (mIU/mL)	5.2±1.01	5.08±1.49	0.228
LH (mIU/mL)	5.24±0.2	5.63±0.61	<0.001*
LH/FSH	1.09±0.03	1.25±0.18	<0.001*
AMH (ng/ml)	5.44±0.6	6.73±0.54	<0.001*
DHEA-S (mg/mL)	1.32±0.2	1.45±0.3	0.649
Total testosterone (ng/mL)	0.51±0.15	1.53±0.13	<0.001*
ESR (mm/hr)	22 ± 7.62	56 ± 11.5	<0.001*
CRP (mg/L)	6.8 ± 0.41	10.3 ± 1.21	<0.001*

MetS , metabolic syndrome ;AFC; antral follicle count, HOMA-IR, homeostasis model assessments of insulin resistance; DHEA, dehydroepiandrosterone. Interleukin, IL.
*Statistically significant (P < 0.05).

Table 2: Pearson correlation coefficient between IL-22 serum and mRNA levels with metabolic, inflammatory and phenotype characteristics of PCOS group.

	IL-22 serum		IL-22 mRNA	
	r	p	r	p
Body mass index (kg/m2)	-0.265	<0.001*	-0.320	<0.001*
Waist/hip ratio	- 0.251	<0.001*	- 0.362	<0.001*
Systolic blood pressure (mm Hg)	- 0.104	0.220	- 0.129	0.140
Diastolic blood pressure (mm Hg)	-0.140	0.148	-0.135	0.112
Hirsutism score	-0.606	<0.001*	-0.424	<0.001*
Ovarian volume (cm^3)	- 0.127	0.208	- 0.127	0.208
AFC (number)	- 0.781	<0.001*	- 0.449	<0.001*
Triglycerides (mg/dL)	- 0.777	<0.001*	- 0.650	<0.001*

	IL-22 serum		IL-22 mRNA	
	r	p	r	p
HDL cholesterol (mg/dL)	0.041	0.667	0.041	0.667
Fasting plasma glucose (mg/dL)	- 0.351	<0.001*	- 0.494	<0.001*
Fasting serum insulin (lU/mL)	- 0.696	<0.001*	- 0.820	<0.001*
HbA1c	-0.365	<0.001*	-0.558	<0.001*
HOMA-IR	-0.345	<0.001*	-0.552	<0.001*
FSH (mIU/mL)	-0.187	0.051	-0.107	0.208
LH (mIU/mL)	- 0.073	0.394	- 0.142	0.095
DHEA-S (mg/mL)	-0.041	0.667	-0.041	0.667
Total testosterone	- 0.351	<0.001*	- 0.351	<0.001*
ESR (mm/hr)	- 0.238	<0.001*	- 0.238	<0.001*
CRP (mg/L)	-0.365	<0.001*	-0.365	<0.001*

*Statistically significant (P < 0.05).

Table 3: linear regression analyses in PCOS women to test the influence of the main independent variables against IL-22 serum and mRNA levels (dependent variable) .

Model		Unstandardized Coefficients		Standardized Coefficients	t	P value	95% C.I.	
		B	SE	Beta			Lower Bound	Upper Bound
Serum IL-22	Constant	2.138	0.141		15.161	<0.001*	1.859	2.417
	HbA1c	0.078	0.036	0.079	2.132	<0.001*	.006	0.149
	HOMA-IR	-0.168	0.021	-0.629	-7.858	<0.001*	-0.210	-0.125
	Waist/hip ratio	-0.006	0.007	-0.068	-0.800	0.425	-0.020	0.009
	BMI	-0.005	0.002	-0.086	-2.081	<0.05*	-0.010	0.000
	TG	0.006	0.008	0.023	0.750	0.455	-0.010	0.022
	ESR(mm/hr)	-0.047	0.020	-0.066	-2.377	<0.05*	-0.086	-0.008
	Hirsutism score	-0.021	0.006	-0.346	-3.634	<0.001*	-0.033	-0.010
IL-22	Constant	2.138	0.141		15.161	<0.001*	1.859	2.417
mRNA	HbA1c	-0.007	0.002	-0.159	-4.157	<0.001*	-0.010	-0.004
	HOMA-IR	0.005	0.00	0.545	11.657	<0.001*	0.004	0.006
	Waist/hip ratio	-0.003	0.001	-0.182	-3.917	<0.05*	-0.004	-0.001
	BMI	0.078	0.036	0.079	2.132	<0.001*	0.006	0 .149
	TG	-0.168	0.021	-0.629	-7.858	<0.001*	-0.210	-0.125
	ESR(mm/hr)	-0.006	0.007	-0.068	-.800	0.425	-0.020	0.009
	Hirsutism score	-00.005	0.002	-0.086	-2.081	<0.05*	-0.010	0.000

*Statistically significant (P < 0.05).

