Rzeszów University Press 2025
ISSN 2544-1361 (online)
doi: 10.15584/ejcem.2025.3.27

http://www.ejcem.ur.edu.pl
European Journal of Clinical and Experimental Medicine
Eur J Clin Exp Med 2025; 23 (3): 692–700

ORIGINAL PAPER

Evaluation of corin and copeptin as novel biomarkers for polycystic ovary syndrome – diagnostic accuracy and associations with cardiometabolics

Rehab Refaat Raheem [1], Hanan Jassim Hammod [2]

[1] Department of Medical Laboratory Techniques, College of Health and Medical Techniques, Kufa, Al-Furat Al-Awsat Technical University, Kufa, Iraq
[2] Department of Physiology, Babylon Technical Institute, Al-Furat Al-Awsat Technical University, Kufa, Iraq

ABSTRACT

Introduction and aim. Polycystic ovary syndrome (PCOS) is a common endocrine disorder that affects 5–18% of women of reproductive age and is intricately linked to metabolic dysfunction and cardiovascular risks. This study aimed to evaluate the diagnostic utility of copeptin and corin as potential biomarkers in PCOS and their association with cardiometabolic risk factors.

Material and methods. This case-control study included 60 women diagnosed with PCOS (Rotterdam criteria) and 30 healthy controls. Serum levels of copeptin and corin and metabolic parameters were measured using enzyme-linked immunosorbent assay kits. Statistical analyses included receiver operating characteristic (ROC) curves, logistic regression, and correlation tests.

Results. The results revealed significantly elevated corin (1450.23±264.91 vs. 619.17±159.19 pg/mL, $p<0.001$) and copeptin levels (5.81±1.66 vs. 2.46±0.64 ng/mL, $p<0.001$) in patients with PCOS compared to controls. Both biomarkers were strongly correlated with insulin resistance (HOMA-IR: $r=0.648$ for corin and $r=0.750$ for copeptin) and dyslipidemia. ROC analysis demonstrated exceptional associative biomarker precisions for corin (AUC=1.00) and copeptin (AUC=0.89). Univariate regression identified corin (odds ratio [OR]=1.018) and copeptin (OR=1.344) as independent predictors of PCOS.

Conclusion. This study identified plasma corin and copeptin levels as potential biomarkers for PCOS diagnosis and risk stratification. Elevated corin levels predict infertility, while copeptin levels correlate with metabolic dysfunction, particularly in obese, insulin resistant phenotypes.

Keywords. copeptin, corin, dyslipidemia, insulin resistance

Introduction

Polycystic ovarian syndrome (PCOS) is one of the most prevalent endocrinopathies, affecting 5 to 18% of women worldwide, with manifestations spanning the reproductive, metabolic and psychological domains.[1] PCOS is characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology, and arises from a complex interplay of genetic susceptibility, epigenetic modifications, hypothalamic-pituitary-ovarian axis dysregulation, and metabolic disturbances.[2] The Rotterdam criteria, first published in 2003 and updated in 2023, continue to provide the fundamental diagnostic framework for PCOS. Diagnosis requires the presence of at least two of the following three characteristics: clinical or biochemical hyperandrogenism, oligomenorrhea or amenorrhea (indicating ovulatory dysfunction), and

Corresponding author: Rehab Refaat Raheem, e-mail: rehabmontather@gmail.com

Received: 15.03.2025 / Revised: 14.05.2025 / Accepted: 18.05.2025 / Published: 30.09.2025

Raheem RR, Hammod HJ. Evaluation of corin and copeptin as novel biomarkers for polycystic ovary syndrome – diagnostic accuracy and associations with cardiometabolics. *Eur J Clin Exp Med.* 2025;23(3):692–700. doi: 10.15584/ejcem.2025.3.27.

polycystic ovarian morphology (PCOM) confirmed by ultrasound or elevated levels of anti-Müllerian hormone (AMH) levels.[3]

The prevalence of PCOS ranges from 6% to 18% and is influenced by diagnostic criteria (NIH, Rotterdam or Androgen Excess-PCOS Society) and population characteristics.[4] The Rotterdam criteria, when applied broadly, identified four phenotypes with distinct metabolic and reproductive risks. Phenotype A (hyperandrogenism + ovulatory dysfunction + polycystic ovaries) represents more than 60% of cases and correlates with severe metabolic dysfunction, while phenotype D (ovulatory dysfunction and polycystic ovaries) exhibits milder manifestations.[5] Geographical disparities exist, with a higher prevalence in South Asian and Middle Eastern populations, likely due to genetic admixture and environmental factors.[1] The prevalence of infertility has been reported to be 70–80% in PCOS.[6]

PCOS is a complex endocrine metabolic disorder characterized by intersecting pathways of insulin resistance, chronic inflammation, and androgen excess with significant clinical heterogeneity in all phenotypes.[7] PCOS exhibits a complex bidirectional relationship with metabolic dysfunction, characterized by insulin resistance in 65–80% of lean and 95% of obese individuals, regardless of body mass index (BMI).[8] Approximately 50-80% of affected women exhibit insulin resistance due to defects in post-receptor signaling defects in skeletal muscle and adipose tissue, characterized by excessive serine phosphorylation of insulin receptor substrate-1 (IRS-1), which affects GLUT4 translocation and glucose uptake.[9] This metabolic dysfunction coexists with dyslipidemia in 40-55% of cases and android obesity in 52–64% of patients, creating a pro-inflammatory environment marked by elevated tumor necrosis factors α, interleukin 6, and oxidative stress, even in lean individuals.[10] Early diagnosis remains critical given the association between PCOS and a 4-fold increased risk of type 2 diabetes and a 2-fold increase in cardiovascular events, compounded by a 28–57% prevalence of anxiety/depression.[11]

