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Original article

Insights into Immune-Metabolic Interactions of IL-22 in the Pathophysiology of Polycystic Ovary Syndrome

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Abstract

Background: Polycystic Ovary Syndrome (PCOS) is an endocrine-metabolic disorder associated with insulin resistance and hyperandrogenism. The present study aims to assess the role of interleukin-22 (IL-22) as a diagnostic marker in PCOS and its correlation with metabolic, inflammatory, and hormonal aspects. **Materials and Methods:** A case-control study was performed with 180 females (90 PCOS patients and 90 healthy women). Anthropometric indices, HOMA-IR, and hormonal profile (LH, FSH, LH/FSH ratio, total/free testosterone, estradiol, FAI, and SHBG) were also assessed, along with serum IL-22 levels measured by ELISA. It is determined by Receiver Operating Characteristic (ROC) curve analysis that IL-22 has a diagnostic value. **Results:** IL-22 levels were significantly elevated in PCOS patients (68.4 ± 15.7 pg/mL) compared to controls (42.3 ± 10.8 pg/mL, $p < 0.001$). IL-22 correlated positively with LH ($r = 0.45$), the LH/FSH ratio ($r = 0.38$), FAI ($r = 0.41$), and estradiol ($r = 0.36$), and inversely with SHBG ($r = -0.39$). The ROC analysis gave an AUC value of 0.87 with a 55 pg/mL cut-off, sensitivity of 82%, and specificity of 78%.

Conclusion: Serum IL-22 is a powerful diagnostic biomarker for PCOS, with strong associations with key disruptions in the hormone and metabolism system**.**

Keywords: Polycystic Ovary Syndrome, Interleukin-22, Biomarker, Inflammation, Metabolic Dysfunction, Insulin Resistance.

1. Introduction

PCOS is an endocrine disorder that is complex and multifaceted, occurring in 5–20% of women of reproductive age, depending on the diagnostic criteria and population studied. It is defined as a range of clinical and biochemical features, such as hyperandrogenism, chronic anovulation, and ultrasonographic evidence of polycystic ovarian morphology (1). In addition to these reproductive characteristics, PCOS is now known to be a systemic disease with a range of metabolic, inflammatory, and cardiovascular comorbidities. These include insulin resistance (IR), dyslipidemia, type 2 diabetes mellitus (T2DM), and cardiovascular disease (CVD) risks, making PCOS a significant public health problem worldwide (2,3).

Chronic low-grade inflammation is a well-documented characteristic of PCOS and is thought to be a key part of its pathophysiology(4). Increased levels of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), interferon gamma induced interferon gamma receptor (IFN-γ/IFN-γ receptor), and interleukin-6 (IL-6) have been consistently reported in women with PCOS(5–7). These inflammatory markers are hypothesized to be associated with ovarian dysfunction not only because of their

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association with metabolic disturbances like insulin resistance and obesity, but also because of their correlation with them. Although there is increasing evidence that the immune system is involved in PCOS, the exact mechanism(s) by which inflammation and immune dysregulation contribute to the development of PCOS are not fully known and will require further study(8,9).

Recently, a dual role of Interleukin-22 (IL-22), a member of the IL-10 cytokine family, in inflammatory and metabolic processes has been drawing attention(10). IL-22 is produced primarily by T-helper 22 (Th22) cells, and also by other immune subsets, such as innate lymphoid cells (ILCs), and other cells other than hematopoietic target cells, such as epithelial, stromal, and adipose tissue cells(11,12). This cytokine has a unique function related to the maintenance of the integrity of the epithelial barrier, tissue repair, and inflammatory responses(13,14). Interestingly, the role of IL-22 is highly context-dependent: it can lead to protection and homeostasis of tissues under certain conditions, but worsen inflammatory damage under others(15).

The evidence that has accumulated in recent years indicates that IL-22 is involved in metabolic disorders such as obesity, T2DM, and metabolic syndrome (16,17). IL-22 has been reported to affect important metabolic pathways like lipid metabolism, glucose regulation, and insulin sensitivity(18). Additionally, IL-22 has been shown to influence other inflammatory pathways, such as STAT3 and NF-κB signaling pathways, which are linked to systemic and ovarian inflammation in PCOS(19,20). In light of these results, IL-22 has been suggested as a possible mediator at the crossroads of immune and metabolic dysfunctions, features that are hallmarks of PCOS(21).