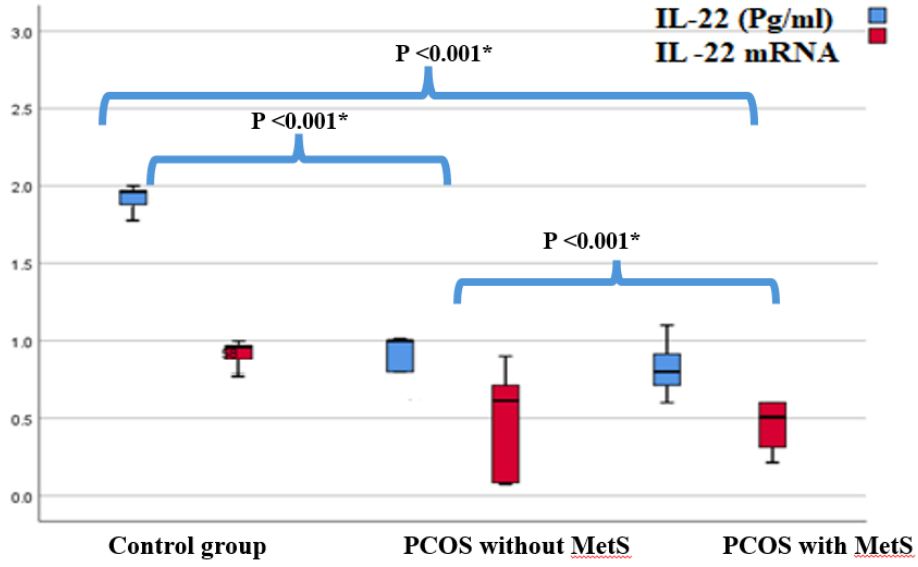
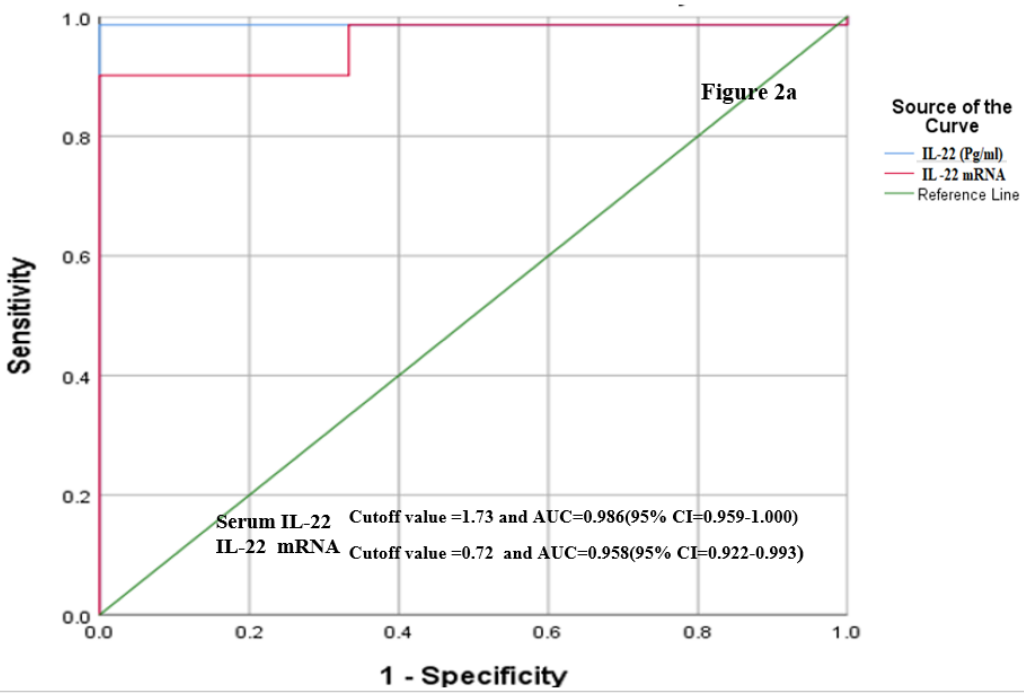