Metabolic syndrome (MetS) affects 33–46% of patients, with abdominal obesity and insulin resistance exacerbating ovarian dysfunction through adipose-derived cytokine signaling and altered steroidogenesis.[12] MetS, defined as a group of conditions including insulin resistance, abdominal obesity, hypertension, and dyslipidemia, has become a major health risk in society. This syndrome negatively affects reproductive function and leads to ovarian dysfunction and other hormonal disorders that can increase infertility and menstrual irregularities.[13,14]

Copeptin, a glycosylated 39-amino acid peptide derived from the C-terminal segment of pre-provasopressin (preproAVP), has emerged as a promising biomarker for PCOS. As a cleavage product of preproAVP, copeptin is synthesized along with arginine vasopressin (AVP) and neurophysin II during transport from the hypothalamus to the posterior pituitary. Although AVP plays a central role in fluid homeostasis, vascular tone regulation, and endocrine stress responses, it also serves as a stable surrogate marker for AVP due to its equimolar secretion and stability in circulation.[15]

Insulin resistance is a central feature of PCOS, affecting up to 70% of patients, regardless of obesity status. Copeptin has been implicated in metabolic dysfunction through its association with AVP-mediated pathways that influence glucose homeostasis and lipid metabolism.[16] Serum copeptin levels correlate with systolic and diastolic blood pressure, in addition to various factors associated with metabolic syndrome, including obesity and hypertriglyceridemia. Women with PCOS may exhibit elevated copeptin levels compared to those without the condition. One of the risks of PCOS is an increased likelihood of developing type 2 diabetes mellitus. Copeptin serves as a novel biomarker of clinical significance in patients with PCOS, potentially enhancing the identification of diabetes susceptibility.[17]

Corin is a transmembrane serine proteinase (EC 3.4.21) with a complex molecular architecture essential for its enzymatic function and cellular localization. Human corin is a unique mosaic protein consisting of an N-terminal cytoplasmic tail, a transmembrane domain, and an extensive extracellular region containing two frizzled-like domains (Fz1 and Fz2), eight low-density lipoprotein (LDL) repeats (LDLR), a scavenger receptor (SR) domain, and a C-terminal serine protease domain harboring the catalytic triad of histidine, aspartic acid, and serine residues.[18] This exceptionally large protein comprises 1042 amino acids with 19 predicted N-linked glycosylation sites in its extracellular region, conferring an apparent molecular mass of approximately 150-200 kDa in SDS-PAGE analysis. The human corin gene is located on chromosome 4p12, spanning over 200 kb with 22 exons, making it one of the largest protease genes identified to date.[19] Structurally, the LDLR8 module contains a critical DSSDE motif that regulates specific apical trafficking in polarized epithelial cells, highlighting the sophisticated cellular machinery that governs corin localization and function.[20] The insulin resistance characteristic of PCOS likely influences corin expression and activity through complex endocrine and metabolic pathways. Dysfunctional adipose tissue signaling and altered natriuretic peptide profiles contribute to cardiovascular risk in patients with PCOS, potentially mediated by aberrant corin-ANP interaction.[19]

Aim

To evaluate the diagnostic precision of plasma corin and copeptin as potential new biomarkers of PCOS, we assessed their association with cardiometabolic risk factors (insulin resistance, dyslipidemia, and obesity).

Material and methods

A total of 60 samples were collected from women of reproductive age (20-43 years) during their visits to the gynecological departments of the Al Zahraa Teaching Hospital and the Fertility Center of the Al Sadr Medical City from October 1, 2024, to January 24, 2025. These women were diagnosed with PCOS by gynecologists according to Rotterdam criteria. Demographic data, laboratory results, family history, and blood pressure data were collected using a structured questionnaire. The inclusion criteria required that participants be married and meet Rotterdam's diagnostic criteria, while the exclusion criteria excluded women with a history of smoking, chronic diseases (eg, diabetes, autoimmune diseases, thyroid disorders, hypertension, cardiovascular disease, chronic renal failure, or malignancies), or use of medications such as lipid-lowering agents, ovulation stimulants, corticosteroids, or antidiabetic medications. In addition, a control group of 30 healthy and fertile women aged 20 to 43 years was selected with no history of smoking, regular menstrual cycles, normal ovarian morphology, or underlying medical conditions, as confirmed by gynecological evaluation. Both groups were matched for age and reproductive status to ensure comparability. Before sample collection, all research participants were notified and each gave their verbal consent to be obtained from each participant. On 1 October 2024, document number 5578 stated that the local ethics commission of the College of Health and Medical Techniques of Al-Furat Al-Awsat Technical University, Al-Kufa, Iraq reviewed and approved the research protocol, consent form, and subject data.