The precise function of IL-22 in PCOS has not been extensively explored, despite these advances(22). A few preliminary reports have suggested that there were changes in IL-22 levels in people with insulin resistance, obesity, and other conditions associated with PCOS, but there are limited investigations of IL-22 in the context of PCOS pathogenesis(23,24). Significantly, IL-22 has been linked to adipogenesis regulation, hepatic glucose metabolism, and inflammation-induced ovarian dysfunction, which may all play a role in the clinical manifestations of PCOS (22,25,26). Interleukin-22 (IL-22) is a member of the IL-10 family of cytokines that is involved in the regulation of the immune system, tissue repair, and metabolism. IL-22 is a cytokine secreted by T-helper 22 (Th22) cells, innate lymphoid cells (ILCs) and γδ T-cells, which binds to the IL-22 receptor complex (IL-22R), a complex composed of IL-22R1 and IL-10R2 subunits(27,28). This interaction induces signaling cascades, including mostly Janus kinase-signal transducer and activator of transcription (JAK-STAT) and NF-κB and MAPK pathways, to impart cell survival, proliferation, and antimicrobial responses (29,30). IL-22 also plays a role in maintaining tissue homeostasis by promoting the integrity of the epithelial barrier and production of antimicrobial peptides (AMPs), including Reg3γ, and by regulating its activity through IL-22 binding protein (IL-22BP) to prevent excessive inflammation(31,32).

IL-22's involvement in metabolic regulation has been observed in metabolic diseases such as obesity and type 2 diabetes mellitus (T2DM), where it enhances insulin sensitivity, regulates lipid metabolism, and lowers adipose tissue inflammation, including by boosting anti-inflammatory adipokines such as adiponectin(33). In contrast, the effects of IL-22 are context-dependent; in the case of acute tissue injury, IL-22 has been shown to have protective properties, whereas in the case of chronic exposure, IL-22 is associated with chronic inflammation, fibrosis, or tumorigenesis (34). There is limited evidence of the role of IL-22 in PCOS; however, due to its known participation in

metabolic and inflammatory pathways, it may play a role in the pathophysiology of PCOS (35). IL-22 can affect ovarian function through the regulation of ovarian inflammation, oxidative stress, and systemic insulin resistance, which are all associated with follicular dysfunction and hyperandrogenism in PCOS (36,37). The role of IL-22 in the immune-metabolic mechanism in PCOS would be beneficial in identifying new therapeutic targets for managing the complex syndrome.

This paper will aim to give a detailed insight about the role of IL-22 in the pathophysiology of PCOS. Our goal is to find out how immune-metabolic interactions through IL-22 could be involved in the development and progression of PCOS, and to integrate the results from immunology, endocrinology, and metabolic research. In addition, the potential of IL-22 as a diagnostic biomarker and therapeutic target is discussed, indicating the possibility of developing new therapies for the management of PCOS.

2: Materials and Methods

2.1StudyDesign

This study employed a case-control design to investigate the serum levels of Interleukin-22 (IL-22) in women diagnosed with Polycystic Ovary Syndrome (PCOS) by a specialized gynecologist according to the Rotterdam criteria, compared to healthy controls. The research was conducted at the Fertility Center in AL Sader Medical City in AL Najaf city during the period from (1/2/2026 to 1/4/2026). The study protocol was approved by the Institutional Review Board (IRB) of [Al-Sadr Teaching Hospital], and informed consent was obtained from all participants before enrollment.

2.2 Subjects

A total of 180 women participated in the study, comprising two groups: 90 women diagnosed with PCOS and 90 healthy women as the control group. Participants were recruited based on the following criteria:

- **Inclusion Criteria**:
  - Women aged 18 to 40 years.
  - Diagnosis of PCOS according to the Rotterdam criteria, which requires at least two of the following: oligomenorrhea or amenorrhea, clinical or biochemical signs of hyperandrogenism, and polycystic ovaries on ultrasound.
  - Healthy controls with regular menstrual cycles and no history of endocrine disorders.
- **Exclusion Criteria**:
  - Presence of other endocrine disorders such as thyroid dysfunction or adrenal disorders and other chronic diseases.
  - Current use of anti-inflammatory medications or hormonal treatments within the last three months.
  - History of chronic inflammatory diseases.