Figure 1: comparison between studied groups regards IL-22 serum and mRNA levels



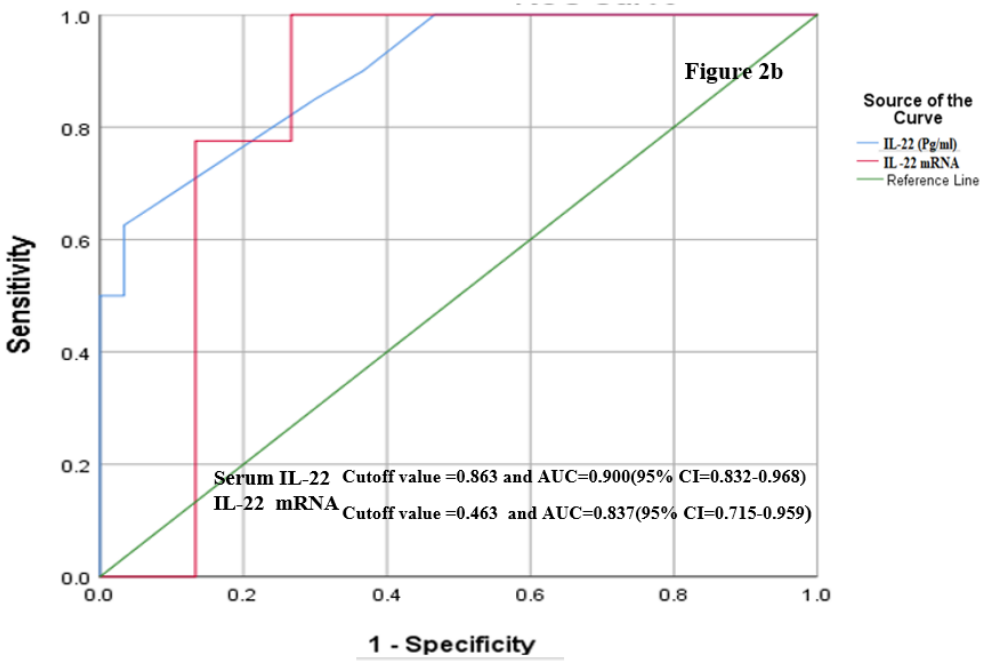


Figure 2a: ROC curve of IL-22 serum and mRNA for Prediction of PCOS among studied groups. **Figure 2b: :** ROC curve of IL-22 serum and mRNA levels for differentiation between PCOS women with MetS and the others without MetS.

Discussion

A preponderance of evidence implies that PCOS had higher cardiac and metabolic risk than the general population [11]. Interesting studies reveal that PCOS is a lifelong syndrome that affects women during their whole life [12]. The pathophysiology of PCOS mainly results from complex mechanisms that are still not fully documented [13]. Consequently, we need further research to explore the hypothesis underlying PCOS [14]. Accordingly, we constructed this study to evaluate IL-22 mRNA and serum levels in PCOS and to evaluate its association with metabolic dysfunction and reproductive features of PCOS.

As we know age and sex could affect study results and level of gene expression thus in the current research we matched age and sex, already study was conducted on women only. As expected, our findings disclosed that PCOS patients with MetS had higher values of metabolic and reproductive dysfunction compared to patients without Mets. Similar findings were detected in our previous research [15-17]. The current work findings revealed that 57.1% of studied PCOS women had MetS. Similar to the current study findings, a study conducted by Glueck et al detected a high prevalence of metabolic syndrome in PCOS, they detected that about 46.4% of studied PCOS women had MetS [18].

Another study conducted in the USA detected a high frequency of MetS among women with PCOS which was around 43% [19]. In Iranian women according to Zahiri et al, the frequency of MetS in patients with PCOS was 28.8% [20]. This variation of the frequency may be related to participants' characters and ethnicity.

One of the interesting findings from our current study is that inflammatory markers such as ESR and CRP were increased in PCOS with MetS compared to patients without MetS. Likewise, another research suggested that PCOS is associated with inflammatory markers such as CRP [21,22].