Sample collection

Samples were obtained from women diagnosed with PCOS and from healthy controls without endocrine or metabolic disorders. Five milliliters of venous blood was collected on the second day of the menstrual cycle and transferred to gel tubes for serological and immunological tests. An enzyme-linked immunosorbent assay (ELISA) kit was used to conduct the experiment: a human copeptin ELISA kit from BT Laboratory Cat. No E1129Hu and a Human Corin (CRN) ELISA kit from Sunlong Catalog Number: SL1938Hu. ELISA kits (ELabscience, USA) were used to measure fasting insulin (FINS) and a fluorescent immunoassay (Minividas, Biomerieux, France) was used to measure luteinizing hormone (LH) VIDAS®REF30 407-01, follicle stimulating hormone (FSH) VIDAS REF30 40601 H, and total testosterone levels. Insulin resistance (IR) Determination of human insulin level Cat. No: E-EL-H2665 was estimated using the homeostatic model assessment of insulin resistance (HOMA-IR) according to the formula: HOMA-IR=(fasting insulin [μU/mL]×fasting glucose [mg/dL])/405. According to the World Health Organization, overweight and obesity are defined based on body mass index (BMI), with overweight defined as BMI <25 kg / m^2 and obesity as BMI ≥30 kg/m^2.[21]

Blood lipid level analysis: These tests rely on enzyme-based colorimetric methods and are performed using a spectrophotometer. The test uses: enzymatic conversion: specialized enzymes break down lipids in the sample, ultimately producing hydrogen peroxide. Color formation: hydrogen peroxide reacts with special reagents, aided by the enzyme peroxidase, to form a colored dye. Measurement: The optical absorbance meter measures the intensity of this color at a wavelength of 500 nanometers, where the intensity is directly proportional to the lipid concentration. The concentration is calculated by comparing the absorbance to a standard of known concentration. Main analysis methods: total cholesterol (TC) and triglycerides (TG): The serum sample is mixed directly with the enzyme reagents, then incubated, and the light absorbance of the resulting dye is measured. The high-density lipoprotein (HDL): this involves a preliminary step of precipitating other lipoproteins (such as LDL) from the serum. The remaining HDL in the clear fluid is then analyzed using the same enzymatic colorimetric method. LDL cholesterol: This is not measured directly but is calculated using the Friedewald equation.

LDL (mg/dL)=total cholesterol - HDL - (triglycerides/5)which is based on the results of total cholesterol, HDL, and triglyceride (reference values: normal <100 mg/dL, suspected 150 mg/dL, elevated 190 mg/dL).

Statistical analysis

All data were tested for normality. For data comparison, an independent t-test was applied, while the chi-square test was used when appropriate. was analyzed using the receiver ROC curve analysis. The Pearson correlation test was used to evaluate associations between parameters related to PCOS characteristics. Univariate logistic regression was used to assess the predictive capacity of biomarkers. Statistical analyses were performed using SPSS v.28 (IBM, IL, USA), and statistical significance was set at $p<0.05$.

Results

This study compared the demographic and clinical characteristics of PCOS individuals and healthy controls (Table 1). The mean age of PCOS patients (28.15 years) was marginally higher than that of controls (27.6 years), and the difference was not statistically significant ($p=0.663$). However, PCOS patients exhibited a significantly elevated mean BMI ($p = 0.004$), 33.3% classified as obese compared to 10% of controls, highlighting metabolic disparity. Hyperandrogenism-related clinical markers were markedly prevalent in PCOS, including hirsutism (86.7% vs. controls, $p<0.0001$) and menstrual irregularities (80% vs. 6.7% regular cycles in controls, $p<0.0001$), aligning with diagnostic criteria. In partic-

ular, 56.7% of PCOS patients were nulliparous versus none of the controls (p<0.0001).

Table 1. Demographic information on POCOS and the healthy women groups*

Demographic features	Categories	Studied groups: PCOS patients n=60		Healthy control n=30		p
		n	%	n	%	
Age (year)	Mean±SD	28.15±5.96		27.6±4.93		0.663[a]
	≤25 years	22	36.7	10	33.3	X^2=0.097
	>25 years	38	63.3	20	66.7	0.755[b]
BMI (kg/m²)	Mean±SD	28.42±4.44		26.14±2.85		0.004[a]
	Normal weight	13	21.7	10	33.3	X^2=5.883
	Overweight	27	45	17	56.7	0.053[b]
	Obesity	20	33.3	3	10	
Hirsutism	Yes	52	86.7	0	0	X^2=61.579
	No	8	13.3	30	100	0.0001[b]
Menstrual cycle	Regular	12	20	28	93.3	X^2=43.56
	Irregular	48	80	2	6.7	0.0001[b]
No. children	Non	34	56.7	0	0	X^2=28.407
	One	17	28.3	18	60	0.0001[b]
	Two	7	11.7	11	36.7	

* [a] independent T-test, [b] – Chi-square

Table 2 presents a comparison of metabolic and glycemic parameters between individuals diagnosed with PCOS and healthy controls. All measured parameters, including fasting blood sugar (FBS), insulin levels, HOMA-IR, TC, TG, LDL, and HDL, showed statistically significant differences (p=0.001). PCOS patients exhibited elevated levels of FBS (104.32±15.23 vs. 86.47±7.08 mg/dL), insulin (14.91±3.01 vs. 8.22±2.47 µU/mL), HOMA-IR (3.77±1.01 vs. 1.74±0.52), TC, TG, and LDL compared to healthy controls. On the contrary, HDL levels were significantly lower in PCOS patients (28.63±2.44 vs. 36.23±2.06 mg/dL).