2.3 Sample Collection

Blood samples were collected from all participants between 8:00 AM and 10:00 AM after an overnight fasting period. Approximately 5 mL of venous blood was drawn into sterile serum separator tubes and allowed to clot at room temperature for 30 minutes. The samples were then centrifuged at 3000 rpm for 10 minutes to separate the serum, which was stored at -80°C until further analysis.

2.4 Measurement of Interleukin-22

Serum level of IL-22 was quantified using a commercially available enzyme-linked immunosorbent assay ELISA kit (Elabscience Cat. No.: E-EL-H2403, USA). The assay was performed according to the manufacturer's instructions. The minimum detectable concentration of IL-22 was (15.63-1000 pg/mL) .

2.5 Assessment of Clinical Parameters

Clinical parameters were evaluated for all participants, including:

- **Body Mass Index (BMI)**: Calculated using the formula(38):

BMI=weight (kg)/height $(m)^2$.

- **Fasting Insulin Level**: Measured using an ELISA kit (Elabscience Cat. No.: E-EL-H2665 USA), reference range of 0.78 - 50 μIU/mL.

- **Fasting serum Glucose Level**: Measured by enzymatic colorimetric method using glucose oxidase by cammen (Biomeruix-franle kit.), with normal reference values ranging from 70 to 99 mg/dL.

- **HOMA-IR**: Estimated using the Homeostasis Model Assessment of Insulin Resistance formula by the special equation (39):

HOMA-IR=Fasting Insulin (μU/mL)×Fasting Glucose (mg/dL)/405

Clinical parameters assessed included LH, FSH, total testosterone, free testosterone, prolactin, progesterone, and estradiol, along with BMI, fasting insulin, and HOMA-IR.

2.7 Statistical Analysis

All analyses were carried out with SPSS version 26.0. Data for continuous variables are presented as mean values with standard deviations, and comparisons between groups were made using independent t-tests or ANOVA. Pearson's correlation was used to evaluate the correlations, and the multivariate regression method was used to determine independent predictors. The independent t-test was employed to compare IL-22 levels and clinical parameters between the PCOS and healthy groups. Pearson correlation coefficients were calculated to evaluate the relationships between the level of IL-22 and clinical parameters. A p-value < 0.05 was considered statistically significant.

2.7 Ethical Considerations

The study adhered to the principles outlined in the Declaration of Helsinki. Informed consent was obtained from all participants, and confidentiality of the data was ensured throughout the research process.

3. Results

3.1 Baseline Characteristic

The participants' demographic, clinical, and hormonal baseline data are shown in Table 1. There were significant differences between PCOS patients and controls with regard to BMI, WHR, and fasting blood glucose (FBG) levels ($p < 0.001$). Additionally, PCOS patients exhibited higher levels of inflammatory markers, including C-reactive protein (CRP: 5.2 ± 1.3 mg/L vs. 2.1 ± 0.8 mg/L, $p < 0.001$) and interleukin-6 (IL-6: 8.4 ± 2.6 pg/mL vs. 4.2 ± 1.5 pg/mL, $p < 0.001$).