There are intriguing reports confirmed that IL-22 as one member of the IL-10 superfamily, has various metabolic functions as it improves insulin sensitivity, and lipid metabolism as well as decreases inflammation [23] these important metabolic functions of IL-22 were done through variations of

mucosal immunity [24]. We, therefore, examined whether serum and expression of IL-22 were associated with metabolic syndrome parameters and phenotypic features of PCOS women.

Our analysis indicated that the PCOS group had decreased levels of IL-22 serum and mRNA levels compared to the control. Even more importantly, among PCOS patients, women with MetS had significantly lower levels of IL-22 serum and mRNA compared to women without MetS. Similar results were detected in Qi et al study, they investigated serum IL-22 in patients with PCOS and they found that the level was lower compared to general populations [25].

Our findings are similar to results recognized by Geng et al, they suggested that the PCOS group had lower values of serum IL-22 levels in comparison to the healthy group [26]. Also, other studies' results supported this hypothesis [27-29].

Though some reports are controversial, Aksun et al found no differences between PCOS and controls regards serum IL-22 levels at the beginning of the clinical trial but after treatment of PCOS the level of serum IL-22 level increased in PCOS women, and these findings were similar to our results hypothesis [30].

For further assessment and confirmation of our results, we compared studied markers ; serum and mRNA Expression levels of IL-22 with metabolic and reproductive as well as inflammatory markers among PCOS women and we detected that there were statistically significant negative associations between serum and mRNA Expression levels of IL-22 with metabolic parameters such as BMI, waist/hip ratio, TG, fasting serum insulin, HbA1c, and HOMA-IR as well as reproductive parameters such as hirsutism score as well as total testosterone. Mysteriously, ESR and CRP were significantly negatively correlated with serum and mRNA Expression levels of IL-22. Similar results were obtained in another interesting study, Qi et al detected that the decreased IL-22 in PCOS patients is adversely associated with metabolic dysfunction components [25].

Concerning PCOS prediction, we discovered that serum and mRNA Expression levels of IL-22 had higher AUC values of serum and mRNA levels of IL-22(0.986, 0.958, respectively) with a sensitivity of 98.6%, and 90.1%, respectively, and specificity of 91.3%, 99%, and respectively at cutoff values (1.37 and 0.72, respectively).

This work's findings are novel as this research implements a robust estimation of the diagnostic power of both IL-22 serum and mRNA levels in the prediction of MetS among PCOS. The AUC of serum and mRNA levels of IL-22 (0.900 ,0.837, respectively) had a sensitivity of 90%, and 77.5%, respectively, and a specificity of 66%, and 87.3%, respectively at the cutoff values (0.863 and 0.463, respectively). Thus, we confirmed that the lower IL-22 serum and mRNA levels could be used as diagnostic markers of PCOS patients, particularly with MetS.

The present study's strengths included using a novel comprehensive search strategy. According to our knowledge, it is the first study that implements a robust estimation of the diagnostic power of serum and mRNA levels of IL-22 in predicting MetS among PCOS**.**

Limitations of the study were the small sample size, and this study did not compare treated PCOS women with non-treated women. Therefore, the following research will enroll more and different groups of PCOS patients and we will include a treated group to compare them regards these studied biomarkers.

Conclusion

PCOS patients particularly those with MetS had significantly lower serum and mRNA levels IL-22 than controls. serum and mRNA levels of IL-22 levels were significantly negatively associated with metabolic syndrome components, inflammatory markers, and reproductive features of PCOS. The current evidence emphasizes the valuable role of IL 22 for PCOS-associated metabolic dysfunction diagnosis, which may facilitate prevention, and treatment of PCOS as well as its associated metabolic dysfunction.