Table 2. Comparative analysis of metabolic and glycemic parameters in PCOS patients versus healthy controls (independent T-test, mean±SD)

Parameters	PCOS patients n=60	Healthy control n=30	p
FBS (mg/dL)	104.32±15.23	86.47±7.08	<0.001
Insulin (µU/mL)	14.91±3.01	8.22±2.47	<0.001
HOMA-IR	3.77±1.01	1.74±0.52	<0.001
TC (mg/dL)	226.57±27.47	178.67±7.93	<0.001
TG (mg/dL)	168.15±16.25	106.63±12.02	<0.001
HDL (mg/dL)	28.63±2.44	36.23±2.06	<0.00
LDL (mg/dL)	152.22±11.81	128.27±2.73	<0.001

Table 3 provides a comparative analysis of serum corin and copeptin levels between women diagnosed with PCOS and healthy controls. Serum corin concentrations were significantly elevated in the PCOS cohort (1450.23±264.91 pg/mL) compared to the control group (619.17±159.19 pg/mL), demonstrating a statistically significant difference (p<0.001). Similarly, copeptin levels were substantially higher in the PCOS group (5.81±1.66 ng/mL) than in healthy controls (2.46±0.64 ng/mL), with a significant disparity (p<0.001).

Table 3. Comparison of serum corin and copeptin levels between women with PCOS and healthy controls (independent T-test, mean±SD)

Parameters	PCOS patients n=60	Healthy control n=30	p
Corin (pg/ml)	1450.23±264.91	619.17±159.19	<0.001
Copeptin (ng/ml)	5.81±1.66	2.46±0.64	<0.001

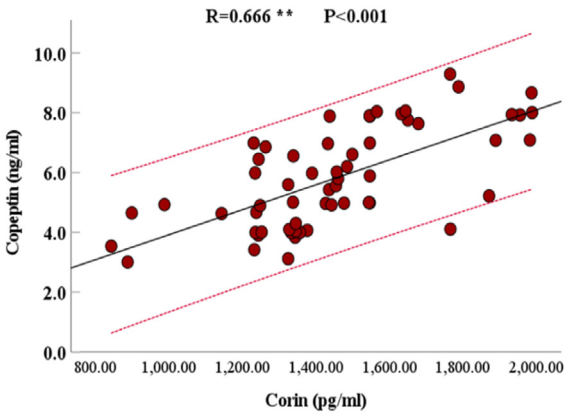

Fig. 1. Correlations between corin and copeptin in PCOS patients

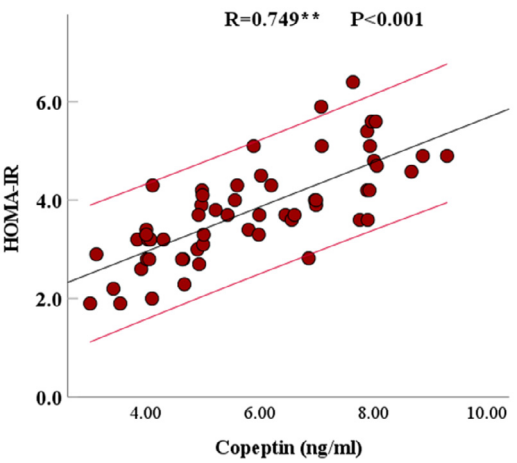

Fig. 2. Correlations between copeptin and insulin resistance in PCOS patients

Correlation coefficients (R) and the corresponding p-values for associations between circulating corin (pg/mL) and copeptin (ng/mL) levels and various clinical and biochemical parameters. For corin, significant negative correlations with FSH were observed (R = -0.359, p=0.005), while strong positive correlations were identified with FBS (R=0.515, p<0.001) and insulin levels (R=0.648, p<0.001). Similarly, copeptin was significantly and positively associated with FBS (R=0.375, p=0.003)

and insulin (R=0.750, p<0.001). Age, BMI, testosterone, lipid profiles (TC, TG, HDL, LDL) and LH levels showed no statistically significant correlations with either biomarker. The figure shows a strong correlation between corin and copeptin levels, where increasing chlorine levels are associated with increasing copeptin levels, and vice versa. There was a strong positive correlation between copeptin levels and HOMA-IR. As copeptin levels increased, HOMA-IR levels also increased, indicating increased insulin resistance (Fig. 1 and 2).

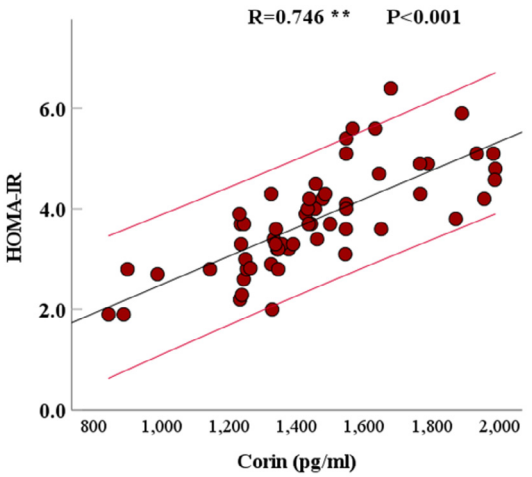

Fig. 3. Correlation of circulating corin levels with insulin resistance in a PCOS patient

Table 4. Univariate logistic regression analysis of risk predictors in PCOS patients*