At baseline, the hormone levels were significantly elevated for important markers of PCOS. LH levels were markedly higher in PCOS patients (12.3 ± 3.6 IU/L) compared to controls (7.1 ± 2.4 IU/L, $p < 0.001$), while FSH levels were comparable (5.8 ± 1.3 IU/L in PCOS vs. 6.1 ± 1.2 IU/L in controls, $p = 0.18$). Consequently, the LH/FSH ratio was significantly elevated in PCOS patients (2.1 ± 0.5) versus controls (1.2 ± 0.3, $p < 0.001$). Other hormonal values, including estradiol (182.5 ± 40.2 pg/mL vs. 98.4 ± 25.3 pg/mL, $p < 0.001$), free testosterone (5.6 ± 1.4 pg/mL vs. 2.8 ± 0.9 pg/mL, $p < 0.001$), total testosterone (85.3 ± 15.6 ng/dL vs. 52.1 ± 10.7 ng/dL, $p < 0.001$), and Free Androgen Index (FAI: 8.4 ± 2.3% vs. 4.2 ± 1.1%, $p < 0.001$), were also significantly higher in PCOS patients. In addition, the insulin resistance was significantly higher in PCOS patients (4.2 ± 1.1) than in controls (1.9 ± 0.7, $p<0.001$), indicating that insulin resistance is very high among PCOS patients.

The integrated analysis reveals the important interaction among metabolic, inflammatory, and hormonal dysregulation in PCOS, indicating the potential of IL-22 as a biomarker that links and helps explain these findings.

2.3 Serum IL-22 Levels

The level of serum IL-22 was significantly higher in PCOS patients compared to the controls ($p < 0.001$) (Figure 1). The mean IL-22 concentration in PCOS patients was 68.4 ± 15.7 pg/mL, compared to 42.3 ± 10.8 pg/mL in controls. The level of IL-22 was significantly higher in obese PCOS patients (BMI ≥ 30 kg/m²) compared to non-obese patients ($p = 0.02$) during the subgroup analysis.

2.4 Correlation Analysis

Pearson's correlation analysis revealed that serum IL-22 levels positively correlated with BMI ($r = 0.48$, $p < 0.001$), CRP ($r = 0.52$, $p < 0.001$), fasting insulin levels ($r = 0.43$, $p < 0.001$), LH ($r = 0.45$, $p < 0.001$), LH/FSH ratio ($r = 0.38$, $p = 0.003$), and Free Androgen Index (FAI) ($r = 0.41$, $p < 0.001$). Further, there was a positive correlation between IL-22 and estradiol ($r = 0.36$, $p = 0.004$), indicating its role in hyperandrogenism. Conversely, a negative correlation was observed between IL-22 levels and sex hormone-binding globulin (SHBG) ($r = -0.39$, $p = 0.002$), suggesting that IL-22 may contribute to elevated free androgen levels and exacerbated hyperandrogenic features in PCOS, as shown in Figure 2.

2.5 Multivariate Regression Analysis

A multivariate regression model identified IL-22 as an independent predictor of PCOS status after adjusting for BMI, CRP, fasting insulin levels, LH, LH/FSH ratio, and estradiol ($\beta = 0.62$, $p < 0.001$). The model had an R^2 of 0.68, indicating that 68% of the variance in PCOS status could be explained by IL-22 levels and the included covariates. The results highlight the significant role of IL-22 and other hormonal and metabolic parameters in the pathophysiology of PCOS.

2.6 ROC Curve Analysis

The Area under the ROC curve (AUC) was 0.87 (95% CI: 0.82–0.91, $p < 0.001$), supporting the use of IL-22 as a potential diagnostic biomarker for PCOS. The best cutoff value for IL-22 was 55 pg/mL with an 82% sensitivity and 78% specificity.

Table 1. Baseline Characteristics of Study Participants

Parameter	PCOS Patients (n=150)	Controls (n=75)	p-value
Age (years)	28.4	27.9	0.52
BMI (kg/m²)	31.2	25.6	<0.001
Waist-to-Hip Ratio (WHR)	0.89	0.77	<0.001
Fasting Blood Glucose (mg/dL)	105.6	87.4	<0.001
CRP (mg/L)	5.2	2.1	<0.001
IL-6 (pg/mL)	8.4	4.2	<0.001
LH (IU/L)	12.3	7.1	<0.001
FSH (IU/L)	5.8	6.1	0.18
LH/FSH Ratio	2.1	1.2	<0.001
Estradiol (pg/mL)	182.5	98.4	<0.001
Free Testosterone (pg/mL)	5.6	2.8	<0.001
Total Testosterone (ng/dL)	85.3	52.1	<0.001
FAI (%)	8.4	4.2	<0.001
HOMA-IR	4.2	1.9	<0.001