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Citation

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Supplementary File

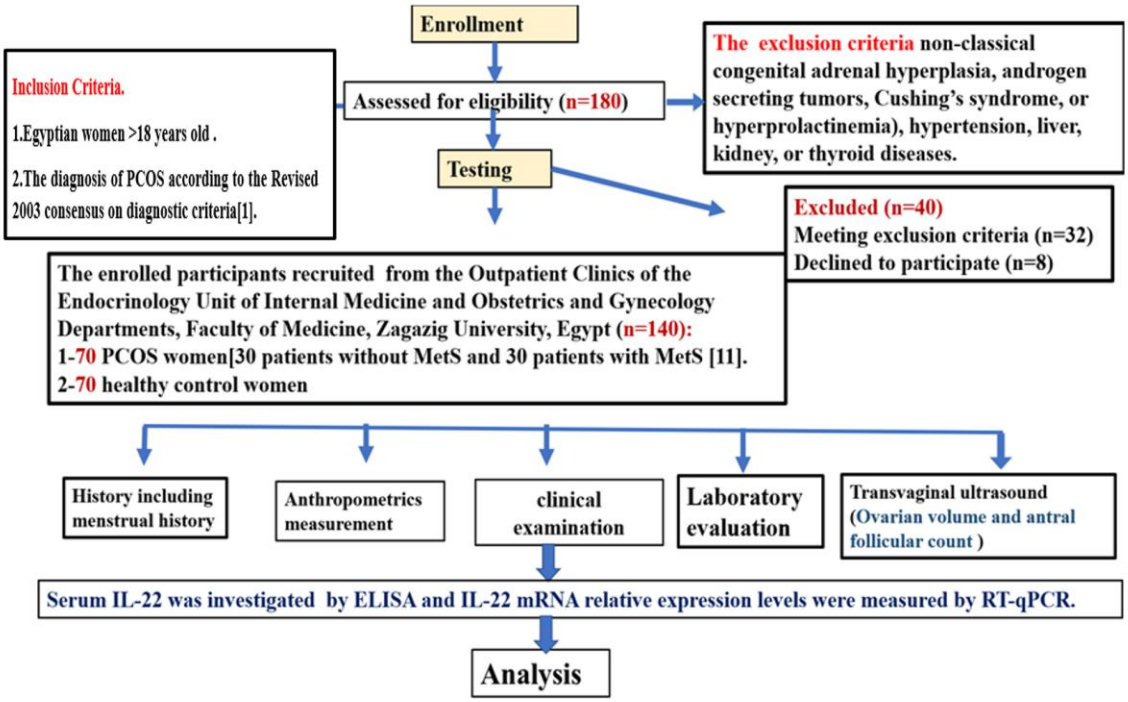

Figure 1: flowchart of the study.

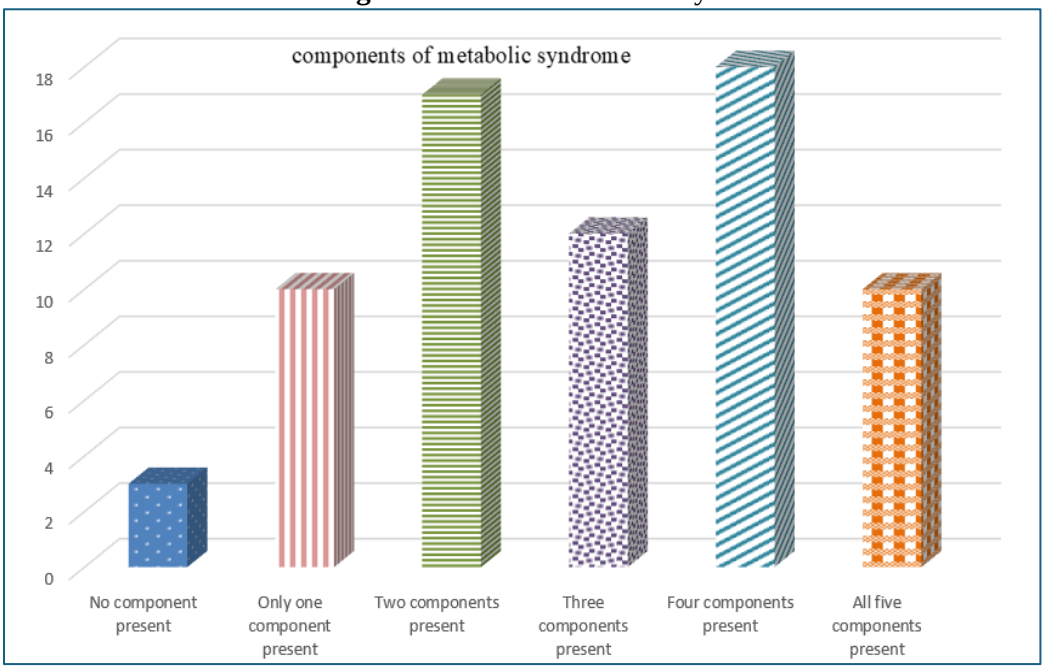

Figure 2: Prevalence of various components of metabolic syndrome by NCEP among PCOS women