PCOS patients[a]	p	OR	95% CI	
Age (year)	0.394	0.964	0.886	1.049
BMI (kg/m^2)	0.197	1.115	0.945	1.316
LH (mIU/mL)	0.0001	2.730	1.566	4.759
FSH (mIU/mL)	0.0001	0.238	0.118	0.482
Total testosterone (ng/mL)	0.040	3.318	1.055	10.436
FBS (mg/dL)	0.005	1.165	1.046	1.298
Insulin (µU/mL)	0.0001	2.064	1.434	2.971
HOMA-IR	0.0001	1.53	1.293	1.819
TC (mg/dL)	0.0001	1.004	1.002	1.007
TG (mg/dL)	0.0001	1.008	1.004	1.011
HDL (mg/dL)	0.036	1.015	1.001	1.028
LDL (mg/dL)	0.0001	1.006	1.003	1.009
Corin (pg/mL)	0.015	1.018	1.003	1.033
Copeptin (ng/mL)	0.0001	1.344	1.196	1.511

* [a] The reference category was healthy controls, CI confidence interval, OR – odds ratio

Table 4 presents the results of the univariate logistic regression analysis that evaluates the risk predictors for PCOS compared to healthy controls. Key hormonal and metabolic biomarkers, including LH, FSH, testosterone, HOMA-IR, and lipid profiles, were analyzed. Significant predictors of PCOS included elevated LH (OR=2.730, 95% CI: 1.566–4.759, p<0.01), reduced FSH (OR=0.233, 95% CI: 0.118–0.482, p<0.01), and higher testosterone levels (OR=3.328, 95% CI: 1.055–10.436, p<0.05). Metabolic markers such as insulin resistance (HOMA-IR: OR=1.533, p<0.01) and dyslipidemia (LDL: OR=1.006, p<0.01) were strongly associated with PCOS. The novel biomarkers corin (OR=1.018, p<0.05) and copeptin (OR=1.344, p<0.01) also showed significant positive associations.

Table 5 summarizes the diagnostic performance of corin and copeptin evaluated using AUC. All biomarkers demonstrated statistically significant discriminative power (p<0.0001). Corin and copeptin achieved near-perfect AUC values (1.00 and 0.99, respectively), indicating exceptional potential diagnostic accuracy. Corin exhibited the highest sensitivity (0.93 and 0.95), while copeptin showed balanced sensitivity (0.98) and marginally higher specificity (0.03) compared to other markers.

Table 5. Diagnostic accuracy of serum biomarkers based on ROC analysis

Markers	Area	p	95% CI		Cutoff	Sensitivity	1-Specificity
			Lower bound	Upper bound			
Corin (pg/mL)	1.00	<0.001	0.99	1.00	>987.35	0.95	0.00
Copeptin (ng/mL)	0.99	<0.001	0.98	1.00	>3.11	0.98	0.03

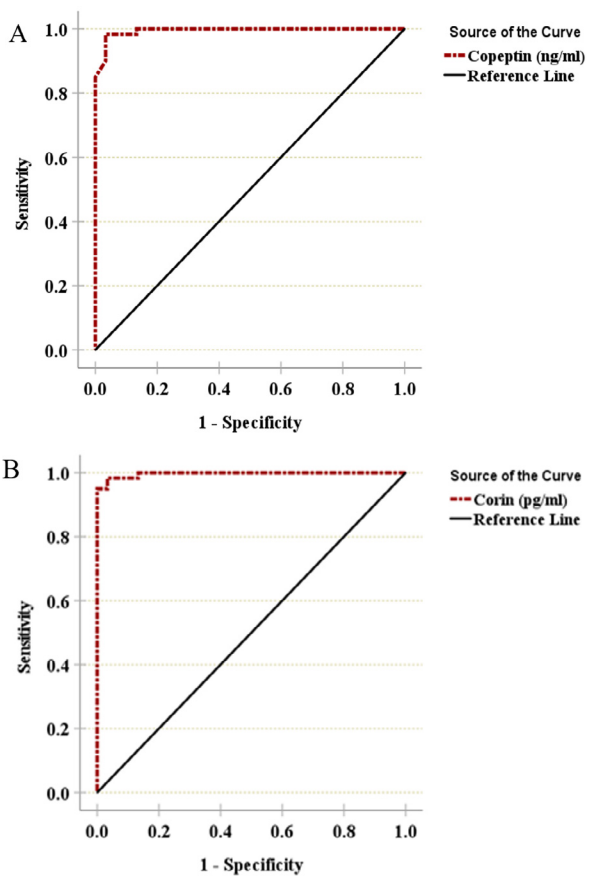

Fig. 4. Analysis of the ROC curve of A: copeptin and B: corin

Discussion

PCOS is a major health problem in women.[22] The pathological mechanisms underlying PCOS are complex and have not yet been completely elucidated. Dysregulation of adipose tissue metabolism in PCOS indicates the significant role of regulatory factors of adipose tissue in disease pathogenesis. The findings of the current study of elevated HOMA-IR levels in patients with PCOS corroborate the well-documented centrality of insulin resistance in the pathophysiology of PCOS. A meta-analytical synthesis of prior research indicates that approximately 75% of individuals with PCOS exhibit insulin resistance, highlighting its predominance as a metabolic hallmark of the disorder.[23] This metabolic aberration is further evidenced by consistent reports of elevated fasting insulin concentrations in PCOS cohorts compared to controls matched in age and BMI, strengthening the association of the syndrome with a hyperinsulinemic state.[24] In particular, the interplay between insulin resistance and PCOS appears to be intrinsic rather than secondary to adiposity, although obesity may enhance its severity. A longitudinal investigation carried out in a university cohort demonstrated that women with PCOS exhibited significantly higher insulin resistance indices than controls in all BMI strata, independent of body weight variations.[24,25]

Corin, a transmembrane serine protease integral to the natriuretic peptide system, facilitates proteolytic activation of ANP, a key regulator of cardiovascular and metabolic homeostasis. Despite its established role in ANP processing, the broad physiological and pathological functions of corin remain unclear. Unlike other membrane-bound proteases, corin undergoes proteolytic cleavage, generating a soluble form that is detectable in circulation.[26] Notably, this circulating corin retains its ability to activate ANP, mirroring the activity of its membrane-bound counterpart.[27] Given this functional equivalence, soluble corin has been hypothesized to contribute to the pathogenesis of PCOS.