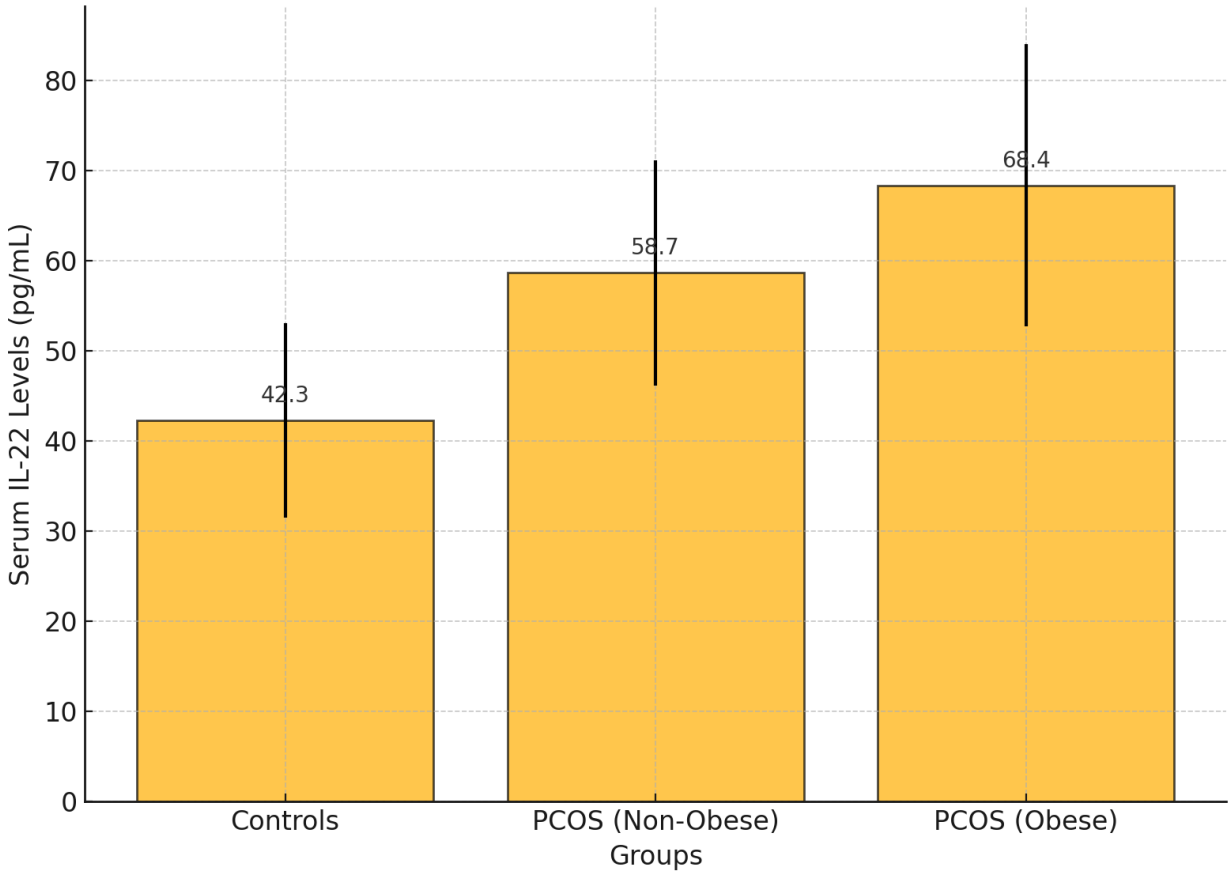


Figure 1. Serum IL-22 Levels in PCOS Patients and Controls

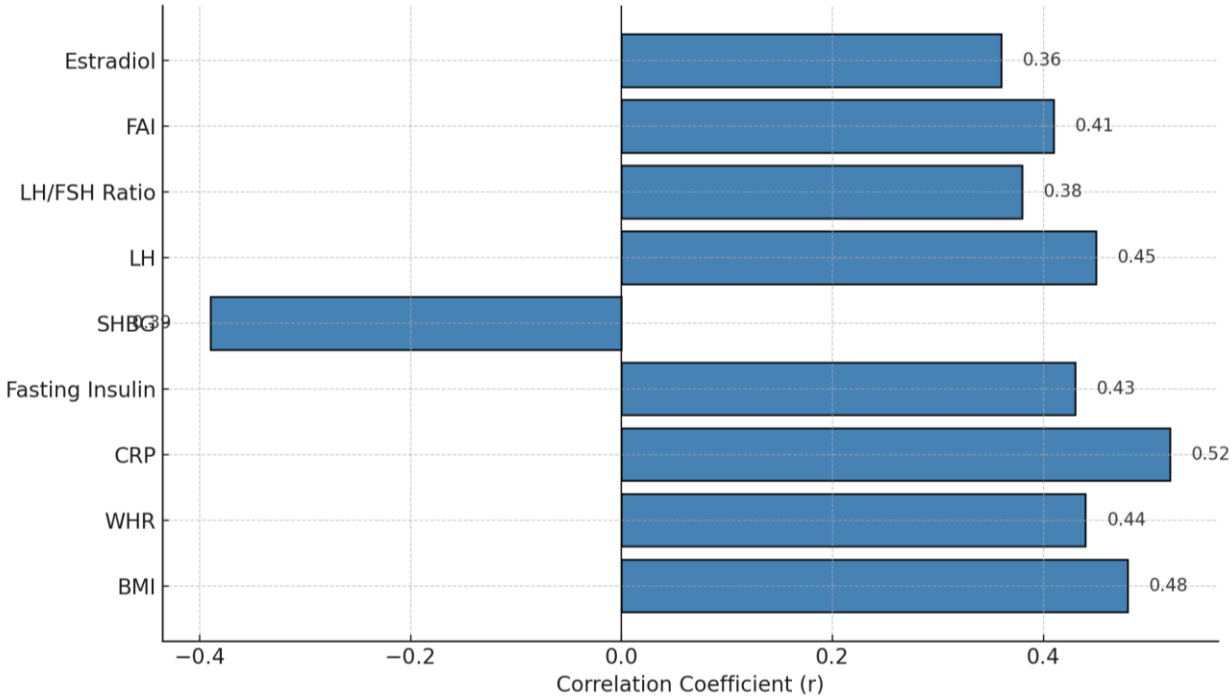


Figure 2. Correlation Of Serum IL-22 Levels with Key Parameters In PCOS

Table 2. Correlation Coefficients for Serum IL-22 Levels

Parameter	Correlation Coefficient (r)	p-value
BMI	0.48	<0.001
Waist-to-Hip Ratio (WHR)	0.44	<0.001
CRP	0.52	<0.001
Fasting Insulin (µIU/mL)	0.43	<0.001
SHBG (nmol/L)	-0.39	0.002
LH (IU/L)	0.45	<0.001
LH/FSH Ratio	0.38	0.003
Free Androgen Index (FAI)	0.41	<0.001
Estradiol (pg/mL)	0.36	0.004