The present study confirms this hypothesis, demonstrating significantly elevated plasma corin levels in PCOS patients compared to healthy controls. A 2024 case-control investigation comprising 70 women diagnosed with PCOS and 70 age-matched healthy controls revealed a marked elevation in median plasma corin concentrations (optimal diagnostic threshold: 1186 pg/mL) in the PCOS cohort. This cutoff exhibited robust diagnostic accuracy, achieving 100% sensitivity and 97.1% specificity for discriminating PCOS cases from controls. Furthermore, elevated plasma corin concentration was independently associated with infertility in the PCOS group (odds ratio, 5.9), underscoring its potential clinical utility as a biomarker. The observed elevation may reflect compensatory cardiovascular and metabolic adaptations linked to PCOS pathophysiology, potentially mediated by the role of corin in ANP processing and cardiovascular homeostasis.[19] In contrast, corin levels in other biological compartments showed divergent trends. For example, endometrial flushing fluid collected during the implantation window exhibited marginally reduced mean corin concentrations in women with PCOS; a comparison with controls revealed a difference that did not achieve statistical significance.[28] The findings presented here demonstrate concordance with the results of the current study, thereby corroborating the proposed hypotheses.

The present study corroborated that individuals diagnosed with PCOS exhibit significantly elevated serum copeptin concentrations compared to healthy controls. In particular, this observation was particularly pronounced in specific PCOS subgroups. Previous studies have consistently reported higher mean copeptin levels in PCOS cohorts than in healthy controls,[29] with obese PCOS patients demonstrating a marked increase in copeptin concentrations compared to BMI-matched controls. These levels were positively correlated with insulin concentrations and HOMA-IR.[30] Furthermore, copeptin has been inversely associated with HDL cholesterol and positively associated with elevated insulin levels, BMI, HOMA-IR, and waist circumference.[31] A case-control study involving 158 women with PCOS identified copeptin as the strongest predictor of HOMA-IR, underscoring its potential role in the pathophysiology of IR within this population.[32] These findings align with cross-sectional analyses indicating significantly higher copeptin levels in PCOS patients, particularly those with obesity, compared to the control groups.[33] Researchers have postulated that copeptin may contribute to metabolic dysregulation and atherogenesis in hyperandrogenemic, insulin-resistant PCOS patients.[29]

On the contrary, the relationship between PCOS and copeptin appears to depend on metabolic status. A 2024 case-control study demonstrated that normoglycemic, normal weight PCOS patients without IR exhibited lower copeptin levels than healthy volunteers.[34] Similarly, comparative analyses of non-obese PCOS patients and non-obese controls revealed no statistically significant differences in copeptin concentrations, suggesting that metabolic status, rather than PCOS itself, may be the primary driver of copeptin elevation.[30] Clinically, elevated copeptin levels in obese PCOS patients correlate with cardiometabolic markers, including total testosterone, HOMA-IR, waist-hip ratio (WHR), BMI, and hirsutism scores, positioning copeptin as a potential biomarker for cardiovascular risk stratification in this population.[35] Although both corin and copeptin show promise as biomarkers in PCOS, their associations appear distinct: corin is more closely related to cardiovascular sequelae, while copeptin demonstrates stronger associations with met-

abolic dysfunction and stress response pathways.[36] Recent evidence indicates that increased circulating copeptin levels correlate with various components of metabolic syndrome, such as dyslipidemia, insulin resistance, glucose intolerance, hyperinsulinemia, hypertension, and abdominal obesity.[37]

Study limitations and strengths

This study has significant strengths, including the potential investigation of corin and copeptin as possible potential diagnostic candidates for PCOS, supported by solid ROC analyses (AUC=1.00 and 0.99, respectively), complete metabolic profiling and adherence to standardized diagnostic criteria. Its phenotype-aware design and stringent statistical methods further improve its clinical relevance by relating biomarkers to infertility and cardiometabolic risks. Despite these strengths, the moderate sample size and lack of a priori power analysis can limit the generalizability of the findings. Future studies should incorporate power calculations to ensure adequate sample sizes to detect clinically meaningful differences, which may allow larger, longer-term studies to validate discoveries and clarify molecular pathways. The lack of phenotype-specific analyzes (e.g., phenotype A vs. D) restricts our understanding of biomarker variability between PCOS subtypes.

Conclusion

This study highlights the potential of plasma corin and copeptin as biomarkers for the diagnosis and risk stratification. Corin levels increase, are highly diagnostic of PCOS, and serve as a potential predictor of infertility in these women. Copetin, which is classified as an endocrine marker, is also significantly elevated in patients with PCOS, particularly those with obesity and insulin resistance, which attests to its correlation with metabolic dysregulation. Analysis of both markers will provide a thorough perspective on the metabolic and reproductive risks associated with PCOS, which could lead to a better diagnosis and personalized therapy. Furthermore, the nature of the relationship between copeptin and PCOS is context-dependent: elevation is most pronounced in metabolically compromised phenotypes, whereas non-obese, insulin-sensitive PCOS is associated with lower levels than controls. This highlights the diversity of the PCOS phenotype and where biomarker profiles are concerned, and the importance of a common assessment of metabolic status.