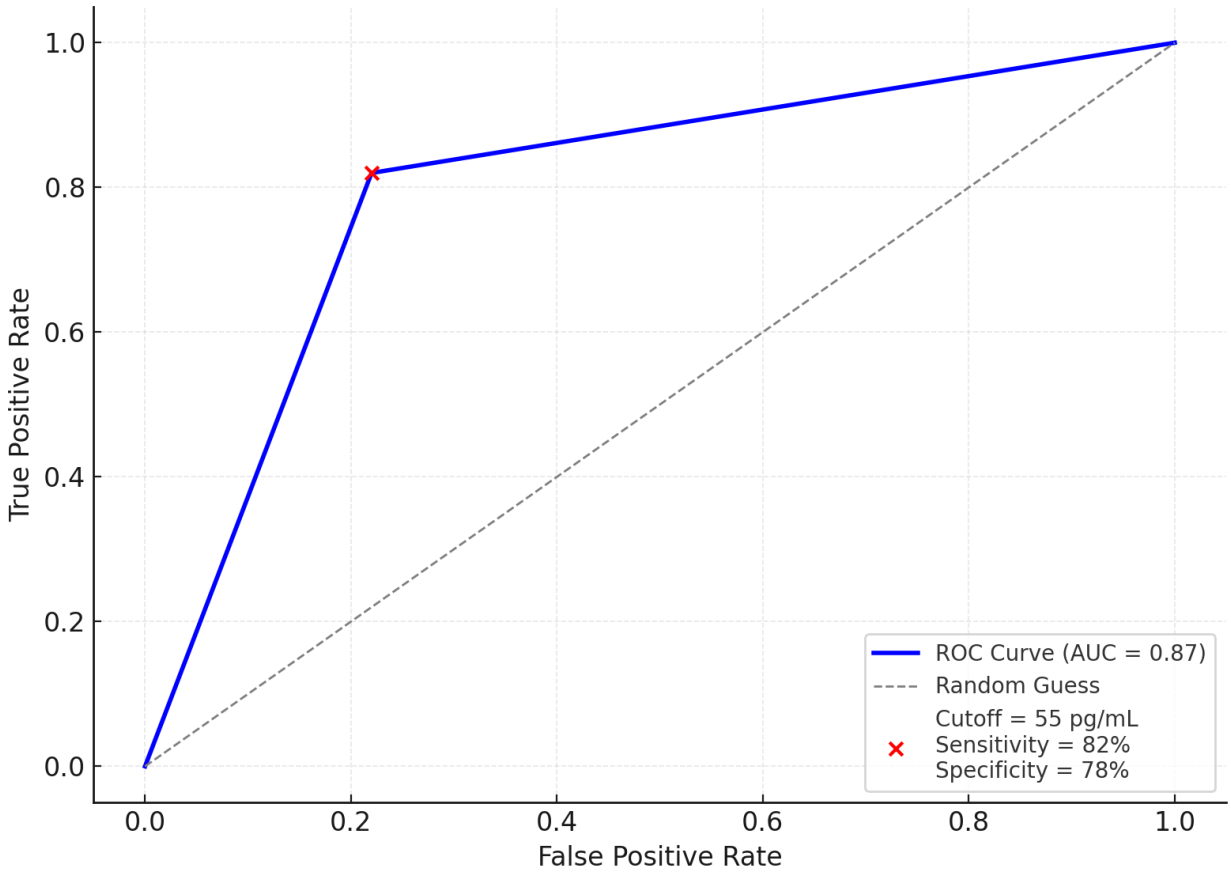


Figure 3. ROC Curve is a Plot of the Serum IL-22 Level as a Biomarker for PCOS

Key Findings:

1. The levels of serum IL-22 are significantly higher in PCOS patients and are associated with important metabolic and inflammatory markers.
2. IL-22 has the potential to be a diagnostic biomarker for PCOS, as it is sensitive and specific.
3. IL-22 can contribute to the pathophysiology of PCOS by regulating inflammation, dysregulated metabolism, and ovarian dysfunction.

The results offer new clues as to the role of IL-22 in PCOS and highlight its potential as a therapeutic target. Further studies are needed to elucidate its mechanism of action in PCOS and to identify therapeutic approaches aimed at the IL-22 pathway.

3. Discussion

This study has pointed out the important role of interleukin-22 (IL-22) in the pathophysiology of Polycystic Ovary Syndrome (PCOS) and its possible role as a biomarker and mediator of such metabolic, inflammatory, and hormonal dysfunctions. PCOS patients had higher levels of serum IL-22 compared with controls (68.4 ± 15.7 pg/mL vs 42.3 ± 10.8 pg/mL, $p < 0.001$), suggesting its role in systemic inflammation, metabolic imbalance, and hormonal imbalance. The elevated IL-22 levels in obese PCOS patients further support IL-22 as a link to metabolic comorbidities, which are also a hallmark of PCOS.

The known effects of IL-22 on glucose and lipid metabolism, such as through the STAT3 pathway, correlate with the positive associations with estradiol ($r = 0.36$, $p = 0.004$) and Free Androgen Index (FAI) ($r = 0.41$, $p < 0.001$). The findings indicate that IL-22 could worsen insulin resistance (IR), chronic inflammation, and hyperandrogenism that are characteristic of PCOS.