Acknowledgements

We express their sincere gratitude to the medical and administrative staff of the Babel Teaching Hospital for Pediatrics and Gynecology, the Imam Sadiq Teaching Hospital, and the Iskandaria General Hospital for their invaluable support throughout the study. The authors express their appreciation to the Institutional Review Board for granting ethical approval to all participants who generously contributed their time and effort.

Declarations

Funding

No funds were received to carry out this work.

Author contributions

Conceptualization: R.R.R. and H.J.H.; Methodology, R.R.R.; Software, R.R.R.; Validation, R.R.R. and H.J.H.; Formal Analysis, R.R.R.; Investigation, R.R.R.; Resources, R.R.R.; Data Curation, R.R.R.; Writing – Original Draft Preparation, R.R.R.; Writing – Review & Editing, R.R.R. and H.J.H.; Visualization, R.R.R.; Supervision, H.J.H.; Project Administration, R.R.R. and H.J.H.; Funding Acquisition, R.R.R.

Conflicts of interest

The authors have nothing to disclose.

Data availability

Study data is available from the corresponding author upon reasonable request.

Ethics approval

On 1 October 2024, document number 5578 stated that the local ethics commission reviewed and approved the research protocol, consent form, and subject data.

Reference

1. Che Y, Yu J, Li YS, Zhu YC, Tao T. Polycystic Ovary Syndrome: Challenges and Possible Solutions. *J Clin Med*. 2023;12(4):1500. doi: 10.3390/jcm12041500
2. Joham AE, Norman RJ, Stener-Victorin E, et al. Polycystic ovary syndrome. *Lancet Diabetes Endocrinol*. 2022;10(9):668-680.
3. Forslund M, Melin J, Stener-Victorin E, et al. International evidence-based guideline on assessment and management of PCOS-A Nordic perspective. *Acta Obstet Gynecol Scand*. 2024;103(1):7-12. doi: 10.1111/aogs.14725
4. Joham AE, Piltonen T, Lujan ME, Kiconco S, Tay CT. Challenges in diagnosis and understanding of natural history of polycystic ovary syndrome. *Clin Endocrinol (Oxf)*. 2022;97(2):165-173.
5. Chang KJ, Chen JH, Chen KH. The Pathophysiological Mechanism and Clinical Treatment of Polycystic Ovary Syndrome: A Molecular and Cellular Review of the Literature. *Int J Mol Sci*. 2024;25(16). doi: 10.3390/ijms25169037
6. Melo AS, Ferriani RA, Navarro PA. Treatment of infertility in women with polycystic ovary syndrome: approach to clinical practice. *Clinics*. 2015;70(11):765-769. doi: 10.6061/clinics/2015(11)09
7. González F. Inflammation in Polycystic Ovary Syndrome: underpinning of insulin resistance and ovarian dysfunc-