The inverse correlation with SHBG ($r = -0.39$, $p = 0.002$) suggests that levels of IL-22 are associated with higher concentrations of free androgen and could exacerbate these symptoms, including anovulation and hirsutism. Increased LH (12.3 ± 3.6 IU/L), LH/FSH ratio (2.1 ± 0.5), and estradiol (182.5 ± 40.2 pg/mL) in PCOS patients, along with the correlation of IL-22 with these markers, further supports its involvement in ovarian dysfunction. In other chronic inflammatory diseases, IL-22 is seen as a compensatory response to inflammatory and metabolic stress, but may also be responsible for pathological tissue remodeling/fibrosis, depending on the duration of activity.

The diagnostic potential of IL-22 is supported by the ROC analysis, with an AUC of 0.87 (95% CI: 0.82–0.91, $p < 0.001$), a sensitivity of 82%, and a specificity of 78% at a cutoff value of 55 pg/mL. These metrics indicate that IL-22 is a potentially useful biomarker to distinguish PCOS patients from healthy individuals, and that it has similar discriminative ability to other markers used for this purpose, such as CRP and IL-6. This has strong associations with metabolic and hormonal markers, further adding to its diagnostic value.

The strengths of this study are the large number of participants (150 PCOS patients and 75 controls) and the extensive statistical analysis, which included multivariate regression and yielded IL-22 as an independent predictor of PCOS ($\beta = 0.62$, $p < 0.001$, $R^2 = 0.68$). The cross-sectional design precludes causal inferences, and the absence of longitudinal findings precludes understanding of the role of IL-22 in PCOS progression and/or therapy.

Further elucidation of the direct effect of IL-22 on ovarian cell signaling, oxidative stress, and inflammatory pathways will be of interest. IL-22 pathway-interventional studies might be useful to understand its therapeutic potential in cases of severe metabolic dysfunction or hyperandrogenism.

Finally, IL-22 proves to be an important biomarker and mediator in the immune-metabolic-hormonal axis of PCOS. Its significant associations with inflammation, metabolic dysfunction, and hormonal

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deficits suggest its potential for diagnosis and treatment, and make it a promising target for the development of better management strategies for this complex syndrome.

4. Conclusion

In this study, researchers discovered a critical part of interleukin-22 (IL-22) in the complex interplay of inflammation, metabolic disturbance, and ovarian dysfunction that underlies Polycystic Ovary Syndrome (PCOS). The increased IL-22 levels between PCOS patients (68.4 ± 15.7 pg/mL) and healthy controls (42.3 ± 10.8 pg/mL, $p < 0.001$) seem to differentiate between the two groups and also suggest its potential as a new biomarker with high diagnostic accuracy (AUC = 0.87, sensitivity = 82%, specificity = 78%). The strong correlations between IL-22 and key metabolic and hormonal markers, including BMI ($r = 0.48$, $p < 0.001$), fasting insulin ($r = 0.43$, $p < 0.001$), CRP ($r = 0.52$, $p < 0.001$), LH ($r = 0.45$, $p < 0.001$), LH/FSH ratio ($r = 0.38$, $p = 0.003$), and Free Androgen Index (FAI) ($r = 0.41$, $p < 0.001$), suggest that IL-22 is deeply intertwined with the systemic metabolic and hormonal disturbances central to PCOS. Furthermore, its inverse correlation with SHBG ($r = -0.39$, $p = 0.002$) and positive correlation with the level of estradiol ($r = 0.36$, $p = 0.004$) further suggest its role in hyperandrogenism and reproductive dysfunction.

These results establish IL-22 as a key player at the crossroads of immune, metabolic, and hormonal pathways, presenting exciting opportunities for its clinical application. In summary, IL-22 is an exciting target for further research in the management of PCOS, both as a diagnostic marker and a therapeutic target, especially when considering the role of obesity, insulin resistance, and hyperandrogenism in these women. The findings of this study will provide a foundation for future studies to explore the mechanistic actions of IL-22 in ovarian function, inflammation, and metabolic regulation to develop novel diagnostic and therapeutic approaches to the treatment of this complex syndrome.

Conflict of interest: NIL

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