tion. *Steroids*. 2012;77(4):300-305. doi: 10.1016/j.steroids.2011.12.003
8. Yang Y, Ding M, Di N, Azziz R, Yang D, Zhao X. Close correlation between hyperandrogenism and insulin resistance in women with polycystic ovary syndrome-Based on liquid chromatography with tandem mass spectrometry measurements. *J Clin Lab Anal*. 2019;33(3):e22699. doi: 10.1002/jcla.22699
9. Chen W, Pang Y. Metabolic Syndrome and PCOS: Pathogenesis and the Role of Metabolites. *Metabolites*. 2021;11(12). doi: 10.3390/metabo11120869
10. Akram W, Fadhil A, Nori W. Unveiling Systemic Immune Inflammation Index Correlations in Women with Polycystic Ovary Syndrome: A Cross-sectional Study. *Al-Rafidain J Med Sci*. 2024;6(2):156-161.
11. Cena H, Chiovato L, Nappi RE. Obesity, polycystic ovary syndrome, and infertility: a new avenue for GLP-1 receptor agonists. *J Clin Endocrinol Metab*. 2020;105(8):e2695--e2709. doi: 10.1210/clinem/dgaa285
12. Lentscher JA, Decherney AH. Clinical presentation and diagnosis of polycystic ovarian syndrome. *Clin Obstet Gynecol*. 2021;64(1):3-11. doi: 10.1097/GRF.0000000000000563
13. Saklayen MG. The global epidemic of the metabolic syndrome. *Curr Hypertens Rep*. 2018;20(2):1-8.
14. Marchiani S, Tamburrino L, McPherson N, Baldi E. The role of obesity and metabolic syndrome in couple infertility. *Front Endocrinol (Lausanne)*. 2021;12:784716. doi: 10.3389/fendo.2021.784716
15. Görkem Ü, Yıldırım E. Copeptin: A potential marker for the prediction of poor ovarian reserve in the ınfertile women. *Turkish J Obstet Gynecol*. 2022;19(4):281. doi: 10.4274/tjod.galenos.2022.55856
16. Ali AI, Hassan WNM, Alrawi S. A copeptin as a predictor marker for insulin resistance among women with polycystic ovary syndrome. *Curr Womens Health Rev*. 2022;18(4):67-72.
17. Franzén A, Pikkemaat M, Melander O, Bennet L, Enhörning S. The association of copeptin with metabolic risk markers is modified by region of origin. *Sci Rep*. 2023;13(1):19651. doi: 10.1038/s41598-023-46908-0
18. Li H, Zhang Y, Wu Q. Role of corin in the regulation of blood pressure. *Curr Opin Nephrol Hypertens*. 2017; 26(2):67-73.
19. Ibrahem MA moniem, Saber Al-Karamany A, Esawy MM, Elasy AN. Plasma Corin: A New Biochemical Marker for Polycystic Ovary Syndrome. *Reprod Sci*. 2024;31(8):2219-2227. doi: 10.1007/s43032-024-01531-w
20. Zhang C, Chen Y, Sun S, et al. A conserved LDL-receptor motif regulates corin and CD320 membrane targeting in polarized renal epithelial cells. *Elife*. 2020;9:e56059. doi: 10.7554/eLife.56059
21. Spinelli A, Buoncristiano M, Nardone P, et al. Thinness, overweight, and obesity in 6-to 9-year-old children from 36 countries: The World Health Organization European Childhood Obesity Surveillance Initiative-COSI 2015-2017. *Obes Rev*. 2021;22:e13214. doi: 10.1111/obr.13214
22. Bakeer E, Radwan R, El Mandoury A, Abd El Rahman A, Gad M, Abd El Maksoud S. Anti-müllerian hormone as a diagnostic marker in Egyptian Infertile polycystic ovary syndrome females: correlations with vitamin D, total testosterone, dyslipidemia and anthropometric parameters. *J Med Biochem*. 2018;37(4):448.
23. Patil V, Belwalkar GJ, Nagane NS, Dhonde SP. Study of lipid profile and insulin resistance in polycystic ovarian syndrome. *Int J Clin Biochem Res*. 2022;9(3):272-275.
24. Guo F, Gong Z, Fernando T, Zhang L, Zhu X, Shi Y. The lipid profiles in different characteristics of women with PCOS and the interaction between dyslipidemia and metabolic disorder states: a retrospective study in Chinese population. *Front Endocrinol (Lausanne)*. 2022;13:892125. doi: 10.3389/fendo.2022.892125
25. Vatier C, Christin-Maitre S, Vigouroux C. Role of insulin resistance on fertility–Focus on polycystic ovary syndrome. In: *Annales d'Endocrinologie*. Elsevier; 2022;83:199-202.
26. Zhang X, Gu X, Zhang Y, Dong N, Wu Q. Corin: a key mediator in sodium homeostasis, vascular remodeling, and heart failure. *Biology (Basel)*. 2022;11(5):717. doi: 10.3390/biology11050717
27. Ichiki T, Huntley BK, Heublein DM, et al. Corin is present in the normal human heart, kidney, and blood, with pro–B-type natriuretic peptide processing in the circulation. *Clin Chem*. 2011;57(1):40-47. doi: 10.1373/clinchem.2010.153908
28. Şeyhanlı Z, Demir M, Türkyılmaz FO, et al. Identification of Corin and Procalcitonin in Endometrial Flushing Fluid Between Women with Polycystic Ovary Syndrome, Endometrioma, Unexplained Subfertility, and Fertile Healthy Women. *Clin Res*. 2024;34(2):212-218.
29. Karbek B, Ozbek M, Karakose M, et al. Copeptin, a surrogate marker for arginine vasopressin, is associated with cardiovascular risk in patients with polycystic ovary syndrome. *J Ovarian Res*. 2014;7:31. doi: 10.1186/1757-2215-7-31
30. Matta RA. Apelin-36 and Copeptin Levels in Polycystic Ovary Syndrome. *J Infect Dis*. 2017;3(1):3.
31. Coelho JM, D'CUNHA P, Shivashankara AR. Serum copeptin as a biomarker of polycystic ovarian syndrome and its correlation with metabolic syndrome components: a cross-sectional analytical study. *J Clin Diagnostic Res*. 2024;18(7).
32. Widecka J, Ozegowska K, Banaszewska B, et al. Is copeptin a new potential biomarker of insulin resistance in polycystic ovary syndrome? *Ginekol Pol*. 2019;90(3):115-121. doi: 10.5603/GP.2019.0021
33. Elboghdady AA, Abd El-Fattah AI, Mohamed ES, Saeed AM. Copeptin and Obestatin Levels in Polycystic Ovary women and their Relation to Obesity, insulin metabolism and Cardiovascular diseases. *Al-Azhar Int Med J*. 2020;0(0):0-0. doi: 10.21608/aimj.2020.27820.1197

34. Yıldırım E, Görkem Ü. Association between serum copeptin levels and non-obese normoglycemic polycystic ovary syndrome: A case control study. *Turkish J Obstet Gynecol*. 2024;21(4):280.
35. Szmygin H, Szydełko J, Matyjaszek-Matuszek B. Copeptin as a novel biomarker of cardiometabolic syndrome. *Endokrynol Pol*. 2021;72(5):566-571. doi: 10.5603/EP.a2021.0072
36. Rojas-Humpire R, Soriano-Moreno DR, Galindo-Yllu B, Zafra-Tanaka JH. Association between copeptin and metabolic syndrome: a systematic review. *J Nutr Metab*. 2022;2022(1):5237903. doi: 10.1155/2022/5237903
37. Łukaszyk E, Małyszko J. Copeptin: pathophysiology and potential clinical impact. *Adv Med Sci*. 2015;60(2):335-341. doi: 10.1016/j.advms.2015.07.002